ISBN 978-82-326-2728-8 (printed ver.)
ISBN 978-82-326-2729-5 (electronic ver.)
ISSN 1503-8181

Doctoral thesis

Margrét Ólafía Tómasdóttir

Doctoral theses at NTNU, 2017:330

NTNU
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Multimorbidity in the Norwegian HUNT population

An epidemiological study with reference to the concept allostatic load

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Thesis for the Degree of
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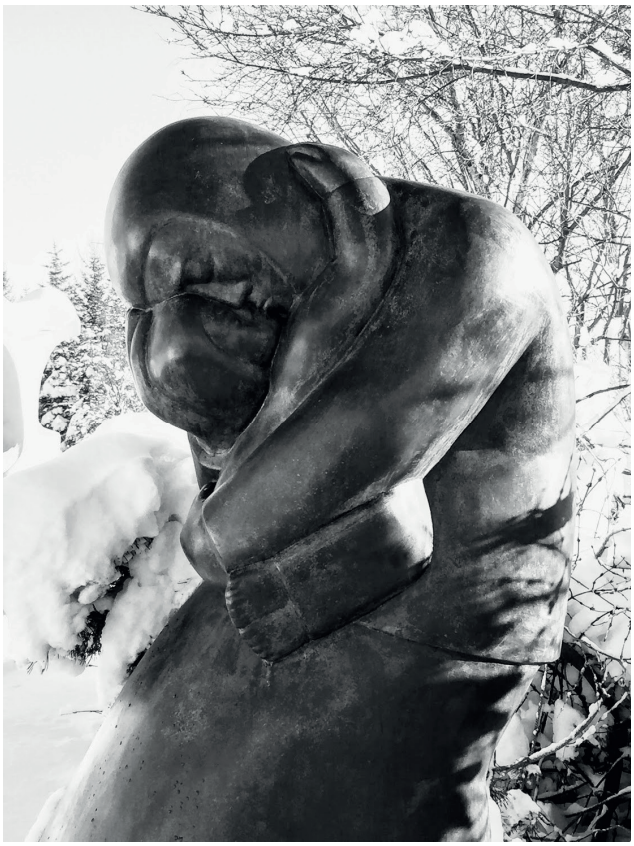
Printed by NTNU Grafisk senter



Fýkur yfir hæðir (e. Motherlove)
by Ásmundur Sveinsson

Hvur er in grátna sem gengur um hjarn
götunnar leitar, og sofandi barn
hylur í faðmi og frostinu ver,
fögur í tárum, en mátturinn þverr –
hún orkar ei áfram að halda.

Who is the woman who wanders the snow,
weeping, unsure what direction to go,
clutching her slumbering son to her breast,
slipping and falling and stopping to rest,
weak from exertion and weary?

Jónas Hallgrímsson, Móðurást (e. Motherlove)

For my grandmothers, whom I am named after.
For their generation of women, it was not a possibility, especially not for a single mother with two children, to follow through with a dream of higher education.
Because of their generation of women, I am able to.

For my parents, who have always encouraged me to get as much education as I seek for.

For my children, Tómas and Sigrún,
in hope that their future will be filled with acceptance and kindness.

Norsk sammendrag

Multimorbiditet i den norske HUNT populasjonen

En epidemiologisk studie med referanse til begrepet allostatisk belastning

Bakgrunn: Multimorbiditet defineres som to eller flere kroniske sykdommer/tilstander samtidig hos en person/pasient. I de senere år har kunnskapsgrunnlaget knyttet til multimorbiditet vokset raskt. Multimorbiditet viser seg å være så utbredt at enkelte forskere har omtalt det som „en av medisinens største utfordringer i det 21 århundre". Individer med multimorbiditet trenger ofte en kompleks, persontilpasset medisinsk tilnærming som gjerne involverer flere nivå i helsetjenesten og forutsetter effektivt samarbeid mellom disse. Til tross for den høye forekomsten av multimorbiditet, vet vi fortsatt lite om fenomenets tilgrunnliggende årsaker og risikofaktorer, spesielt i yngre aldersgrupper. Blant leger er det imidlertid en utbredt klinisk erfaring at komplekse sykdomsmønstre ikke sjelden finnes hos mennesker med vanskelige livserfaringer.

Forskning fra flere fagfelt, og ikke minst basalforskning, viser stadig tydeligere hvordan langvarig, akkulmulert stress og/eller påkjenninger som går ut over individets tålegrense, leder til dysregulering av kroppens fysiologiske (psyko-nevro-endokrino-immunologiske) tilpasningssystemer. Innen stressforskning kalles dette allostatísk overbelastning (eng. allostatic overload). Allostatisk overbelastning anses å være en medvirkende eller utløsende årsak både til somatiske og psykiske lidelser. Med andre ord er det grunnlag for å hevde at belastende livsbetingelser (stress og traumer), via allostatisk overbelastning og fysiologisk dysregulering, kan utgjøre en vesentlig, tilgrunnliggende årsaksfaktor bak kompleks sykelighet og multimorbiditet. På dette feltet er kunnskapsgrunnlaget imidlertid fortsatt begrenset, og avhandlingens mål var å utforske denne hypotesen nærmere.

Mål med avhandlingen: Det første målet var å dokumentere forekomsten av multimorbiditet og eventuelt typiske mønstre av sykdomssammensetning i en generell, norsk befolkning. Dernest var målet, i lys av teorien om allostatisk overbelastning, å undersøke mulige sammenhenger mellom vanskelige livsbetingelser, henholdsvis i barndom og i voksenlivet, og utvikling av fysiologisk dysregulering og multimorbiditet i den samme befolkningen.

Materiale og metode: Studien er basert på data fra Helseundersøkelsen i Nord-Trøndelag (HUNT), både HUNT2 (1995-97) og HUNT3 (2006-8). Til sammen deltok 47 959 personer mellom 20-79 år í HUNT3, hvorav 73% også hadde deltatt i HUNT2. Definisjonen av multimorbiditet var i utgangspunktet basert på 21 selvrapportrete sykdommer/tilstander. Allostatisk overbelastning ble vurdert på bakgrunn av 12 tilgjengelige biomarkører (kroppsmål og blodprøver). Deltakernes selv-vurderte opplevelse av egen barndom ble i HUNT3 undersøkt med ett enkelt spørsmål. Vanskelige livsbetingelser i voksenlivet ble vurdert ut fra 11 spørsmål hentet fra spørreskjemaene i HUNT2 som dekket temaene manglende selvfølelse, mangel på tilfredshet i livet, opplevelse av tilværelsen som lite meningsfylt, og opplevelse av svake sosiale bånd. Vi definerte forsøksvis et nytt begrep – „eksistensiell utilpasshet" (eng. existential unease) - som en samlende term for disse erfaringene.

Resultater: Nesten halvparten av deltakerne i HUNT3 kunne defineres som multimorbide. Psykiske og somatiske lidelser opptrådte svært ofte sammen, men det var stor variasjon i

sykdomsmønstrene og ingen sykdoms-kombinasjoner som dominerte bildet (artikkel 1). Litt over fire prosent av deltakerne i HUNT3 rapporterte en vanskelig eller svært vanskelig barndom. Sammenhengen mellom selvrapportert bardom og multimorbiditet i voksenlivet var tydelig og gradert, idet forekomsten av multimorbiditet steg i samsvar med vanskeligheter i barndommen for 19 av de 21 undersøkte sykdommene/tilstandene. For de biologiske parametrene som inngikk i vurderingen av allostatisk overbelastning, fant vi at individer som rapporterte en vanskelig eller svært vanskelig bardom i gjennomsnitt var mer kortvokste, med bredere midjemål, høyere kroppsmasseindeks (KMI) og lavere blodtrykk enn de som rapporterte en meget god barndom (artikkel 2). Den tredje studien tok utgangspunkt i voksne deltakere i HUNT2. Her fant vi en sammenheng mellom rapportert eksistensiell utilpasshet og utvikling av multimorbiditet i løpet av de neste 11 år (HUNT3). Vi fant en signifikant sammenheng mellom de fleste enkelt-elementene som inngikk i eksistensiell utilpasshet og utvikling av multimorbiditet, og dernest en dose-respons sammenheng mellom antallet elementer og multimorbiditets-utvikling (artikkel 3).

Konklusjoner: I samsvar med prosjektets overordnede hypotese og teorigrunnlag, tyder resultatene på at vanskelige livsbetingelser, både i barndom og voksenlivet, må anses som vesentlige, medvirkende årsaker til utvikling av multimorbiditet. Dernest er det rimelig å snakke om dose-respons-sammenhenger på gruppenivå. Totalt sett bidrar avhandlingen til å konsolidere den framvoksende kunnskapen om hvordan livserfaringer „innskrives“ i menneskets biologi, og at dette skjer på måter som systematisk overskrider skillelinjene mellom, og innenfor, de psykiske og somatiske diagnosegruppene.

Navn kandidat: Margrét Ólafía Tómasdóttir
Institutt: Avhandlingen er et samarbeid mellom Norges Teknisk-Naturvitenskapelige Universitet (NTNU) og Islands universitet (HI)
Veiledere: Linn Getz, professor, ph.d. (NTNU) og Johann Agust Sigurdsson, professor Dr.med. Islands universitet (HI)
Finansieringskilder: Det islandske allmennpraktikerfondet, Heilsugæsla höfuðborgarsvæðisins, Reykjavik og Allmennmedisinsk forskningsenhet, Institutt for Samfunnsmedisin og Sykepleie, NTNU

Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden ph.d i Samfunnsmedisin.
Prøveforelesning og disputas finner sted i Auditorium MTA i Medisinsk Teknisk Forskningssenter (MTFS), Olav Kyrres gt. 9, 7030 Trondheim 7. desember 2017
Prøveforelesning kl. 10.15
Disputas kl. 12.15

Íslensk samantekt

Fjölveikindi meðal íbúa Norður-Þrændalaga (HUNT-rannsóknin)

Faraldsfræðileg rannsókn með vísan til streituþátta tengdum hugtakinu allostatískt álag

Bakgrunnur: Þegar sami einstaklingur þjáist af tveimur eða fleirum langvinnum sjúkdómum er það kallað fjölveikindi (e.multimorbidity). Á undanförnum árum hefur rannsóknum á fjölveikindum fleygt fram og algengi þeirra verið metið svo mikið að fjölveikindi hafa verið nefnd ein stærsta áskorun læknisfræðinnar á 21.öldinni. Sýnt hefur verið fram á að fjölveikir einstaklingar krefjast annarrar og flóknari nálgunar við læknisfræðilega meðhöndlun og meðferð og þurfa oftar að þyggja þjónustu á öllum stigum heilbrigðiskerfisins. Samt sem áður er lítið vitað um mögulega orsakaþætti fjölveikinda, sérstaklega hjá yngra fólki. Í reynsluheimi heimilislækna er það vel þekkt að flókinni sjúkdómsmynd fylgir oft flókin og erfið reynslusaga einstaklings.

Rannsóknir hafa í vaxandi mæli sýnt fram á að langvinn uppsöfnuð streita eða streita yfir þeim mörkum sem einstaklingurinn þolir, veldur vanstillingu á öllum helstu líffræðilegu stjórnkerfum líkamans. Sú vanstilling hefur verið kölluð allostatískt ofálag (e. allostatic overload) og getur með tímanum leitt til sjúkdómsástands. Það mætti því mögulega segja að allostatískt ofálag sé líkamleg birtingarmynd erfiðrar lífsreynslu eða tilvistarkreppu einstaklings og þannig möguleg undirliggjandi orsök flókinnar sjúkdómsþróunar eða fjölveikinda.

Markmið: Megin markmið þessa doktorsverkefnis var að meta algengi og mynstur fjölveikinda hjá almennu norsku þýði og skoða möguleg tengsl milli fjölveikinda og erfiðra aðstæðna, bæði í barnæsku og á fullorðinsárum, með hliðsjón af hugmyndafræði allostatísks ofálags.

Efni og aðferðir: Notaðar voru upplýsingar úr Nord-Trøndelag Health Study (HUNT), áfanga 2 (1995-97) og áfanga 3 (2006-8). Samtals tóku 47 959 einstaklingar 20-79 ára þátt í HUNT3 og 73% þeirra tóku einnig þátt í HUNT2 ellefu árum áður. Til mats á fjölveikindum var skoðaður 21 langvinnur sjúkdómur út frá spurningalista. Allostatískt álag var metið út frá 12 líffræði-og lífeðlisfræðilegum þáttum sem mældir voru hjá þátttakendum.

Upplifun á æsku var metin með stakri spurningu en ellefu þættir voru skoðaðir til mats á upplifðum tilvistarvanda á fullorðinsárum. Hugtakið tilvistarvandi (e. existential unease) var notað til að lýsa skorti sjálfsáliti, vellíðan, lífsmarkmiðum og félagslegri tengingu.

Niðurstöður: Næstum helmingur þátttakenda reyndist fjölveikur. Sterk tengsl voru milli líkamlegra og andlegra veikinda en annars voru mynstur sjúkdómanna mjög ólík. Rétt rúmlega 4% einstaklinga lýstu erfiðri eða mjög erfiðri æsku. Tengslin milli upplifunar á æsku og fjölveikinda á fullorðinsárum voru sterk og jókst algengi fjölveikinda samfara erfiðari upplifun á æsku. Þegar einstakir sjúkdómar voru skoðaðir sáust þessi sömu tengsl í tilviki 19 sjúkdóma af 21.

Svipað samband fannst milli tilvistarvanda á fullorðinsárum og þróunar fjölveikinda. Það voru marktæk tengsl milli flestra þátta tilvistarvandans og þróunar fjölveikinda, með auknu algengi fjölveikinda eftir því sem tilvistravandi varð fjölþættari.

Þegar þættir til mats á allostatísku álagi voru skoðaðir með hliðsjón af erfiðri æsku reyndust þeir sem uppliðu mjög erfiða æsku að meðaltali vera lægri, með stærra mitti og hærri líkamsþyngdarstuðul, hraðari hvíldarhjartslátt og lægri blóðþrýsting en þeir sem upplifðu mjög góða æsku.

Ályktanir: Niðurstöðurnar benda til tengsla milli erfiðra aðstæðna, bæði í barnæsku og á fullorðinsárum, og fjölveikinda seinna á ævinni. Tengslin verða sterkari við aukna erfiðleika, hvort sem það er erfiðari upplifun á barnæsku eða fjölþættari tilvistarvandi á fullorðinsárum. Með hliðsjón af mynstrinu sem sást varðandi allostatíska þætti styrkir þetta upphaflegu kenningu okkar. Þannig mætti leiða að því líkum að erfiðar aðstæður skrifist í líkamann með því að valda vanstillingu líffræðilegra stjórnkerfa sem svo leiða til þróunar flókinna sjúkdómsmynstra svo sem fjölveikinda.

Abstract

Background: Multimorbidity, the coexistence of two or more chronic diseases in the same individual, has been termed one of the biggest medical challenges of the 21st century. It is extremely prevalent and as a concept, it poses many challenges to modern health care systems. However, little is known of possible aetiological factors pertaining to its development. Experience from general practice indicates that complex disease clustering and difficult life experiences often occur in the same individuals.

A growing body of research indicates that chronic dysregulation of the major biological adaptive systems, caused by accumulated/toxic stress and termed *allostatic overload,* could represent a common underlying aetiological pathway. Allostatic overload could therefore serve as a means for translating through human biology the embodiment of difficult subjective experiences or existential hardships leading to possible complex disease development or multimorbidity.

Aims: The main objective of this project was to analyse and describe prevalence and patterns of multimorbidity in a general Norwegian population and explore possible associations between multimorbidity and challenging life circumstances, both in childhood and adulthood, in light of allostatic load. The specific goals of the project were:

- To document the prevalence and potential clustering patterns of multimorbidity in a general Norwegian population.
- To estimate the associations between subjective childhood difficulties and adult multimorbidity, on one hand, and adult allostatic load, on the other.
- To explore possible prospective associations between stressful or existentially demanding circumstances in healthy adults and the development of multimorbidity later in adulthood.

Material and methods: This dissertation is based on analyses of data from the Nord-Trøndelag Health Study (HUNT) phases 2 (1995-97) and 3 (2006-8). In total 47 959 individuals aged 20-79 years participated in HUNT3, with 73% also taking part in HUNT2 eleven years earlier. Multimorbidity was defined as two or more chronic conditions in the

same individual. The analyses for papers I and II included 21 self-reported chronic diseases or conditions in the definition of multimorbidity, but paper III, comparing data prospectively between HUNT2 and HUNT3, included 17 self-reported chronic diseases with 11 years of follow-up.

For measurements of allostatic load, 12 secondary allostatic parameters were available from the HUNT database. In paper III, in line with classification of allostatic parameters, disease development in general and multimorbidity in particular, were deemed relevant as tertiary indicators of allostatic overload.

Subjective experience of childhood was addressed by one single question. Eleven items pertaining to *existential unease* (a term coined for the thesis) assessed subtle subjective stress in adulthood. Existential unease was introduced to describe a person's lack of self-esteem, well-being, experienced meaning and/or social interrelatedness.

Results: Nearly half of the adult general Norwegian population was found to have multimorbidity. The connection between mental and somatic health conditions was strong, but otherwise the disease patterns were complex and diverse, transgressing conventional biomedical dichotomies. Just over 4% of the population reported a difficult or very difficult childhood. The association between experience of childhood and adult multimorbidity was strong, with increasing prevalence of multimorbidity in response to worse experience of childhood. The same was true regarding all but two of the individual conditions.

A similar relationship was found for development of multimorbidity with regard to existential unease. There was a significant correlation between most of the unease factors and the development of multimorbidity, with a dose-response effect as the number of unease factors increased.

Finally, examining allostatic parameters with regard to childhood experience showed that those experiencing a very difficult childhood were in their adult life, on average, shorter, with a larger waist and higher BMI, with a higher resting heart rate and lower blood pressure than those reporting a very good childhood.

Conclusions: The results indicate a correlation between demanding circumstances, both during childhood and adulthood, and multimorbidity later in life. The correlation becomes stronger with increasingly difficult circumstances, be it worse experience of childhood or more stress factors in adulthood. Along with the pattern seen when assessing allostatic parameters, this strengthens the original hypothesis, describing how embodiment of adversity translates through the biological disturbances of allostatic load to complex disease development.

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Main supervisor in Iceland, Co-supervisor in Norway: Professor Jóhann Ág. Sigurðsson, MD, dr. med.

Icelandic doctoral committee: Professor Jóhann Ág. Sigurðsson, MD, dr. med.; Professor Irene Hetlevik, dr.med.; Professor Linn Getz, MD, PhD; Professor Inga Dóra Sigfúsdóttir, PhD and Professor Unnur Valdimarsdóttir, PhD.

Project Funders: The General Practice Research Unit at NTNU, Trondheim; The Research Fund of the Icelandic College of Family Physicians and Primary Health Care of the Capital Area, Iceland.

Declaration of contribution: The author´s leading and independent contribution to each part of this work, i.e. the thesis and published papers, has been explicitly documented in accordance with regulations of the Norwegian University of Science and Technology and the journal publishers. The corresponding requirements of the University of Iceland are thereby also fulfilled, in accordance with the joint agreement between the two universities.

Table of Contents

Acknowledgements

For me, it has been a true privilege to go through this PhD process. It came about kind of by surprise, as the best things often do. It has followed me through many important life steps. At the beginning of the study my son was two years old and I was about to get married. Then I had my daughter, went through trauma and a divorce, built myself up again, finished my specialization, fell in love again, and started a new family. Seven very eventful years. And often, when struggling with life as a single mother with two children, the possibilities brought to me by my supervisors and the people around them have literally been lifesaving. And for that I am eternally thankful.

So, first of all, I am grateful for my supervisors, Linn and Jóhann, who have been endlessly supportive. When it came clear that I wouldn't be moving to Norway to go through with the PhD project, they made it possible for me to travel back and forth as needed. They have taken me into their home, where I have truly felt as a part of their family. In the morning Jóhann makes breakfast and *"matpakker"* to bring to work, just as my dad always did. I have often wondered how many supervisors (even in Norway) make packed lunches for their PhD students. I will as well always remember the time Jóhann stood in his nightgown and slippers, outside in the rain, holding an umbrella for me as I waited for the taxi to the airport.

They have so often pulled me out of the hectic and often chaotic life in Iceland and sat me down by the computer in their living room in Trondheim with a glass of red wine at my side, with nothing to focus on other than my project. It will be what I miss most when finishing the thesis. Their great advice and help, regarding the project, life as a GP in Iceland and especially at hard times in life, have been extremely wise and lifesaving at times. Their interplay as a couple is as well something that I admire a lot. While Linn takes me on a speculative brainstorm through science and philosophy, Jóhann listens carefully and at crucial moments pulls us back down to earth by suggestions such as: "*Well, if we now focus on table 2…"*

Secondly, I am grateful for the wonderful people at the General Practice Research Unit (AFE) in Trondheim. I remember a colleague in Iceland telling me when I started with the project: "Well, even if the only thing you get out of this is to get to know Irene Hetlevik and Anna Luise Kirkengen, that would be worth the trouble". I agree. I have been privileged to

get to know these two great thinkers, and their professional advice and personal friendship has been extremely inspirational, they are true role-models. To Irene and AFE Trondheim I am also thankful for the financial help they provided despite the fact that I was not living in the country.

I am thankful for the support from my friend, Hálfdán Pétursson, who was taking his last steps in the PhD process as I was starting mine. Being an Icelander at NTNU and a fellow researcher and co-author he has helped me enormously, especially though by being my friend. His extreme pessimism has been a very important counterweight to my over-optimism and I am looking forward to our cooperation for many years to come.

To NTNU and the University of Iceland I am thankful for the joint agreement regarding the PhD studies. That has as well provided me with a PhD committee in Iceland, where I have been honoured to get advice and support from two very inspiring women, Inga Dóra Sigfúsdóttir and Unnur Valdimarsdóttir. At NTNU I have had statistical help from Tom Ivar Lund Nilsen, who has taught me important differences between epidemiology and biostatistics.

In Iceland, I´ve been lucky in other matters as well. The Icelandic College of Family Physicians has literally carried me on their hands through this project and made it possible for me to focus on the project (and my family as well) in between hectic work in hospital rotations and at the clinic. Furthermore, I am extremely grateful for my supervisors at my health care clinic in Efstaleiti, Alma Eir Svavarsdóttir and Gunnar Helgi Guðmundsson, who have been very flexible and supportive. My colleague Elínborg Bárðardóttir was also a life safer, stepping in as program director for the speciality training when I had to reduce work to be able to write the thesis.

I have been very fortunate during these years to have the opportunity to speak at many conferences, both in Iceland and abroad, and as a keynote speaker at the Nordic Congress for General Practice in Gothenburg in 2015. I am very honoured to have had these opportunities. Furthermore, I was taken into the Nordic Risk Group, a collaboration of Nordic academics with the vision of promoting general practice. Through their work, I have gotten to know many inspiring people, whom I look forward to working with in the future. Among this group, I must especially mention Minna Johansson, my sister in research – who I deeply

admire, both as a person and as a visionary scientist – as well as Bente Prytz Mjølstad and Henrik Vogt.

At the personal level I am most thankful for my parents. It is obvious that you don't do this alone, finishing a PhD as a single mother, well, even finishing a medical specialization as a single mother, without much support. I am thankful for them being always supportive, always willing to help with my children, giving them the important gift of a strong relationship with their grandparents. I am also so very grateful for my dear friend and piano teacher, Brynja Guttormsdóttir, who has encouraged me through the years to move my mind from diligent, strict studying to believing in myself and my own thoughts.

As for my children, I am thankful how they have made me a better person and a better doctor. I count myself extremely lucky to be their mother, they are gifted, sensitive and empathetic, and together we can always see the funny side of things. I am grateful for our Friday night disco evenings, that they will probably not be willing to participate in for so much longer.

Finally, to Heiðar. It was not really what I had planned, to meet you at a bar one November evening, when I was starting the final year of my PhD. However, you saw through my resistance, well actually, you seem to see me completely. Since I first met you, not a day has gone by without you being there. Thank you for showing me how truly beautiful love can be.

List of papers

This thesis is based on the following original research papers:

I. Co-and multimorbidity patterns in an unselected Norwegian population: cross-sectional analysis based on the HUNT study and theoretical reflections concerning basic medical models. Tomasdottir MO, Getz L, Sigurdsson JA, Petursson H, Kirkengen AL, Krokstad S, McEwen B, Hetlevik I. *European Journal for Person Centred Healthcare* 2014;2:335-345

II. Self-Reported Childhood Difficulties, Adult Multimorbidity and Allostatic Load. A Cross-Sectional Analysis of the Norwegian HUNT Study. Tomasdottir MO, Sigurdsson JA, Petursson H, Kirkengen AL, Krokstad S, McEwen B, Hetlevik I, Getz L. *PLoS ONE* 2015;10(6):e0130591

III. Does 'existential unease' predict adult multimorbidity? Analytical cohort study on embodiment based on the Norwegian HUNT population. Tomasdottir MO, Sigurdsson JA, Petursson H, Kirkengen AL, Nilsen TIL, Hetlevik I, Getz L. *BMJ Open* 2016;6:e012602

Abbreviations

ACE	Adverse Childhood Experiences
ANOVA	Analysis of variance
BMI	Body mass index
BPS	Biopsychosocial
CATS	Cognitive Activation Theory of Stress
CI	Confidence Interval
CIRS	Cumulative Illness Rating Scale
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
CVD	Cardio-vascular diseases
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EBM	Evidence-Based Medicine
EGPRN	European General Practice Research Network
GERD	Gastroesohpageal reflux disease
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HDL	High Density Lipoprotein
HPA axis	Hypothalamic–pituitary–adrenal axis
HUGO	Human Genome Organisation
HUNT	The Nord-Trøndelag Health Study (Helseundersøkelsen i Nord-Trøndelag)
ICD-10	International Classification of Diseases, 10th Edition
JAMA	The Journal of the American Medical Association
MRI	Magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NTNU	Norwegian University of Science and Technology
OR	Odds Ratio
PR	Prevalence Ratio
RR	Relative Risk
SES	Socioeconomic status

SOC	Sense of Coherence
WHO	World Health Organization
WONCA	World Organization of Family Doctors

Prologue

Þegar fjöllin fara úr hvítu sloppunum koma fuglarnir í heimsókn. Læknirinn tekur myrkrið og hellir því í bolla, hverfur svo inn í skammdegið á skrifstofunni.

Úti svífur vængjaður tími, frá gegnsæjum bláma að myrkvaðri strönd. Snjórinn í hlíðunum vaknar af svefni.

Þegar fuglarnir fara verður dreggjunum skvett.

Útlægur blámi bankar á glugga.

Í sorta sofa þögul tré.

Einar Már Guðmundsson, Englar alheimsins

When the mountains take off their white coats, the birds pay their visits. The doctor takes the darkness and pours it into a cup, then disappears into the long winter night in his office.

Outside, winged time hovers, from a transparent blueness towards a darkened shore. The snow on the mountainsides awakens from its sleep.

When the birds leave, the dregs will be poured away.

An exiled blueness knocks on the windows.

In the blackness, silent trees sleep.

Einar Már Guðmundsson, Angels of the Universe

I have long been a fan of words. Words in stories, words in poems, words in lyrics. Words by artists, delicately describing the deep and powerful emotions of human beings, of love and happiness, loss and sorrow and suffering. Painting pictures of human nature with the full spectrum of colours. Though the words are often profound, they can be mesmerizing. Even though not completely understood, the description is felt because the feelings are common to us as persons. And we know these feelings. Sometimes we've been there ourselves, other times we can easily imagine how it would be to be there, and still other times we can't even imagine but feel a shadow of the feelings by goose bumps on our skin or stones in our stomach.

It's because artists are good at describing human nature, and although often without scientific background or facts on anatomy or brain chemistry, they have the sense of humanity. And they're spot on.

Ég geng í hring í kringum allt sem er
og innan þessa hrings er veröld þín.

Minn skuggi féll um stund á gluggans gler.

Ég geng í hring í kringum allt sem er
og utan þessa hrings er veröld mín.

Steinn Steinarr

I walk in a circle around everything which is
and within this circle is your world.

My shadow fell for a moment on the window´s glass.

I walk in a circle around everything which is
and outside this circle is my world.

Steinn Steinarr (translated by Alan Thompson)

They say that one in every ten Icelanders publishes a book in their lifetime. On the side, I always dreamed to be one of them, but I'm probably too practical in nature. After graduation from secondary school, I tried out for a career in medicine. Actually, I was sure of not getting through the needle eye of admission examinations and had a plan to study literature after not getting into medicine. But in I went, and how grateful I am now.

But I wasn't to begin with. It all felt very technical and mechanistic. And un-personal. There were muscles and machinery, chemistry and pharmacology, science on biology and functions and sub-functions of the body. The body. Not the human being. There was no heart-bleed or butterflies in the stomach. No gut-wrench, except for our own close to exams. And for me, the passion was missing.

Of course, I see it now, this was the way to go. Or at least an important part of the way. We want medicine to be "hard science". We want to be evidence based. Otherwise, we would not really be striving for the greatest advancements in medicine in general. We want to know the smallest fractions of the body right down to its DNA – well, even further, really. We want to find the right fit for drugs, the right procedure for cutting, the right way of mending and curing and fixing.

We can even go so far as to say that if we cannot fix the problem, many of us doctors have a hard time dealing with the problem at all. We want to cure. But at the same time, our advances as a science have brought us to a place where most of the problems we are dealing with are unfixable. They are manageable, but unfixable – as the fixable things we fix right away (Did I tell you that my mom used to call me Miss Fix-it when I was little?). And that creates frustrations, as these endless grey areas and uncertainties are frustrating for hard science people. And that's where the humanities come in again, luckily for us all.

My view on medicine changed slowly as the years went by. To be honest though, it did not change until I started working as a doctor the summer after my 4th year. Because working as a doctor is something totally different from studying medicine, it does not feel like hard science, and often it is not hard science at all. Although the hard science is working there in the background (which is the magic of studying for years and years), enabling us to do the work needed. At that moment, it is more about connection and communication and just being there for the patient, being able to help – or trying to help, at least.

Finally, after the 5th year, I started working at the emergency department. There I was really in my element, hard work, many patients, big effect. I worked a lot and sometimes forgot to go home. But soon this became a bit mechanistic as well. Protocoled. The same routine, helping at crucial moments with great rewards, but not going into depth at all. I missed following up on people, and as time went by, there were more and more unanswered questions. These kinds of questions haunted me the most: "Why does this woman with a three-year history of severe back-pain choose to come to the emergency clinic at 3 am on a Monday night?" "Why do you think that this dyspnoea you have been feeling on and off for the last two weeks is going to kill you tonight?" "How will you cope with your loss or your disease after you have left the emergency ward?" "Why am I meeting this person here at the emergency department for the fifth time in three months?"

It was the humanities calling. In my final year in medical school, still working at the emergency ward, we had a short course in family medicine. With my questions swelling inside, an article we read hit home. It was about the effect of allostatic load on our biology and future health. As allostatic load is a big part of this thesis, I will not explain it further here, other than saying that it describes chronic toxic stress or negative biological imbalance due to strain. There, at the end of my studies, the professor also taught us about the effect of

disadvantage, violence and neglect on health. There I found the pieces of my puzzle. And I finally met the humanities again. We started learning about being human, not just being a body. And finally, I found my passion.

In 2009, I started my specialization in general practice. That fall I heard a lecture from Linn Getz, entitled "Molecules, Minds, Morrison and Medicine – the 4M Study". Besides illustrating again what had fascinated me about this connection between medical science and the humanities, it added my favourite, the power of lyrics. In the lecture, she illustrated a future vision on bridging the gap between humanistic medicine and biomedicine. Listening to this breakthrough lecture reminded me of many of the patients I was dealing with in my daily praxis. People with many complex conditions, struggling with a heavy medical burden, often with unexplained symptoms, on top of struggling with difficult and demanding life situations. People we meet in practice every day but often have a hard time helping or fully grasping. People that we are not really taught about in medical school as they do not fit the clear-cut profile of black and white, protocolized medicine.

At that same time, I was trying to come up with a research project for my specialization. I had during my time in medical school made a report on Health and Wellbeing of Icelandic children, social and medical aspects. I was searching somewhere in that field, again trying to see the wider picture of health.

But sometimes, I am a very lucky person. And when I met up with the professor in family medicine, Jóhann Ág. Sigurðsson, for the second time, he informed me about a project he and his wife, Linn Getz, were formulating about multimorbidity and allostatic load. At that time, I didn't think I was a science person but because of my fascination about the theme I told him I was ready for a PhD. It was my best decision to that point in life.

So here I am, some 7 years later. Writing the thesis. And still as fascinated. During these PhD years, I've also been finishing my specialization as a GP and working as a specialist since 2014. The themes of both multimorbidity and allostatic load play an important part in my everyday work as a GP. What puzzles me the most is the acceptance I get from my patients when explaining the effects of allostatic load on their health. It seems to me that it is often easier for my patients to understand and accept this than it is for doctors, which often have a hard time accepting and *always* ask if my results are confounded by depression.

My theory is that humanities come natural to us as persons, as they come through books and lyrics. But when we are thinking through science, it becomes so much more difficult. Then we can't let ourselves be controlled by emotions. Not until we can show and prove scientifically that we are in fact all controlled by emotions. And there we are at the bridge again. The bridge between biography and biology. Between humanistic science and biomedical science. This is the bridge we are aiming for in this thesis.

In my practice, I regularly meet a patient of mine, a man around sixty. He is paralyzed from the waist down, wheelchair bound after an accident many years ago. He comes in regularly for control because of his diabetes, but has other conditions as well; frequent infections, pressure wounds and so on. One time we met up, his blood sugar had become way too high and we needed to add to his medication. He got a little frustrated when I started talking to him about his blood sugar and said: "You doctors always want to talk about numbers. Why is that? Don't you understand that it's not my numbers that hurt?"

It is true. We often get caught up in our own medical science and even forget about the patient. Although numbers are important, sometimes words matter more.

As you sit down there by my bed
and ask me how I am today
I never thought I'd be one of those
who cannot even say what I don't want to do
And I'm not worried
I'm just okay
I washed off all my sins today
But I'm afraid
I'm afraid of letting go
Yes, I'm afraid
I'm afraid of letting you know
That I'm not ready
but soon I'll learn to say goodbye

Dikta, Goodbye

1 Origin and focus of this thesis

When I started working on the theme of this thesis in 2010, *the concept of multimorbidity* was rather unknown in the medical literature. Few papers were published on the theme, and the main focus was still on comorbidities to certain index diseases rather than multimorbidity in general. At that time, our main research ideas came from our experience in general practice - meeting patients with multiple chronic conditions and often complex and difficult life stories. Based on clues from many different sources in the medical literature, we wondered if there could be a connection between multimorbidity and existential difficulties, and if treatment of these patients could be improved by taking their life story into account.

Since then, the medical literature has evolved dramatically. As Figure 1 shows, the number of scientific publications on the theme of multimorbidity has risen almost exponentially since 2010. The story is similar regarding publications examining *the concept of allostasis* and *allostatic overload*. Publications on allostasis in 2010 were few, and at that time, researchers focused mainly on particular aspects of the allostatic concept, such as the effects of autonomic, metabolic, or immunologic dysfunction. A common theory was a so-called "spillover effect", that a single chronic condition would commonly cause a wider biological dysfunction. One example would be chronic inflammation that could 'pollute' other organs so as to create other comorbid conditions and even premature mortality (Decramer et al. 2008, Higashi et al. 2009, Deverts et al. 2010, Donath and Shoelson 2011). This theory may well be valid, but as this thesis shows, it is unlikely to provide a sufficient explanation.

In 2010, an article by Parekh and Barton was published in *the JAMA*. To our research group it caused a certain breakthrough in thinking and greatly influenced the hypotheses behind this thesis. The article concluded:

> "The tremendous efforts in the fight against chronic disease have inadvertently created individual disease "silos", which are reinforced by speciality organizations, advocacy groups, disease management organizations, and government at all levels. Transformations from a single chronic conditions approach to multiple chronic conditions approach is needed" (Parekh and Barton 2010).

The concept of 'disease silos' and the need to break them down harmonizes very well with the 'generalist' ideology of general practice/family medicine. The main focus should be on the patient, not individual diseases (McWhinney 2009). Furthermore, Parekh and Barton's

concept could be seen as a cornerstone of the theory we were working with at the beginning of the PhD in 2010. Namely, that instead of the disease silos, as illustrated by my supervisors in Figure 2, we could be searching for common sources that could explain, at least partly, the development of different, complex disease patterns. Moving away from the silo approach and aiming at a wider view of disease aetiology and interaction could furthermore help solve many of the main problems general practitioners have been facing in everyday practice, such as the problem of contradictory advice when working with many different disease-specific clinical guidelines.

We could as well say that the silo approach has changed our view of biological systems/markers, moving on, for example, from individual biological silos of immunology, endocrinology or neurology, to the overarching concept of allostasis and allostatic overload, building a stronger framework for our hypotheses.

In the years since beginning this project, our research questions evolved as a reflection of the evolving literature. However, the main research hypothesis and questions have not changed; our confidence in them has actually become stronger. We have therefore decreased our focus on quantitative descriptions of multimorbidity per se, as it has become such a hot topic for other researchers during this period. We instead increased our focus on fundamental aetiological considerations for the development of multimorbidity or complex disease clustering through the concept of allostatic overload. The concept of allostatic overload serves not only as a set of biological markers but also a philosophical framework and conceptual link between adversity and existential hardship on the one hand and complex disease development on the other. This would not have been possible without the above advances in the scientific literature.

Although our main hypothesis is chiefly untouched, the number of puzzles pertaining to our theory has increased as we have linked together different fields of the evolving scientific literature. Many of these fields have approached each other in very recent years, thereby strengthening the scientific ground for our hypotheses.

In the introduction to this thesis, I thereby decided to include references to scientific literature all the way through the fall of 2016, in line with recommendations from Holen (Holen 2013).

The purpose is to explain as clearly as possible the concepts I have been working with and provide a solid and trustworthy theoretical framework for our empirical work.

The introduction to the thesis encompasses a series of theoretical chapters. These chapters are then summed up by pulling together the different lines of thought and concepts previously described (see section 2.11), moving towards an explanation of our hypotheses and the aims of the study. I will do this both specifically for each of the three articles and more globally for the general hypothesis. The next section will describe the material and methods used. The following section presents the results. Finally, the discussion will reflect upon the main findings in light of current scientific literature, review the strengths and weaknesses of the findings and highlight the clinical and scientific implications of the project.

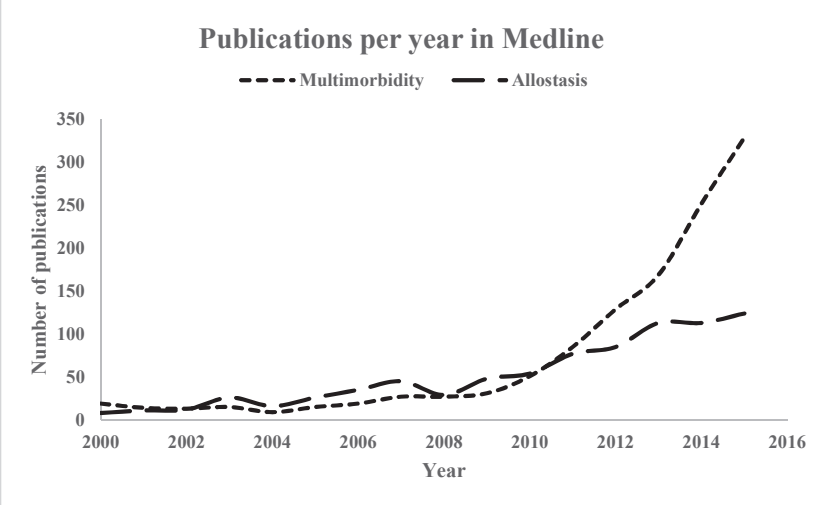

Figure 1. Publications per year in Medline with the term presented in the title or as a key word

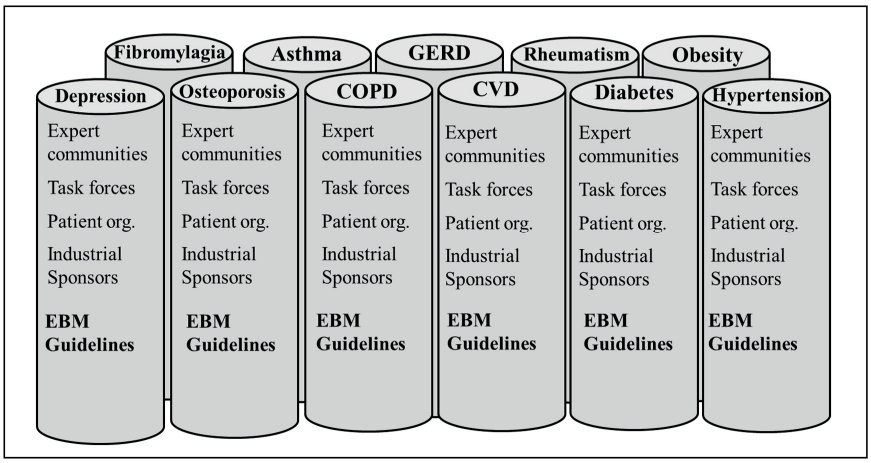

Figure 2. Individual chronic disease silos. Johann Ag. Sigurdsson and Linn Getz, 2010

2 Introduction

2.1 The problem of multimorbidity

2.1.1 Defining multimorbidity for empirical purposes

Multimorbidity as a concept was, to my knowledge, first introduced in German research literature in 1976 (Brandlmeier 1976). Its use remained almost exclusively German until the 1990s when it became internationally recognized (Heuft 1990). However, it was not until the new millennium that multimorbidity became prominent in the research literature, through milestone papers regarding its prevalence (van den Akker et al. 1998, Fortin et al. 2005) as well as the seminal writings of US paediatrician and health care service researcher, Barbara Starfield (Starfield et al. 2003, Starfield 2006), leading up to high profile coverage in world-leading, general medical journals a few years later (Barnett et al. 2012, Mangin et al. 2012).

Traditionally, multimorbidity has been defined as *two or more co-occurring chronic health conditions in the same individual* (WHO 2008). The use of the term in earlier literature did however vary. It was often called comorbidity and sometimes termed multiple chronic conditions. Comorbidity, however, has now been clearly defined as additional diseases in relation to an index disease in one individual as opposed to the presence of multiple diseases without a focus on a specific index disease in multimorbidity (Valderas et al. 2009). As the number of articles on multimorbidity has increased over the last ten years, the terminology has become clearer.

The definition of multimorbidity has nevertheless been a much-debated subject. A recent systematic review from 2013 found 132 different definitions as well as 241 lists, classifications, scales or indexes used to evaluate multimorbidity (Le Reste et al. 2013). Most researchers use a simple count of diseases per individual, whilst others have relied on indexes for evaluating multimorbidity burden, impairment, psychological distress or health care utilization and costs (Valderas et al. 2009).

These indexes include the *Charlson Comorbidity Index*, the *Cumulative Illness Rating Scale (CIRS)*, the *Index of Coexisting Disease* and *Adjusted Clinical Groups.* They were popular in earlier writings on multimorbidity but have not gained general acceptance, maybe because of

their diversity. Most of these indexes include disease diagnoses and risk factors, but only a few of these indexes rate the severity of diseases (Willadsen et al. 2016).

The most extensively studied of the indexes is *the Charlson Comorbidity Index*. It was initially developed to predict one-year mortality among hospitalized patients. It is therefore most useful regarding multimorbid patients' healthcare utilization (Charlson et al. 1987). The same applies to the *Adjusted Clinical Groups Index* developed by the late Barbara Starfield to predict morbidity burden and the use of health care resources (Starfield and Kinder 2011).

The *Cumulative Illness Rating Scale* has often been used in addition to a count of diseases in prevalence studies on multimorbidity (Fortin et al. 2005). It applies a severity score to each of 14 body systems affected by diagnosed conditions. The rating scale therefore provides an estimate of the morbidity burden (Brett et al. 2013). However, multimorbidity research has found it to under-represent the severity burden in mild and moderate severity index categories (Brett et al. 2013).

Research has shown that self-reported disease burden correlates better with quality of life outcomes than the above-mentioned indexes (Bayliss et al. 2005), making easier reporting just as reliable as complicated indexes. However, counting diseases has therefore become the norm in measuring multimorbidity, despite the fact that a simple count of conditions can yield a high prevalence of multimorbidity, even among patients/persons who experience little or no impact on their functional status or quality of life (Valderas et al. 2009). Therefore, the biggest drawback when using registries or self-reported data, as opposed to severity burden, is the equal weight assigned to both major and minor health conditions (Fortin et al. 2012).

More recent publications debate what constitutes "a condition", which diseases or conditions should be included, should they be only chronic or also acute (Le Reste et al. 2013), should multimorbidity also include risk factors and symptoms (Willadsen et al. 2016) or even biopsychosocial factors (Le Reste et al. 2013). The European General Practice Research Network (EGPRN) published the following definition of multimorbidity in 2013:

> "Any combination of a chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor. Any biopsychosocial factor, any risk factor, the social network, the burden of diseases, the health care consumption, and the patient's coping strategies may function as modifiers (of the effects

> of multimorbidity). Multimorbidity may modify the health outcomes and lead to an increased disability or a decreased quality of life or frailty" (Le Reste et al. 2013).

This definition is far more extensive than the WHO's earlier definition from 2008. EGPRN's definition possibly reflects better the daily clinical work in general practice (Willadsen et al. 2016), but, at the same time, it makes measuring multimorbidity for research purposes much more complicated and possibly unattainable.

This leads us to the next problem. How many diseases are sufficient for a valid measurement of multimorbidity? Earlier systematic reviews have concluded that 12 or more of the most common, chronic diseases would account for a fair evaluation of multimorbidity (Fortin et al. 2012). Interestingly, a recent Australian study found that 12 conditions identified slightly less than 80% of the patients defined with multimorbidity when using "all" conditions in the study (Harrison et al. 2014). The study also concluded that multimorbidity defined as three or more chronic conditions would more accurately suggest clinically relevant multimorbidity than the present definitions (Harrison et al. 2014). Furthermore, to find people with a significant morbidity burden, they suggested a definition with three or more chronic conditions affecting three or more body systems. They labelled this "*complex multimorbidity*" (Harrison et al. 2014). It therefore seems that two opposite poles are forming on the use of the term. One takes a broad view of multimorbidity. It includes most events affecting or possibly affecting one's health. The other pole takes a strict view, focusing more on the possible disease burden and complexity of care.

2.1.2 Prevalence of multimorbidity

As could be expected with different methods of evaluation, prevalence estimates of multimorbidity have differed significantly. The biggest factor affecting prevalence is probably the number of conditions used for the evaluation (Fortin et al. 2010, Fortin et al. 2012). On top of the differences stated above, the estimates vary further, based on sampling method—self-reporting, extraction from a registry or from doctors' records. Research has shown that the prevalence seems to be higher in primary care samples or registries than in the general population (Fortin et al. 2010). A recent publication found the prevalence to be 10% higher in a primary health care sample than in a random population sample after age-standardization (Mokraoui et al. 2016). This is likely due to bias from more frequent

attendance at a clinic. Prevalence numbers therefore range from around 13% in young adults up to 95% in the older population (Violan et al. 2014).

Van den Akker published one of the first well-known multimorbidity prevalence studies in 1998, based on a general practice registry in the Netherlands. As could be expected, the study found that multimorbidity increased with age. Its prevalence was 10% in the 0-19-year age group and reached 78% in subjects 80 years and over. Apart from increasing age, a lower level of education was related to multimorbidity (van den Akker et al. 1998). In 2005, Fortin and colleagues in Canada published a study assessing both prevalence by counting disease and severity according to the Cumulative Illness Rating Scale from primary care medical records. They found the prevalence of multimorbidity to be even higher than in van den Akker's study, with a prevalence of over 90% in the oldest age groups. Moreover, they found that nearly 50% of patients between 45 and 64 years of age had five or more chronic conditions (Fortin et al. 2005). Furthermore, they found that the morbidity burden, measured by CIRS, increased as the number of chronic conditions increased, as well as with age (Fortin et al. 2005).

Barnett, Mercer et al. published a milestone study on the prevalence of multimorbidity in *The Lancet* in 2012 (Barnett et al. 2012). The study was based on a primary care medical record register from Scotland. It had information on more than 1.75 million people and a count of 40 different morbidities. The authors found the general prevalence of multimorbidity to be 23.2%, rising from under 2% in children up to 81.5% in those over 85 years. Furthermore, they found that although the prevalence was much higher in older people, more than half of people with multimorbidity were younger than 65 years (Barnett et al. 2012). This was an important finding, as earlier publications related multimorbidity mainly to advanced age and interpreted the rise in prevalence mainly as a consequence of the aging population.

In 2014, Violan et al. published a systematic review of multimorbidity prevalence (Violan et al. 2014). They found 39 studies measuring the prevalence. The overall estimates ranged from 12.9% for participants aged 18 years and older, up to 95.1% in a population over 65 years of age. They noted as well a large variation in sample selection criteria and methods for estimating multimorbidity. The number of eligible conditions ranged from 5 to 335 (Violan et al. 2014). In 2016, Harrison et al. published the largest study to date reporting the prevalence of complex multimorbidity. The study was based on an Australian population (Harrison et al.

2016). They estimated that 47.4% of general practitioners' (GP) patients and 32.6% of the general population had multimorbidity. In addition, they found that 17.4% of GP patients and 17.0% of the general population had complex multimorbidity (Harrison et al. 2016). Another recent study on patients in primary care practices found that about half of the patients attending primary care clinics had multimorbidity defined as three or more chronic diseases and about one patient out of four had a high disease burden (Mokraoui et al. 2016).

A recent international study compared multimorbidity among people over 50 years of age in Russia, Spain, Poland, Finland, India, China, Mexico, Ghana and South Africa. It found the highest multimorbidity prevalence in the high income European countries (Garin et al. 2016). China and Ghana had the lowest prevalence of multimorbidity in this study, but still had prevalence of 45.1% and 48.3%, respectively (Garin et al. 2016). This difference between high and low income countries could partly be explained by increased survival and lower mortality rates for chronic but treatable diseases. That is, the people survive to become multimorbid. In addition, advanced healthcare systems are more likely to examine each citizen more and generate more diagnoses and risk labels. This phenomenon could be inferred from a recent Norwegian study which showed lower prevalence of multimorbidity in immigrants to Norway than in the general Norwegian population (Diaz et al. 2015), followed by another study by the same research group which showed that for all immigrant groups, the prevalence of multimorbidity doubled after five years of living in Norway (Diaz et al. 2015).

An article in 2015 from Ontario, Canada, describes the change in the prevalence of multimorbidity from 2003 to 2009. In this six-year period, the prevalence rose from 17.4% to 24.3%—a 40% increase (Pefoyo et al. 2015). The increase was evident in all age groups but even more evident in the younger age groups. This was especially remarkable as the prevalence of having only one condition remained relatively stable (Pefoyo et al. 2015). The reason for this is still unclear.

2.1.3 Epidemiological determinants of multimorbidity

As mentioned above, it is well documented that the most important determinant of multimorbidity is age (Violan et al. 2014). The prevalence curve based on age has been described as S-shaped, with the most pronounced increase occurring in middle age (Brett et al. 2013). However, when using a cut-off of three or more diseases, the curve is more linear,

providing greater differentiation in older age groups (Harrison et al. 2014) and therefore possibly coming closer to describing the phenomenon in a clinically meaningful manner. With three or more chronic diseases, the increase in prevalence started about 10 years later than for two or more chronic diseases, but seemed to plateau 10 years later as well (Harrison et al. 2014).

A number of studies have assessed the association between multimorbidity and gender. In a systematic review from 2014, Violan et al. found 14 studies reporting prevalence by gender. Nine of them showed a significantly higher prevalence in women. The others showed no significant difference between men and women (Violan et al. 2014).

An important finding in the Barnett study from 2012 was a clear link between socioeconomic status (SES) and multimorbidity. Young and middle-aged adults living in the most deprived areas had the same prevalence of multimorbidity as people aged about 10-15 years older living in the most affluent areas (Barnett et al. 2012). A year earlier Tucker-Seeley et al. had shown similar effects of childhood financial hardship on multimorbidity in adulthood (Tucker-Seeley et al. 2011). This had also been noted by van den Akker in 1998 and Fortin in 2005 (van den Akker et al. 1998, Fortin et al. 2005) and was further verified in a prospective study by Jackson et al. in 2015. In that study lower SES, indicated by lower education and difficulties managing on income, was a significant risk factor for developing multimorbidity (Jackson et al. 2015). The study by Jackson et al. is one of very few studies looking prospectively at risk factors for multimorbidity. Van den Akker's study in 1998 showed that the inverse relationship between multimorbidity and educational level became stronger the higher the number of diseases used as the cut-off for multimorbidity (van den Akker et al. 1998). However, the Tucker-Seeley study in 2011 found that increase in lifetime earnings modified the association of childhood financial hardship and multimorbidity (Tucker-Seeley et al. 2011).

Very few studies have looked at other possible determinants of multimorbidity. An Australian study by Taylor et al. in 2010 assessed the connection of various risk factors and socio-demographic factors in relation to multimorbidity. They found statistically significant relationships to multimorbidity in certain age groups for obese participants, in particular for high waist-hip ratio, current smokers, those who were physically inactive and separated/divorced/widowed participants. Although certain trends were seen with regard to

other factors, the lack of significance for other common life-style factors was likely due to the small sample size (Taylor et al. 2010). A more recent prospective Australian study found a link between overweight/obesity and multimorbidity (Jackson et al. 2015). Furthermore, a study by the same group found a connection between smoking, alcohol intake and physical inactivity and certain multimorbidity patterns (Jackson et al. 2016). Other studies have shown an inverse association between multimorbidity and physical activity in the youngest and oldest age groups after controlling for long-term activity limitations and other possible confounders (Cimarras-Otal et al. 2014).

One prospective study over three years found development of multimorbidity to be related to certain coping styles, an external health 'locus of control' (indicating the belief that health depends on health professionals), living alone, and a smaller social network (van den Akker et al. 2001). Positive life events, an internal locus of control, and an increasing social network seemed protective against multimorbidity (van den Akker et al. 2001).

A very recent prospective Danish study on multimorbidity in relation to stress and mortality also found that those with multimorbidity were less physically active, had unhealthy dietary habits, too high or too low body mass index, a lower educational level, a higher rate of unemployment and were more likely to live alone (Prior et al. 2016).

2.1.4 Multimorbidity patterns

One branch of multimorbidity research has focused on identifying recurrent patterns of disease. This branch aims at simplifying the approach to patients and more clearly understanding possible pathophysiological processes underlying different types of multimorbidity. In addition, it seeks to understand how these patterns change and evolve over time. Finally, it aims at adjusting treatment to different types of patients according to different multimorbidity groups of patterns. A systematic review by Violan et al. in 2014 identified 24 studies providing information on patterns of multimorbidity (Violan et al. 2014). They reported that most of the studies focused on descriptive information pertaining to the frequency of possible disease combinations, but a few used cluster analysis or factor analysis (Violan et al. 2014).

A higher number of somatic disorders is associated with an increasing prevalence of mental health disorders, particularly depression. This is one of the strongest and best documented disease associations found in multimorbidity research (Barnett et al. 2012). This association has also been shown to have a strong social gradient (Barnett et al. 2012).

Regarding descriptive information on disease combinations, their frequency is generally compared to the expected prevalence of the combinations, based on the assumption that diseases occur statistically independent of one another (Harrison et al. 2016). Newer and older studies on patterns agree that for all the common combinations of chronic conditions, the observed prevalence is significantly higher than the prevalence expected by chance alone (van den Akker et al. 1998, Harrison et al. 2016). This shows a general tendency to non-random distribution of diseases and an increased likelihood of developing multimorbidity once one chronic condition is already manifest. It confirms the complexity of approaching the phenomenon of multimorbidity in a disease-specific manner.

Generally, as could be expected, the most common multimorbidity patterns are clusters of the most common chronic diseases, differing slightly between different studies. A recent study by Harrison et al. found that when looking at different combinations of two conditions, the 12 most prevalent combinations involved eight prevalent conditions. The most common combination was hypertension and hyperlipidaemia (Harrison et al. 2016). Likewise, the most prevalent combinations of three chronic conditions involved eight of the nine most common conditions, the most common being hypertension, hyperlipidaemia and osteoarthritis (Harrison et al. 2016).

An Australian study in 2013 examined patterns of multimorbidity according to all 14 different CIRS domains. They found the most common domains to be musculoskeletal, psychiatric, respiratory and vascular (Brett et al. 2013). However, a more recent study looking at different body systems found the most common combination to be circulatory + endocrine/nutritional/metabolic (Harrison et al. 2016). The systematic review by Violan et al. found hypertension and osteoarthritis to be the most frequent combination, followed by different combinations of cardiovascular conditions (Violan et al. 2014).

A recent Canadian study by Pefoyo et al. showed that among individuals with only two chronic conditions, five possible combinations accounted for 50% of the population with that

level of multimorbidity. However, 243 unique combinations of quintets of conditions were required to capture the first 50% of individuals with 5 or more chronic conditions (Pefoyo et al. 2015). Furthermore, the number of clusters required to include 80% of the population increased from 14 among individuals with two conditions to 2744 clusters among individuals with 5 or more conditions (Pefoyo et al. 2015). They also reported that among individuals with four conditions, the largest cluster of conditions represented only 5% of that population. However, no distinct cluster had prevalence higher than 1.5% among individuals with five or more conditions (Pefoyo et al. 2015). Pefoyo et al. concluded that no common typology among individuals with multimorbidity was found.

According to Violan et al., more complex cluster analyses have not identified consistent patterns (Violan et al. 2014). However, factor analyses have shown several factors to be consistent across studies (Violan et al. 2014). Prados-Torres et al. have found patterns through factor analysis that differed between age groups and gender (Prados-Torres et al. 2012). In the younger age groups, the clusters were mainly composed of risk factors; in the middle-aged they consisted of organ disorders, and in the oldest age groups various disease-related complications enter the picture. The authors also showed that all these patterns occurred more frequently than expected by chance (Prados-Torres et al. 2012, Schafer et al. 2012). The largest factor analysis to date comes from a Norwegian register, with approximately 3.7 million persons. It shows, in accordance with other literature, cardiovascular-endocrine cluster patterns, a mental health pattern and a musculoskeletal pattern (Diaz et al. 2015).

The most prominent patterns found through factor analyses are cardio-metabolic (characterized by cardiovascular disease, hypertension, diabetes and obesity), musculoskeletal (primarily characterized by arthritis, joint- and back pain), psychiatric or 'psychosomatic' (characterized, for example, by anxiety, depression and somatic symptoms, including severe tiredness, severe headache, bowel problems and palpitations) and respiratory symptoms (asthma, COPD) (Holden et al. 2011, Jackson et al. 2016). A recent international study found the most common patterns to be cardiorespiratory (angina, asthma and COPD), metabolic (diabetes, obesity and hypertension) and mental-articular (arthritis and depression) (Garin et al. 2016).

In total, the factor analyses seem to agree with simpler analyses that the most common single conditions make up the most common clusters. The patterns overlap in many ways, defy the classic diagnostic 'silos' and transgress the border between somatic and mental disorders. Most importantly, at least to date, the documented patterns do not simplify the challenge of multimorbidity.

2.1.5 Impact of multimorbidity from the ill person´s perspective

As expected, the impact of multiple chronic conditions might seriously affect patients through the perceived morbidity burden. The literature has repeatedly shown this. People with multimorbidity tend to report significant loss of function and poorer quality of life (Barnett et al. 2012). They significantly rate their health worse than those without multimorbidity (Taylor et al. 2010). The full physical and psychological impact of multimorbidity evidently depends on the disease combinations, the severity of coexisting conditions, and the age and frailty of the patient (Smith and O'Dowd 2007). In general, people with multimorbidity have lower health literacy and more often report that their illnesses affect their cognitive function (Hopman et al. 2016). They also feel less happy and more often lonely (Hopman et al. 2016). Furthermore, multimorbidity has knock-on effects for family members who might face dependency issues and social isolation (Smith and O'Dowd 2007).

A recent longitudinal study on predictors of health-related quality of life in people with complex chronic diseases found that the impact of comorbidities on daily activities, the impact of chronic back pain on daily activities, the number of comorbidities, general health functioning and psychological distress were important predictors for health-related quality of life (Tyack et al. 2016).

In multimorbid patients, symptoms and consequences of diseases (e.g. pain and activity limitations, as well as depression), seem to be far more strongly associated with self-rated health than the diseases per se (Nutzel et al. 2014). Qualitative research indicates that patients with multimorbidity identify loss of function as a key problem (Smith and O'Dowd 2007). A paper from 2003 described interviews with 16 multimorbid patients. Fourteen of them reported that symptoms of one of their conditions or lifestyle changes necessitated by one of their conditions interfered with self-care for another condition (Bayliss et al. 2003). The same

was reported regarding the effect of medication. A recent systematic review of qualitative studies on patients' views regarding multimorbidity showed that while most of the qualitative studies focused on specific diseases or disease-combinations, patients' discussions related to specific medical conditions were *strikingly absent* (Liddy et al. 2014). However, people rather uniformly reported a need to discuss difficulties in dealing with physical and emotional symptoms in general. The most common complaints were on sadness, pain and fatigue (Liddy et al. 2014).

Another systematic review of qualitative studies of living with multimorbidity found that every day can be a struggle, exhausting people's capacity to complete everyday tasks. Patients reported loss of active and productive lives and negativity about a life restricted to just managing their multimorbidity (Coventry et al. 2015). For some people, the bodily and emotional effects of multimorbidity damage relations with their family and partner, further increasing loneliness and social isolation (Coventry et al. 2015). This kind of social deprivation or lack of coherence has been shown to lower even further the health-related quality of life in people with multimorbidity (Vogel et al. 2012). Multimorbidity typically follows a pattern of disrupted personal identity. This is associated with multiple medical, emotional and social hardships, followed by adaptation (Wister et al. 2016). A major theme is loss, including loss of valued roles, relationships, and independence. Furthermore, positive adaptation requires significant effort to transition out of this disruption, and strong social support primarily facilitates this process (Wister et al. 2016).

A recent Danish study showed that with an increasing number of chronic conditions, the proportion of people reporting high perceived stress rose consistently (Prior et al. 2016). Furthermore, the study showed that perceived stress, defined by Cohen's 10-item Perceived Stress Scale, was associated with higher mortality rates in all multimorbidity groups, after full adjustment for common confounding factors (Prior et al. 2016). Earlier research has shown an increased risk of mortality with increasing number of chronic conditions. A prospective study with 14-year follow up of people over 65 years old found that the risk of mortality increased by 80% for those with five or more chronic conditions compared to those with no chronic disease (Caughey et al. 2010).

With regard to management of multimorbidity, qualitative research indicates that patients identify difficulties in seeing many different health care providers. They experienced

contradictory and confusing information, poor access to holistic care and challenges with polypharmacy (Liddy et al. 2014). There are therefore multiple barriers to self-care, including physical limitations and aggravation of one condition by symptoms or treatment of another condition (Liddy et al. 2014). It has thus been stated that simultaneous presentation of diseases in one individual may have a multiplicative, rather than additive, effect on the individual's health, and also on healthcare costs (Wolff et al. 2002).

2.1.6 Impact of multimorbidity on the health care system

Patients with multimorbidity are often described as "high impact users" of health care systems. This is because of higher consultation rates in all health care sectors. In the UK, a report from 2007 showed that the 15% of people with three or more chronic conditions accounted for almost 30% of inpatient days (Smith and O'Dowd 2007). Multimorbidity is responsible for 65% of total health care expenditure in high-income countries, due to the extensive use of health services (Parekh and Barton 2010). However, relatively few initiatives address the reality that up to two-thirds of all individuals with chronic conditions have multiple chronic conditions (Wolff et al. 2002).

Contemporary healthcare systems are largely based on a single disease paradigm. Thus, the care of multimorbid patients by specialists is often fragmented and duplicative, with an increasing trend toward super-specialization (Moffat and Mercer 2015). Studies in different countries have shown that it is not chronic conditions by themselves that increase resource use the most, rather it is the added effect of multiple conditions in the same individual, causing increased morbidity burden and complexity of care (Starfield 2011). A paper from 2002 showed that individuals with four or more chronic conditions were 99 times more likely to have had a hospital admission that appropriate primary care could have prevented (Wolff et al. 2002).

The increasing prevalence of multimorbidity may have considerable financial implications over the next few decades, especially in low- and middle-income countries. They face an unfinished agenda of communicable diseases and must now simultaneously address a rapid rise in complex, chronic conditions with scarce resources and limited healthcare systems (Garin et al. 2016). Recognition is therefore growing that increasing levels of multimorbidity

currently threaten the sustainability of healthcare systems around the world (Moffat and Mercer 2015).

As stated above, patients with multimorbidity are frequent attenders in all health care sectors. They make more visits to general practitioners, are more frequent users of specialist care, make more frequent visits to emergency departments, are more frequently admitted to hospital and stay longer and have more postoperative complications (Smith and O'Dowd 2007, Laux et al. 2008, Taylor et al. 2010, Barnett et al. 2012, Palladino et al. 2016). The fragmentation of their care increases the likelihood of medical error, especially because specialist and hospital care is typically focused on treating one disease at a time without considering possible interactions due to other diseases or treatment (Smith and O'Dowd 2007, Barnett et al. 2012).

People with multimorbidity are likely to have complex needs for health care and to account for a high proportion of the healthcare workload (Salisbury et al. 2011). Clinical decision making is more difficult with multimorbid people because clinicians and patients often struggle to balance the benefits and risks of multiple recommended treatments, and because patients' preferences rightly influence the application of clinical evidence (Guthrie et al. 2012). GPs have stated that they find consultations with multimorbid patients to be very complex, that prioritizing care— while dealing with clinical uncertainty, medical complexity, and disease-specific (thus inadequate) guidelines during a short consultation—is very problematic (Sondergaard et al. 2015, Austad et al. 2016). Furthermore, Michael Balint's concept "the collusion of anonymity" (Balint 1968) is very applicable, referring to fragmentation of care and an associated dispersion of professional responsibility for the patient. A recent systematic review identified four areas where general practitioners experienced difficulties in caring for patients with multimorbidity: inadequacy of current disease-specific guidelines, disorganisation and fragmentation of care, challenges in delivering patient-centred care, and barriers to decision making (Sinnott et al. 2013).

2.1.7 The problems of clinical guidelines and polypharmacy

In 2008, the World Health Organization published its report, *Primary Health Care – Now more than ever.* It discussed the shift in global health challenges from acute to chronic diseases and subsequently the expanding problem of multimorbidity (WHO 2008). In

combatting chronic diseases, specialist-driven medicine has focused mainly on developing clinical guidelines based on the best available evidence at the time. However, it overlooks the problem that facing two or more different guidelines at the same time causes. Disease-specific protocols are probably best suited to younger patients with single conditions who have not yet developed other diseases. Excluding more complex patients, such as the elderly, the frail and the multimorbid, from clinical trials on which clinical guidelines are based, makes the guidelines clinically naïve (Wallace et al. 2015). Also, research has shown that about two-thirds of people with a chronic condition have two or more chronic conditions. This fact indicates an urgent need to re-think our healthcare system's single disease strategies, particularly with regard to clinical trials and guidelines (Harrison et al. 2016).

A recent report examined the workload of multimorbid patients when clinical guidelines are applied to them (Buffel du Vaure et al. 2016). The report showed that patients with three chronic conditions complying with all the guidelines would have to take from 6 to 13 medications per day, visit a health care giver from 1.2 to 5.9 times per month and spend from 49.6 to 71.0 hours per month on health-related activities. The potential workload increased greatly as the number of concomitant conditions increased. The workload rose to 18 medications per day, 6.6 visits per month and 80.7 hours per month in health-related activities for patients with six chronic conditions (Buffel du Vaure et al. 2016).

Polypharmacy is an important consequence of clinical adherence to guidelines in the context of multimorbidity. Whether each drug a patient takes can be considered indicated or not, polypharmacy is associated with risks, and it is particularly problematic in elderly, physically frail and/or cognitively impaired people. Polypharmacy has been shown to impose a substantial burden of adverse drug events, ill health, disability, hospitalization and even death (Scott et al. 2015). The number of drugs that a patient is taking has been shown to emerge as the single most important predictor of harm (Scott et al. 2015).

A recent study describes potentially serious drug-disease and drug-drug interactions for drugs recommended by NICE clinical guidelines for type 2 diabetes, heart failure and depression in relation to 11 other common conditions and drugs recommended by NICE guidelines for those conditions (Dumbreck et al. 2015). Possible drug-disease interactions were 32 when diabetes type 2 was the index condition. The corresponding numbers were 6 for depression and 10 for heart failure. At the same time, 133 potentially serious drug-drug interaction pairs

were found for type 2 diabetes, of which 25 (19%) involved one of the four drugs recommended as first line treatments for all or nearly all patients. For the depression guideline, 89 potentially serious drug-drug interactions were found. For heart failure, the number was 111(Dumbreck et al. 2015).

As a consequence of these findings, conscientious GPs will have to modify their application of guidelines as we know them today. Not only must the doctor consider and communicate the risks associated with each manifest disorder the patient might have, but also include medical risks induced by the sum of recommended treatment regimens. Warranted "down-sizing" of drug treatment might however be perceived as abandonment of "best practice", creating uncertainty and unease in the doctor (Sinnott et al. 2013). The burden of complex drug treatments may also exceed the patient's ability and motivation to comply and this may reduce the effectiveness of the treatments most likely to benefit the patient (Mangin et al. 2016). Care that is "measurably better" may therefore be meaningfully worse (Mangin et al. 2012). Due to the disease-oriented and fragmented strategies of contemporary healthcare, multimorbid patients are at considerable risk of receiving "*incomplete, inefficient, ineffective, and even potentially harmful interventions"* (Marengoni et al. 2016).

2.1.8 Clinical management of multimorbidity

Treatment burden describes the demand that the healthcare system makes on patients and their caregivers. This is common for patients with multimorbidity as they manage an increasingly chaotic medical lifestyle. They must negotiate their way through multiple fragmented appointments, investigations and medication regimes. As well as being disruptive for the patient, this can also affect adherence. The suggested solution is "minimally disruptive management" that aims to reduce the workload of managing illness by better co-ordinating care and emphasising patient choice (Moffat and Mercer 2015).

Incorporating patients' priorities and preferences for treatment into their care is an important aspect of an ongoing shift in healthcare. The goal is to minimise the burden of care and harms of overtreatment by prioritising interventions that are most important to the patient (Mangin et al. 2016). This can improve desired outcomes related to doctor-patient communication, such as the patient feeling heard, understood, respected and engaged in their care. It will also possibly motivate them and assist clinicians in their decision making (Mangin et al. 2016). A

function-oriented approach, as opposed to a *disease-oriented* approach, would probably be better suited to complex multimorbid patients. Their management requires complex clinical decision making, particularly in relation to polypharmacy, as well as understanding and minimizing potential harm associated with multiple high-tech interventions. To address these issues properly requires clinical training incorporating a philosophy balancing good medicine, pragmatism, and the consideration of quality of life and function (Smith and O'Dowd 2007).

The term *"patient-centred care"* has long been used when describing a medical approach where the patient's concerns and opinions are actively sought by the clinician. Patient-centeredness thus introduces a necessary focus on each patient's individuality, but the context is typically the consultation here and now (Starfield 2011). In contrast to patient-centred care (at least as described in the current literature with assessments that are visit-based), *person-focused care* is based on accumulated knowledge of people, which provides the basis for better recognition of health problems and needs over time and facilitates appropriate care for these needs in the context of other needs (Starfield 2011, Mjolstad 2015). Patient-centred care can occur in a single consultation but person-focused care adds the additional dimension of care over time. In the context of multimorbidity, this is essential (Mangin et al. 2016). Both patient-centred care and person-focused care require adequate recognition of the health problems people experience. Care is better when it recognizes what patients' experienced problems are, rather than departing from the diagnosis (Starfield 2011). In many studies, the longitudinal nature of the patient-GP relationship has been seen as a major facilitator and elementary component of patient- or person-centred care in multimorbidity (Sinnott et al. 2013).

Person-focused care given by general practitioners who offer continuity of care greatly contrasts with the care fragmentation that both patients and doctors describe as the major problem in managing multimorbidity. And not unexpectedly, continuity of care is associated with improved outcomes, such as delivery of preventive care and reduced preventable admissions to hospitals (Wallace et al. 2015). In the context of multimorbidity, it is of prime importance to elicit what matters most to the patient. Furthermore, it is important for the general practitioner to channel these personal plans into referral letters to other clinicians. The GP thus avoids failure to acknowledge these priorities when specialist referrals are necessary and thereby helps reduce fragmentation (Mangin et al. 2016).

The so-called *Ariadne principles* have recently been developed to support decision making, specifically during general practice consultations involving multimorbidity (Muth et al. 2014). The name Ariadne refers to a Greek goddess involved in mazes and labyrinths, helping the lost to find their way out. The model places the setting of realistic treatment goals as the guiding line of the multimorbidity consultation. The goal setting results from a thorough interaction assessment of the patient's conditions, treatments, consultation, and context; prioritization of health problems, taking into account the patient's preferences; and individualised management to determine the best options of care to achieve these goals (Wallace et al. 2015).

There is increasing recognition of the importance of supporting *self-management* for persons/patients with multimorbidity (Liddy et al. 2014). Self-management relates to "the tasks that individuals must undertake to live well with one or more chronic conditions". Self-management support uses collaborative goal setting and self-efficacy strategies to enable patients to carry out normal roles and activities and better manage the medical and emotional effects of their illnesses in partnership with health care providers (Liddy et al. 2014).

However, on the down side, systematic reviews of interventions for multimorbid patients in primary care have not lead to substantial improvement in the clinical setting. A recent systematic review of tools to assess patients' treatment priorities and preferences found that, despite the value ascribed to taking into account patients' priorities and preferences in decision making for treatments in the context of multimorbidity, few explicit tools were found available to actually support this process (Mangin et al. 2016). None of the studies available measured any effect on health outcomes of importance to the patients (Mangin et al. 2016).

The results of a 2016 Cochrane review of multimorbidity management included 18 relevant studies. In general, it showed mixed findings regarding management, mainly due to a small number of highly rated studies. It suggested an improvement in health outcomes when the interventions were targeted at risk factors, or if they focused on areas where people experienced difficulties, such as functional ability or managing medicine (Smith et al. 2016). It showed that organisational interventions with a broader focus, such as changes in care delivery for individuals with multimorbidity, were less effective (Smith et al. 2016). Two of

three patient-oriented interventions mentioned in the review showed improvements in a range of outcomes. These improvements included reduced mortality following focused and intensive interventions targeting functional difficulties, activity participation and falls prevention. There was no strong focus on clinical outcomes. This may reflect the challenge in researching multimorbidity when disease-specific measures are inadequate (Smith et al. 2016).

2.1.9 Changes on the horizon

In September 2016, the British *National Institute for Health and Care Excellence (NICE)* published its first clinical guidelines for treatment of multimorbidity (NICE 2016). It discusses many of the dilemmas and down-sides associated with the prevailing disease specific approach and presents some concrete, but not very radical approaches that can help clinicians navigate more safely in the most complex clinical situations. The detailed content of these guidelines is beyond the scope of this introduction, but I see the 2016 NICE guidelines on multimorbidity as a medical milestone. However, whilst the guidelines offer important practical help to navigate the most complicated biomedical labyrinths, the clinician on the floor is still left with unresolved questions and reflections pertaining to the aetiology of complex disease clustering.

2.1.10 Implications with relevance for this thesis

The above chapter on multimorbidity discussed the problem medicine faces regarding most, if not all, aspects of multimorbidity. Its overwhelming prevalence seems to demand a paradigm shift, not only in the way medicine approaches patients, but also in the way we build healthcare systems, communicate to specialists and to patients, and approach medicine as a research topic.

Earlier in this introduction, I discussed that multimorbidity has a clear social gradient. This fact represents one important motivator for the research questions I work with in this thesis. As a GP, I have observed how my patients' medical histories appear to be intertwined with their life histories in very complex manners. Starfield stated in 2011 that neither morbidity nor multimorbidity are randomly distributed in populations (Starfield 2011). She writes that people and populations differ in their overall vulnerability to illness and resistance to threats against their health; some have more than their share of illness and some have less. Clustering

of diseases thus results from a complex pattern of interacting influences, extending far beyond inborn, biological vulnerability (Starfield 2011). Therefore, apart from the more classical approach of studying aetiologies of specific diseases, there is interest in the determinants of general disease susceptibility, disease-prone personalities and frailty. It is suggested that generalized body responses in relation to psychosocial variables instead of specific diseases should be studied (van den Akker et al. 2001). So, perhaps comprehensive assessments of patients with multimorbidity should not only describe people's impairments and deficiencies but also their resources and strengths (Boeckxstaens et al. 2016).

In 2016 Boeckxstaens et al. stated that comprehensive interpretation of research findings in this field indicated that:

> "we should step back from a linear cause-consequence model of multimorbidity that aims for a measure of multimorbidity predicting every adverse outcome and providing complete insight into the impact of multimorbidity at the individual patient. In general, multimorbidity research would benefit from a redirected attention from the search for quantitative disease-oriented measures that use a reductionist approach of "counting diseases" toward qualitative person-oriented assessments of people who comprehensively describe the whole patient rather than the complete disease list" (Boeckxstaens et al. 2016).

I agree with this statement. It has in fact been one of the main themes in my research. However, to be able to approach multimorbidity scientifically, I have worked with its established definition and quantification. When working with multimorbidity, many unanswered questions however arise. One of the biggest questions lies at the very core of the concept, where the main philosophical question regarding healthcare rests: *what is disease, how should we define it?* The next chapter deals with this fundamental theoretical question.

2.2 What is disease— a doctor's most radical question?

The definition of multimorbidity is a count of many different types of diseases. As such, it reflects hundreds of years of debate in the fields of medicine and philosophy and the evident lack of universally accepted criteria for establishing what *disease* actually is (Worall and Worall 2001).

Although *disease* and *health* are among the most basic concepts in modern health care, their uses vary greatly, and their functions are diverse. As the philosopher Bjørn Hofmann said in 2005, these concepts are

> "key concepts in defining the purpose of health care activity, such as 'curing disease and promoting health', and they are principal in setting its limits. However, as debates of the purpose and limits of health care are related to fundamental issues of 'the good life', they are controversial. This is probably why *disease* and *health* have been subject to extensive philosophical debate" (Hofmann 2005).

It is quite a shocking discovery for a doctor, even more so after years of working in the field, to find out truly how vague the disease concept is on which she builds her daily professional activities. *The Oxford Textbook of Medicine,* for example, has no definition of disease (Smith 2002). However, *Dorland's Medical Dictionary* states the following definition:

> "Any deviation from or interruption of the normal structure or function of any body part, organ, or system that is manifested by a characteristic set of symptoms and signs and whose aetiology, pathology, and prognosis may be known or unknown" (Dorland's Medical Dictionary 2001).

Although this definition gives some explanation of the concept, it leaves even more questions unanswered. This chapter will touch on some of these questions. The vagueness of the definition reflects decades of studies and analyses within the fields of philosophy and medicine that have failed to reach any consensus on the content of the concept. The concept has therefore been described as both "*slippery"* and "*elusive*" (Hofmann 2010). The debate evidently dates back to the very origins of Western medicine which, one could say, set the stage for our future problems regarding the concept.

2.2.1 From Knidos and Kos to Descartes

The history of Western medicine traces back to the ancient medical schools of Knidos and Kos. These two places are often referred to as the sites where Western medical thought was born (Turgut 2011). They were both in the same geographic region and appeared as leading schools at about the same time. However, their views regarding diseases greatly diverged. The Knidians classified diseases in accordance with the organ affected. The focus was on the disease itself as an *ontological* entity (or something true and existing in nature, almost touchable). Later, the school in Knidos was described as laying the ground for medical sub-specialities (Turgut 2011).

In Kos, physicians were more interested in the general character of disease as a phenomenon. They emphasised the patient rather than the disease per se, relating Koans to general medicine. The school in Kos described disease as disequilibrium between different elements of the body (at that time the four humours) (Turgut 2011). The most famous physician from Kos was Hippocrates, often referred to as the "father" of rational medicine. Hippocrates believed the "healing power of nature" should be directed toward the patient as a physical, mental and spiritual whole (Marketos 1997). This healing power was linked to three elements: the disease, the patient and the physician. Therefore, every patient's interaction with disease was unique (Marketos 1997).

Furthermore, Hippocrates was the first doctor known to link environmental factors to the origin and development of disease (Marketos 1997). His main advancement of rational medicine was thus to release it from the realm of superstition and magic. Despite Hippocrates' leading role in the development of medical ethics, as time passed, Knidian medicine overshadowed his view of diseases and healing. With the age of enlightenment and the industrial revolution, the Knidian approach became the foundation for the dominant part of Western medicine. The Knidian philosophy regarding the disease concept has thus led the scientific revolution in medicine, resting on the ontological aspect of the profession.

The next important milestone on the way to fragmentation of medical science came almost 1700 years later with René Descartes. His theory of mind-body dichotomy suggested that the body worked mainly as a well-designed machine. The mind, on the other hand, was nonmaterial and did not follow the laws of nature (Porter 1997). This notion separated the mind and body, freeing the body from the holiness of the human being. Thereby, it paved the way for ground-breaking research on the body as a material entity (Porter 1997). Later in the 17th century, the development of the microscope opened even more possibilities regarding scientific discoveries of the body.

2.2.2 Contemporary super-division and silo-medicine

Since the beginning of the 18th century, doctors have attempted to classify diseases systematically (WHO 2016). This has been in line with Thomas Sydenham's 17th century definition of diseases as something that could be classified "just like plants and animal species". In other words, diseases had an existence independent of the observer and existed in

nature, ready to be "*discovered*" (Smith 2002). This definition is very much in step with the Knidian ontological school of thought. In the 17th century, the statistical study of disease had begun. It was based on coroners' reports on anatomical pathology noticed in autopsies. Thus, right from the start, health statistics and disease classification were collected, body system by body system, providing the basis for disease classification systems (Starfield 2011).

In 1763, the first attempt to classify diseases systematically was published. This was done by Sauvages under the title *Nosologica methodica.* In all, it included around 2400 diseases (Hofmann 2008). During the 20th century, the lists developed extensively. They became more unified, and compilers adopted the *World Health Organization Classification.* It is the most widely used classification system to date. ICD-10 was published in 1992 with around 14,000 different codes, it can be expanded to over 16,000 codes by using optional sub-classifications. These include codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances and external causes of injury or disease (WHO 2016). How could this happen? How did we come up with thousands of new diseases in just over 200 years?

At the same time, the medical profession developed from general medical doctors to organ-specific specialists and sub-specialists. This was a consequence of ever increasing fragmentation of the profession, with an ever-increasing myriad of diagnoses. The increased focus on specific sub-fractions of the body has inadvertently created individual disease or organ silos, which are reinforced by speciality organizations, advocacy groups, disease management organizations and disease-specific guidelines (Parekh and Barton 2010). At the same time, each doctor's knowledge has contracted to a very specific level.

This development has had two major effects on the medical profession that deserve further consideration. First, the development has diverted medical research away from examining the ill person to investigating isolated medical conditions and human fragments. The result is the collection of information on health problems and treatments, disease by disease, disentangling the problem as much as possible from the subjective reality of the patient (Starfield 2011). Research has attempted to detail divided descriptions of diseases and pharmacological effects. It has thus excluded possible confounding factors as much as possible, as the studies preferably do not include people with simultaneous (co-morbid) disease states. In fact, evidence-based medicine started out as research on middle-aged white men from a single disease perspective and not at all the average patient coming to see a

doctor. Medical data have thereby tended to become biased, and application of the resulting science to real patients might not yield adequate results. As Barbara Starfield said in 2011:

> "Disease-oriented medicine, whether through guidelines or through a focus on particular diseases and their management is thus highly inequitable as it cannot address the adequacy of interventions when people have many problems" (Starfield 2011).

Second, disease-oriented medicine has biased the development of the profession even further by changing the hierarchy of diseases as described below, overemphasising diseases that are easily isolated by organ or technical measurements, easily researched and – ideally – treatable by physiologically rational means. However, this approach disregards complex disease patterns with possibly very complex aetiologies, problems that may actually be inflicting more suffering on our patients.

2.2.3 From diseases to risk factors to optimization of health

One of the biggest changes in the medical profession over the last decades is a shift in focus from '*reactive*' treatment-based medicine to '*proactive*' preventive medicine. Great advances in research, technology and available drugs have brought on this shift, which has also been facilitated by overall better health of Western populations and higher life-expectancies (Getz 2006).

This transition has meant a radical change in the work of doctors. They have moved their focus from reacting to patients' symptoms, to evaluating more or less symptomless people and offering health improvements – sometimes with overstated benefits and understated harms (Getz 2006, Welch et al. 2011).

At the same time, this change has further complicated the challenge of disease definition by further pushing the borders between health and disease in direction of health (Welch et al. 2011). This practice has then spread to the social culture, which is now aiming for unrealistic or utopian health goals instead of a more realistic approach to health and life (Vogt et al. 2016).

I described the definition of disease above as a *deviation from the norm* (Hofmann 2008). But what is the norm? One of the most common definitions of the norm in medical science is statistical—i.e., lying within two standard deviations from the mean on whatever measure is

being used. But by this definition, 5% of all people are abnormal (or diseased?). Running enough tests thus makes it increasingly likely that we all need medical attention (Smith 2002). Trying an alternative definition, we could view the concept of disease as *being unhealthy*. There, however, we stumble over an even more difficult concept to define; *health*, as Linn Getz outlined in her PhD thesis (Getz 2006). Finally, we could look at disease as a cultural or social phenomenon (Hofmann 2008). Health is subject to social, cultural and economic influences that vary over time (Tikkinen et al. 2012). Ivan Illich described this phenomenon of disease as follows:

> "Each civilization defines its own diseases. What is sickness in one might be chromosomal abnormality, crime, holiness, or sin in another" (Illich 1976).

Considering the combined effect of blurring the lines between health and disease, normal and abnormal, and then taking into account the societal effect of utopian expectations with regard to health, the medical profession seems to be facing a tremendous challenge.

This has caused an epidemic of medicalization, in the sense of increased medical intervention in the lives of asymptomatic people. This epidemic has affected most medical specialities. The impact ranges from ever-widening disease definitions—i.e., of hypertension, hyperlipidaemia or diabetes—to technological advance in medical imaging, like MRI. New technology not only offers more precise diagnoses but also incidental findings, including tumours or other abnormalities which lead to repeated imaging, regular follow-up visits or even invasive diagnostic interventions (Getz 2006, Welch et al. 2011). The changes have even extended psychological diagnoses to reactions earlier regarded as normal (Frances 2013). All this is done with good intentions to benefit the patient, but it stretches medical borders ever wider and increases the risk of harm with ever less potential benefit (Moynihan 2011).

2.2.4 The disease definition dilemma seen in light of multimorbidity

The concept of multimorbidity, with its ever-increasing prevalence, has posed a new challenge to the ontological approach to diseases. One could speculate how much of the prevalence is due to people's increased suffering, and how much could be due to increased medicalisation or possibly by an artefact of too much fragmentation in medical research and disease definitions. The *Discussion* chapter will further debate these points.

If we aim to measure clinically relevant multimorbidity, i.e. the genuine disease burden (whether seen from the patient's or the physician's perspective), it pressures us to move away from the descriptive, single-disease, silo-approach in direction of understanding disease aetiology, in particular toward possible explanations of complex disease clustering. Could it be that the Knidian approach to medicine has reached its limits, and that the lack of a whole-person perspective is getting more and more evident? Or, through an ontological approach: to what extent will we find the best answers in the smallest fragments of human biology, in isolation from the person's environment? In the next two chapters, I will explore the approach of Knidian biomedical medicine to potentially complex disease causality and then take a more general, Koan approach to explore this same problem.

2.3 Complex disease clustering – biomedical perspectives

2.3.1 Before and after HUGO

As outlined in the last chapter, extensive progress in science and technology has enabled the ontological biomedical approach to disease and health to examine the human body and its biology down to the molecular level. This "reductionist" biomedical approach has provided many great advances in treating and curing disease, bringing us to the level of high-tech, sophisticated medical care provided in the Western world today.

However, taking these steps has required simplifying biological processes as much as possible, focusing on one process at a time, in order to gain as much insight into that process as possible. In doing this, medicine has deliberately looked away from the complexity of life, in order to attain scientific results (Vandamme et al. 2013) and researchers have looked for answers to the most complex questions about disease causality in the smallest fractions of biology. A major milestone in this development was establishment of the *Human Genome Project* or the HUGO-project in 1990.

When the HUGO-prjoect was initiated, its main aim was to identify and map all the genes of the human genome from both a physical and a functional standpoint, within a timeframe of 15 years (Chial 2008). It is to date the world's largest collaborative biological project and has often been described as leading a new era in medicine (Chial 2008). Its aspirations were that finding the genetic and molecular underpinnings of diseases would lead the way to more

accurate diagnoses and targeted, personalized treatments (Hayden 2010). Six years after the HUGO-project started, in 1996, the Icelandic company DeCode was founded with the aim of identifying the genes underlying the most common non-communicable diseases. The founders had great visions, and numerous Icelandic citizens, professional investors as well as lay persons, invested in the company. Since then DeCode has led several nationwide campaigns to collect genetic data from the largest possible part of the population. It has published hundreds of sophisticated articles on the project, to an increasing extent documenting the immense complexity of genomics. DeCode has thereby made a major contribution to our biological understanding of the human organism, but the original advertised aims of identifying common diseases' "*target genes*" and developing corresponding drug interventions in the very near future have yet to be fulfilled.

The HUGO-project attained its main goal in 2003, launching the sequence of the human genome. It is said to cover 99% of the euchromatic human genome with 99.99% accuracy of the 3.3 billion base-pairs. It stated that 99.5% of the sequence was the same between humans (Chial 2008). Humans therefore seem to have almost identical gene-maps, but the expression of the genes varies widely between us. Analysis of the genome data has definitely deepened our understanding of the highly complex molecular mechanisms underlying most human diseases (Chial 2008), but only very rarely explains the biggest part of the picture. Some personalized treatment modalities have indeed emerged, particularly in oncology, but in general the yield in terms of "actionable" findings is still far from what researchers aimed for (Gonzaga-Jauregui et al. 2012).

In 2010, ten years after the initial launch of the human genome, *Nature* published an article titled *"Life is Complicated"*. Its main conclusion was that "the more biologists look, the more complexity there seems to be" (Hayden 2010). In the article, the author posed a very important question: "Can one ever truly know an organism—or even a cell, an organelle or a molecular pathway—down to the finest level of detail?" She attempted an answer: "The more we know, the more we realize there is to know" (Hayden 2010). Another question I feel is just as important is this: *Is describing an organism in the finest molecular detail the same as truly knowing it?*

To sum up, it has become clear that the pathways of biology are not as simple and linear as scientists once predicted. Information signalling on a cell level is organized through complex

networks of information rather than simple discrete pathways (Hayden 2010). Authors have concluded similarly as Starfield did about disease complexity, but now on a biological level; that the whole is greater than the sum of the parts (Vogt et al. 2014).

2.3.2 Systems medicine

Systems biology, or its medical counterpart *systems medicine,* represents one of the scientific community's attempts to face the fundamental challenge of life's complexity. Systems medicine views medicine as an informational science. It requires global systems methods, integrating a variety of data at all relevant levels of cellular organization with clinical and environmental disease markers (Bousquet et al. 2011). It uses the power of computational and "*big data*" mathematical modelling to search for the mechanisms, diagnosis, prognosis and treatment of disease in a collaboration of many scientific disciplines, such as biology, computer science, engineering, bioinformatics and physics (Bousquet et al. 2011).

Systems medicine promises a transition in medicine to predictive, preventive, personalized and participatory (or P4) medicine. In an article in 2011, Bousquet et al. state:

> "…[it] is a shift from reactive to prospective medicine that extends far beyond what is usually covered by the term personalized medicine. It incorporates patient and population preferences for interventions and health states by implementing effective social actions with an important public health dimension. It is likely to be the foundation of global health in the future" (Bousquet et al. 2011).

The authors envisage that in a decade, P4 medicine will surround the patient with *"a virtual cloud of billions of data points",* predicting small shifts in health before overt clinical problems appear, based on monitoring personal data repeatedly in a "*holistic*" manner (Bousquet et al. 2011). Furthermore, they conclude:

> "The expected results targeted to better support for patients include: (i) better structuring of translational research and development for non-communicable diseases; (ii) greatly enhanced prevention and treatment capabilities; (iii) innovative healthcare systems with implementation of follow-up procedures directly in the homes of patients; (iv) slowing down of health expenditure increase; and (v) new interdisciplinary training curricula" (Bousquet et al. 2011).

However, a big question is how attainable this goal truly is. Is it a realistic possibility that scientists can make computational models from all possible measurements that accurately predict disease? If so, what would that do to the concepts of health, illness and disease? Is the

answer to be found in calculative models; can they possibly become accurate and valid enough? Many have questioned the philosophy of systems medicine. An article by Vogt et al. in 2014 debated how systems medicine could integrate scientific and humanistic conceptions of the patient. The authors conclude:

> "Ultimately, systems medicine may also have to recognize that, to faithfully model a human being, it is necessary to be a human being" (Vogt et al. 2014).

Vogt discusses Bousquet et al.'s vision that systems medicine might become the foundation for primary care medicine in the future at length in his PhD thesis (Vogt 2017). I will not go further into the topic here.

2.3.3 On epigenetics and telomere functioning

When discussing the patient with regard to the effect of his environment, I want to highlight two strands of research, pertaining to epigenetics and telomeres, respectively. Epigenetics is the study of non-DNA sequence-related heredity and gene expression. It is critical in explaining the relationship between an individual's genetic background, the environment, aging and disease (Feinberg 2008). Epigenetics deal with the modifications of DNA or associated proteins, during transcription and cell division. While the DNA remains the same, the epigenetic expression can change according to changes in the internal and external environment (Feinberg 2008), in either the short term or the long term. In contrast to genetic sequence variations, epigenetic alterations are potentially reversible.

Increasing evidence suggests that epigenetic changes can be passed on between generations and thereby bring acquired strengths or weaknesses from parent to a child (Mehler 2008, Jablonka 2012, Hughes 2014). This inheritance, as well as the different behaviour of cells according to their environment, has been called *epigenetic memory* (Feinberg 2008). Serving as an interface between the environment and the genome, epigenetics has been related to a wide range of diseases and health problems, ranging from cancers via behavioural factors to the effect of social adversity on future generations' health (McGowan and Szyf 2010).

In 2009, Elizabeth Blackburn and two colleagues were awarded the Nobel Prize in Physiology or Medicine for the discovery of how chromosomes are protected by telomeres maintained by the enzyme telomerase. Telomeres are a region of nucleotide repetitions at the end of each chromosome, protecting the chromosomes during cell-division (Blackburn et al.

2015). They therefore get shorter as we get older, declining from about 11 kilobases at birth to less than four kilobases in old age (Blackburn et al. 2015). Accelerated telomere shortening has however been shown to happen in both adults and children and is in some ways determined by genetic factors. Therefore, genetically caused variations in telomere maintenance can potentially either raise or lower the risks and progression of diseases, such as cancers. Telomere maintenance has as well been shown to accelerate in relation to stressful conditions, including early life adversity, maltreatments or physical diseases (Drury et al. 2014, Naess and Kirkengen 2015). It is therefore under scrutiny as both a cause and an effect regarding disease development.

To sum up, the "reductionistic" disciplines of epigenetic and telomere research suggest that it is necessary to look at the whole person in his or her environment in order to understand the causes of complex disease development. In the next chapter, I will thus look at complex disease clustering from the more general, Koan perspective.

2.4 Complex disease clustering – epidemiological perspectives

Moving away from the reductionistic bottom-up approach of biomedicine, I will now examine the determinants of health and disease from the top down, i.e. the epidemiological perspective. In a sense, this corresponds to the Koan perspective, describing disease in terms of a disequilibrium pertaining to the whole person in his or her environment. Epidemiology has sometimes been termed *"common sense"* research as it is mainly descriptive and therefore not ranked highly in the hierarchy of medical evidence (Guyatt et al. 2008, page 7). However, we cannot overlook that through medical history, many of the most important insights into disease development and public health have come from this field of research. I will briefly describe some key researchers with high relevance for this thesis.

2.4.1 From Engels, Kermack and Forsdahl…

Friedrich Engels published one of the first landmark epidemiological papers on disease and mortality in the 1840s, "*The Condition of the Working Class in England in 1844".* He described the effects of poor working conditions, little food, bad housing and inadequate medical care as follows:

> "All of these adverse factors combine to undermine the health of the workers. Very few strong, well-built, healthy people are to be found among them…They are for the most part, weak, thin and pale…Their weakened bodies are in no condition to withstand illness and whenever infection is abroad they fall victims to it. Consequently, they age prematurely and die young. This is proved by the available statistics of death rates" (Engels 1958 p.118-119).

Engels was well ahead of his time regarding the effects of social disadvantage. Social epidemiologist Nancy Krieger discussed Engel's work in 2004 (Krieger and Davey Smith 2004) and highlighted two very important observations relevant to recent scientific findings. First, Engels stated:

> "Common observation shows how the sufferings of childhood are indelibly stamped on the adults" (Krieger and Davey Smith 2004).

Second, he recounted how the hands of factory workers in Manchester were worn out at age 40 and looked 10 years older than expected (Krieger and Davey Smith 2004). This resonates with Barnett et al.'s recent description of multimorbidity prevalence in high and low social classes in 2012 (Barnett et al. 2012) (see section 2.1.3). Despite Engel's observations on social disadvantage so early on, the topic did not become a mainstay of epidemiological research until much later (Krieger and Davey Smith 2004).

In 1934, a paper by Kermack, McKendrick and McKinlay was published in *The Lancet*. It concluded that the environmental conditions during the first fifteen years of life determined life expectancy in Britain and Sweden (Smith and Kuh 2001). They found this true for mortality in all age groups except the first year of life. From this finding, they suggested that infant mortality depended on the health of the mother (Smith and Kuh 2001).

In 1973, district physician Anders Forsdahl published another landmark article throwing light on high mortality in Finnmark County, Norway (Forsdahl 2002). The data were from the population living in villages and rural areas in the county from 1890-1967. They had a much higher mortality rate than the rest of Norway. A large part of the population lived under very poor conditions, nutritionally, hygienically and socially, at times even at the level of starvation. This time of poverty and suffering lasted until the last stages of World War 2. The Finnmark studies showed an association between very poor living conditions in childhood and adolescence and high mortality in adulthood. Furthermore, Forsdahl found that the worse the living standard, the higher the later mortality (Forsdahl 2002). This association persisted

even when adult environmental conditions improved (Godfrey et al. 2010). The excess mortality rate was specifically prominent regarding arteriosclerotic disease but applied to other causes of mortality as well (Forsdahl 2002).

These original studies focused mostly on social factors pertaining to premature mortality. More recent studies have then shed light on factors more broadly affecting health and disease.

2.4.2 …to Marmot and Felitti

Arguably, the most prominent epidemiological studies of the social determinants of health are the English *Whitehall Studies*, led by Sir Michael Marmot, professor in epidemiology and public health. The first Whitehall Study was published in 1978. It examined over 17 000 male civil servants working in London. It started in 1967 and spanned a period of 10 years. A clear relationship was documented between grade of employment, coronary risk factors and coronary heart disease (Marmot et al. 1978). Men in the lowest grade had 3.6 times higher cardiovascular mortality than men in the highest employment grade. Furthermore, men in the lower grades were shorter, heavier, had higher blood pressure, higher plasma glucose, smoked more and reported less physical activity. But the most important finding was perhaps that even after correcting for all these factors, the association between employment grade and cardiovascular mortality was still strong (Marmot et al. 1978). The authors concluded:

> "It appears, then, that the evidence available to us on these men's risk factor status when they entered the study leaves unexplained a large part of the subsequent intergrade differences in death from coronary heart disease. This suggests either that there are other major risk factors which we did not measure, or else perhaps that the pattern of risk was already determined by genetic constitution or earlier upbringing" (Marmot et al. 1978).

In 1984, the *Whitehall II Study* was started. It is a prospective cohort study of over 10 000 men and women. Its follow-up is still ongoing. The study has confirmed a social gradient for a wide range of diseases in both genders, including heart disease, some cancers, chronic lung disease, gastrointestinal disease, depression, suicide, sickness absence, back pain and general feelings of ill-health (Marmot et al. 1991, North et al. 1993, Hemingway et al. 1997). Furthermore, the researchers have linked factors such as perceived unfairness, job insecurity, effort-reward balance as well as influences from early life and social influences outside work to the social gradient in health (Marmot et al. 2001, Kuper and Marmot 2003, De Vogli et al. 2007).

In 2010 Michael Marmot published his review "*Fair society, healthy lives*" on social inequalities and health in Britain. The report states:

> "In England, people living in the poorest neighbourhoods will, on average, die seven years earlier than people living in the richest neighbourhoods. Even more disturbing, the average difference in disability free life expectancy is 17 years. (…) To illustrate the importance of the gradient: even excluding the poorest five per cent and the richest five percent the gap in life expectancy between low and high income is six years, and in disability free life expectancy 13 years" (Marmot 2010).

Furthermore:

> "These serious health inequalities do not arise by chance, and they cannot be attributed simply to genetic makeup, "bad", unhealthy behaviour, or difficulties in access to medical care, important as those factors may be. Social and economic differences in health status reflect, and are caused by, social and economic inequalities in society" (Marmot 2010).

Around 1985, Dr. Vincent Felitti started to investigate the health impact of adverse childhood experiences at Kaiser Permanente in San Diego, USA. At that time, he ran an obesity clinic and found that more than half of his patients dropped out. It did not seem to be those not achieving weight-loss, in fact, often the contrary was true. He therefore started interviewing the patients that dropped out. What he found, was that many of his severely obese patients had experienced adversity and abuse in childhood (Stevens 2012). In 1995, Felitti started the *Adverse Childhood Experiences* (or ACE) study with his co-worker Robert Anda, affiliated with Centers of Disease Control and Prevention. The ACE study included around 17 000 middle-aged, middle-class participants from San Diego (The ACE Study Homepage). A seminal ACE study article, published in 1998, related childhood experiences of abuse and household dysfunction to many of the leading causes of death in adulthood (Felitti et al. 1998).

Felitti and co-workers defined seven categories of adverse childhood experiences. These experiences were self-reported in questionnaires from people attending standardized examinations through their health insurance. The categories involved psychological, physical or sexual abuse; violence against mother; living with household members who were substance abusers, mentally ill or suicidal or imprisoned, as well as parental separation/divorce. In practice, more than half of the respondents reported at least one type of adverse childhood experience, and one-fourth reported two or more such categories (Felitti et

al. 1998). The most striking finding in the 1998 ACE study was a dose-response relationship between the number of ACE categories and adult health problems, including: ischaemic heart disease, cancer, chronic lung disease, skeletal fractures, liver disease, alcoholism, drug-abuse, depression, obesity and sexually transmitted disease. Subsequent ACE publications have linked adverse childhood experiences to other diseases, such as frequent headaches (Anda et al. 2010), autoimmune disease (Dube et al. 2009) as well as poor self-rated health and lower health-related quality of life (Edwards et al. 2004).

In January 2017 Felitti held a lecture in Iceland. One of his slides read as follows:

> "Many of our most common and intractable public health problems are unconsciously attempted solutions to personal problems dating back to childhood, buried in time, and concealed by shame, by secrecy, and by social taboo" (Felitti 2017).

In an English translation of a German article in 2002, he also stated:

> "Most physicians would far rather deal with traditional organic disease. Certainly, it is easier to do so, but that approach also leads to troubling treatment and to the frustration of expensive diagnostic quandaries where everything is ruled out but nothing is ruled in" (Felitti 2002).

The milestone epidemiological works of Felitti, Marmot and co-workers have shed very important light on social and environmental determinants of health and disease. This will be further deliberated in the *Discussion.* In more recent years, both Felitti and Marmot have started to work in collaboration with researchers in the field of stress biology. Jointly, they have attempted to describe pathways and mechanisms by which early life experiences translate to ill health and disease development.

2.5 The bio-psycho-social model

The research discussed above represents a fundamental challenge to the classic biomedical model described in sections 2.2 and 2.3. The biopsychosocial model at least partially represents a response to this challenge.

In 1977, the internist George L. Engel published a renowned article in *Science* where he challenged the traditional so-called biomedical model of disease. As an alternative, he

proposed the *biopsychosocial (BPS) model* (Engel 1977), taking into account biological factors (such as genetic and biochemical), psychological factors (mood, personality, behaviour, etc.) and social factors (cultural, familial, socioeconomic, to name a few). Engel had studied psychoanalysis and had a special interest in psychosomatic medicine (Tavakoli 2009). The main purpose of the BPS model was to counterbalance reductionism of the biomedical model with more holism, by viewing patients as individuals with complex behaviour and emotions that affect their physical ailments (Ghaemi 2009).

Although the BPS model has been promoted as the foundation upon which medicine today should build, the biomedical aspects still dominate medical research and practice. Furthermore, a growing body of literature is critical of the BPS model as such, charging it with lacking philosophical coherence, and providing no safeguards against either the dominance or the under-representation of any one of the three domains of bio, psycho, or social (Ghaemi 2009, Benning 2015). The *Discussion* will further deal with this criticism.

In 2008, WHO published a report named *"Primary Health Care (Now more than ever)".* One of the main themes of the report is non-communicable (or chronic) diseases. It states:

> "The growing reality that many individuals present with complex symptoms and multiple illnesses challenges service delivery to develop more integrated and comprehensive case management. (…) Insufficient recognition of the human dimension in health and of the need to tailor the health service's response to the specificity of each community and individual situation represent major shortcomings in contemporary health care, resulting not only in inequity and poor social outcomes, but also diminishing the health outcome returns on the investment in health services" (WHO 2008).

It is therefore clear that there are increasingly loud voices in the field of medicine stating the importance of a stronger focus on the social and relational determinants of health and disease.

It is a common saying that "Genetics loads the gun, and environment pulls the trigger." However, a gun needs a firing mechanism as well, without which there will be no bang. We could perhaps say that *stress* might represent the fuse or firing pin. Beyond this, however, the gun (i.e. machine) metaphor will soon confuse our thinking. The associations between adversity, experience and health are by no means linear and predictable, and one will even have to take into consideration that the environment tends to fire back and modify the gun. Furthermore, people apparently differ considerably in their responses and vulnerability, an

insight reflected in the increasingly popular term *resilience*. To develop valid insight into the intricate and dynamic interrelatedness of the human biology and experience, we need more adequate concepts to start with. The most important concepts with relevance for this thesis are introduced in the next chapters. The first concept I will consider is *embodiment*.

2.6 Embodiment

In 2005, Harvard Social epidemiologist Nancy Krieger introduced the notion of embodiment as a new glossary term for epidemiologists. The construct invites researchers to consider how our bodies, each and every day, accumulate and integrate experiences and exposures, both major and minor (Krieger and Davey Smith 2004). Krieger states:

> "Recognising that we, as humans, are simultaneously social beings and biological organisms, the notion of "embodiment" advances three critical claims:
>
> 1) bodies tell stories about—and cannot be studied divorced from—the conditions of our existence;
> 2) bodies tell stories that often—but not always—match people's stated accounts; and
> 3) bodies tell stories that people cannot or will not tell, either because they are unable, forbidden, or choose not to tell" (Krieger 2005).

> "…As has long been argued, although not always widely appreciated, it is no accident that from population patterns of health, disease, and wellbeing it is possible to discern the contours and distribution of power, property, and technology within and across nations, over time. Or, more pointedly, from the conditions of our bodies (…) you can gain deep insight into the workings of the body politic" (Krieger 2005).

Krieger's statements are in many ways contrary to medicine's conception of fragmented body parts. The implication, for epidemiology, is that our explanations of health, illness and disease cannot be complete in the absence of a more integrated approach. As biological organisms we exist, i.e. reproduce, develop, grow, interact and evolve, in time and space. As relational beings we are at the same time fundamentally dependent on our societal context (Krieger 2005). According to Krieger, consideration of all these integral aspects of our bodily existence is key to understanding both public health and social inequalities in health (Krieger and Davey Smith 2004). From my perspective as a general practitioner, the term embodiment also makes deep sense at the level of individuals and families. Many of my colleagues might intuitively agree as I say this, but the claim still has a very limited research foundation. Professor in general practice Anna Luise Kirkengen has however contributed very important

work in the field, including theoretical considerations about embodiment from the perspective of phenomenology, as I will outline below.

The word embodiment was not invented by Nancy Krieger. She presents the concept with reference to the 20th century French philosopher Maurice Merleau-Ponty. As a phenomenologist, Merleau-Ponty described the human body as a perceiving organism, directly intertwined with its environment. Human beings thus experience the world *by means of* their bodies, literally incorporating their experiences (Merleau-Ponty 1989). A thorough presentation of Merleau-Ponty's works is far beyond my competence, and in the following, I will lean on Kirkengen' s presentation of his works, in particular his book *Phenomenology of Perception* from 1945. In her own book, *The Lived Experience of Violation,* Kirkengen quotes Merleau-Ponty:

> "This table bears traces of my past life, for I have carved my initials on it and spilt ink on it. But these traces in themselves do not refer to the past; they are present; and, in so far as I find in them signs of some "previous" event, it is because I derive my sense of the past from elsewhere, because I carry this particular significance within myself. If my brain stores up traces of the bodily process which accompanied one of my perceptions, and if the appropriate nervous influx passes once more through these already fretted channels, my perception will reappear, but it will be a fresh perception, weakened and unreal perhaps, but in no case will this perception, which is present, be capable of pointing to a past event, unless I have some other viewpoint on my past enabling me to recognize it as memory" (Merleau-Ponty 1989).

Kirkengen explains the passage further in her own words, with emphasis on the notion of *lived body*:

> "Sensory perception and cognitive consciousness, when integrated, acquire the specific meaning of own action and experience. Together, they make up a very special "lived" meaning. This idea encompasses the lived body. (…) The expression "lived meaning" opens the world of perceptions and memories that every human being carries within and is formed by" (Kirkengen 2010).

Kirkengen's own research originally focused on how experiences of abuse became inscribed in the human body, potentially with very detrimental effects on the individual's health as an adult (Kirkengen 2001). Her methodological approach was qualitative in-depth interviews with individuals who had experienced sexual abuse. Based on her findings, and in accordance with Merleau-Ponty, Kirkengen states:

> "Applied on the diseased body, the traditional distinction between mind and matter as a basic concept is transcended. This position renders human experience and particularity sources of valid knowledge, relevant for an understanding of the impact of lived life on health. The view of the body as history and memory allows an integration of perception and experience into cognition and meaning. Thereby, an approach to the lived meaning of what a person has experienced and embodied, is provided. Since lived meanings are central to all incorporation of experiences, they are salient for any exploration of trauma impact" (Kirkengen 2008).

Later in the same article, she says:

> "The path from violation to sickness in a particular person is informed by personal appraisal of experience within a socio-cultural, historical and biographical context. Thus, a theory of the lived body and of incarnate experience is a more adequate means to gain insight into the process of the transformation from violation to disease. A theoretical shift from the body of biomedicine to the lived body implies a shift of perspective: from "that" to "how"" (Kirkengen 2008).

The construct of embodiment invites us to consider how our bodies, each and every day, accumulate and integrate experiences and exposures, both major and minor (Krieger and Davey Smith 2004). It can provide evidence that puts self-report as well as biological measurements in context and invites a wider, more holistic approach to the patient. As can be seen from the author list in the *included papers,* Kirkengen has contributed to the publications of this thesis. As Kirkengen's insights have been developed based on qualitative in-depth methodology, transfer to an epidemiological study setting evidently posed a great challenge to our research group. In a tentative but quite ambitious effort to build a methodological bridge from Krieger's epidemiological concept to Kirkengen's explorations of subjective experience of trauma, we ended up with a new, global survey question (the "childhood question" as the basis of Paper II) as well as a new theoretical concept ("existential unease" as the basis of paper III). One may discuss at length how successful those efforts have been, and what can be learnt from them, but that is a matter for the *Methods* and *Discussion* sections.

2.6.1 Embodied life: The patient as a person

Central to the speciality of family medicine/general practice is the approach to the patient as a person, which, WONCA's European definition of General Practice from 2015 describes as follows:

> "Family medicine deals with people and their problems in the context of their life circumstances, not with impersonal pathology or "cases". The starting point of the

> process is the patient. It is as important to understand how the patient copes with and views their (sic) illness as dealing with the disease process itself. The common denominator is the person with their beliefs, fears, expectations and needs" (Allen et al. 2015).

Nevertheless, the traditional methodology of biomedicine has long failed to take account of

> „the self-aware, meaning-seeking, purposeful and relational nature of humans. Doctors therefore lack theoretical understanding of how experiences associated with self-image, relations and values become inscribed in the body" (Getz et al. 2011).

This incongruity makes general practitioners everyday work especially challenging. American physician and philosopher Eric Cassell, a professor of public health, has described this incongruity as an ethical problem, arising from clinical medicine's theoretical roots in pathology and science, rather than in people's experiences and lifeworld. Cassell has stated that the wise doctor knows that the problem with modern medicine is that it has no bearing on people and lived life since its focus is merely on the diseased organ (Cassell 2004).

Bente Prytz Mjølstad, a fellow GP, recently defended her PhD thesis on *Knowing Patients as Persons*, where she describes this theme thoroughly. She states in her thesis:

> "There is reason to claim that human beings' lives are not actually taken into consideration in mainstream, contemporary, Western medical thought and practice. The ever-increasing evidence that adverse lifetime experience is related to health problems would indicate that medicine ought to address this: any comprehensive overview should, in addition to the biomedical approach of health and disease, include the person's past and current life stressors, as well as social and cultural situation. Optimal treatment of a person's health problem has to be based on an understanding of the whole person in his/her context" (Mjolstad 2015 page 135).

The above statements, combined with epidemiological evidence discussed in the previous chapter, indicate a strong relationship between experienced pain, fear and powerlessness and subsequent problems later in life in the form of complex health problems. In a paper from 2012, Kirkengen and Thornquist present the evolving insight in this field (Kirkengen and Thornquist 2012). So far in this introduction, I have discussed the relevance of this knowledge to general practice and the patient encounter. However, I have only stated *that* experience and complex health problems are related. I have yet to cover in more detail *how* and *why* this can happen (Kirkengen and Thornquist 2012). In the next few chapters, I will zoom in on *how adversity gets under the skin,* in terms of biomolecular mechanisms.

2.7 The phenomenon of stress

Stress, as a concept, had been used to describe human experience and behaviour long before science formally defined it (Hinkle 1974). During the 18th and 19th century, its usage denoted

> ""force, pressure, strain or strong effort" exerted upon a material object or a person – or upon a person´s "organs or mental powers". It then carried with it the connotation of an object´s (or person´s) being acted upon by forces from without, resisting the distorting effects of these forces, attempting to maintain its integrity and trying to return to its original state" (Hinkle 1974).

At that time—and up to the early 20th century—the term was used mainly in a non-scientific sense but had still been thought of as possibly causing unspecific "ill health" and "mental disease".

Hinkle discussed this point in is article on stress in 1975. There he quoted from the famous Canadian physician Sir William Osler's lectures on "Angina Pectoris" in 1910. There Osler stated that the condition was especially common among Jewish businessmen:

> "Living an intense life, absorbed in his work, devoted to his pleasures, passionately devoted to his home, the nervous energy of the Jew is taxed to the uttermost, and his system is subjected to that stress and strain which seems to be a basic factor in so many cases of angina pectoris" (Hinkle 1974).

The concept of stress has gained increasing popularity since the Second World War (Jones et al. 2001 page 5). Most scholars attribute the formal description of the concept to the Hungarian endocrinologist Hans Selye (Selye 1998). In his letter to the editor of *Nature* in 1938, Selye described the general alarm reaction of his experimental rats as a non-specific adaptive response to various kinds of agents (Szabo et al. 2012). His idea stemmed from the notion that, in the long history of medicine, doctors had spent so much time and energy discovering and treating individual diseases but had given little thought to "the syndrome of feeling ill" (Selye 1955). In a 1955 paper in *Nature* on stress and disease, he stated:

> "Ever since man first used the word disease, he has had some inkling of the stress concept. The very fact that this single term has been used to denote a great variety of manifestly distinct maladies clearly indicates that they have been recognized as having something in common. They possess, as we would now say, some "nonspecific features" (the feeling of being ill, loss of appetite, and vigour, aches and pains, loss of weight, and so forth), that permit human beings to distinguish illness from the condition of health. Yet precisely because these manifestations are not characteristic of any one disease, they

> have received little attention in the comparison with the specific ones. They were thought to be of lesser interest to the physician, for, unlike the specific symptoms and signs, they did not help him to recognize the "eliciting pathogen" or to prescribe an appropriate specific cure" (Selye 1955).

Selye later described his findings as a general adaptation syndrome and finally coined the term "stress syndrome" (Selye 1955). Being an endocrinologist, he further described the concept biologically, which the next chapter will further detail.

In recent years, it is mostly within psychology that the more general description of stress has been used, commonly described as *a feeling of strain or pressure*. However, the term is very vague and has a multitude of different definitions that ultimately point in the same direction. They range from highly specific to very broad and general, encompassing both stimulus for stress and response. For example, stress has sometimes been conceptualised in terms of specifying environmental conditions which were considered stressful, or in terms of perceived "frustration or threat". More advanced definitions incorporated both stimuli and response, as well as the relationship between the two (Jones et al. 2001).

In Lazarus and Folkman's model of stress from 1984, stress occurs when environmental demands exceed people's *perception* of their ability to cope (Karatsoreos and McEwen 2011). The model highlights human subjective experience of their situation as a defining key. When we ourselves feel overpowered and *think* the demands placed on us exceed our ability to cope, we experience stress (Karatsoreos and McEwen 2011).

2.7.1 Positive, tolerable and toxic stress

Three categories have been proposed for describing stress experience: *positive*, *tolerable* and *toxic* stress (Shonkoff et al. 2009). The purpose is to underline that an individual needs challenges to grow and reach her or his potential as a human being. The idea behind the definition is to differentiate life challenges that are growth promoting from those that present potential or unequivocal threats to long-term health and thereby warrant interventions and preventive measures. The three categories refer to the physiological manifestations of stress, not the stressor itself, as personal response to different stressors varies between individuals (Shonkoff 2010).

Positive stress involves moderate, short-lived episodes of physiological arousal that ultimately have positive effects. They increase people's function, performance and capacity and thereby help build their health. Positive stress is typically experienced in the context of stable and supportive relationships that facilitate adaptive responses and thereby restoration of biological balance (Karatsoreos and McEwen 2011). Tolerable stress refers to a physiological state that could potentially cause long-term biological disruption and undermine health but is buffered by supportive relationships that facilitate adaptive coping and strengthen the person's *resilience* (Shonkoff 2010).

Toxic stress refers to strong, frequent and/or prolonged activation of the body's physiological response systems in the absence of buffering protection and opportunities to recover. It involves stress that becomes so demanding (intense and/or long-standing) that the system can no longer adequately respond and thereby protect the organism from damage (Karatsoreos and McEwen 2011). As the name implies, toxic stress is by definition harmful. But again, what constitutes toxic stress, depends on the person and the circumstances.

2.7.2 Resilience

Researchers have proposed the term resilience to describe a person's capacity to maintain health in the presence of adverse events/experiences that would otherwise be expected to have negative outcomes (Wister et al. 2016). Resilience has been broadly defined as a dynamic adaptive process through which individual traits, characteristics of the environment and internal and external resources are mobilized in the face of adversity. The resources might involve psychological, social, cultural and physical aspects (including genes) that help sustain health and well-being. It also enables people, both individually and collectively, to use the resources that are provided and experienced in culturally meaningful ways in their society (Ungar 2008).

Resilience describes the salutogenic processes connected to quality of life and well-being and emphasizes positive pathways of coping and adaptation (Wister et al. 2016). It therefore has a buffering effect in the presence of stress, both in childhood and adulthood (Wister et al. 2016).

In this chapter, I have made references to the body's physiological adaptation systems. The increasing recognition that stress plays an important part in disease development has

motivated an extensive field of research looking at *the biology of stress* which I will now present.

2.8 The biology of stress

When describing his experiments on the general alarm reaction in 1938, endocrinologist Hans Selye originally called it a syndrome produced by diverse nocuous agents. He described, among other effects, thymico-lympathic involution, gastric ulcers and loss of lipoids and chromaffin from the adrenal gland (Selye 1998). Selye's original definition of stress was "the non-specific neuroendocrine response of the body", but he later dropped neuroendocrine from the definition as he found, in addition, that the stress response affects almost every other organ system (Szabo et al. 2012). Stress was described as the body's reaction to stressors that pushed human biology away from its *ideal homeostatic state* of equilibrium (Szabo et al. 2012). Walter Cannon, a contemporary scientist of Selye, originally described homeostasis.

Selye described three possible stages of stress. First, he described the "alarm reaction" or "fight or flight mode" as a response to a sudden increase in stress, like environmental threat. Most of the time this stage is short-lived and Selye concluded that no organism could sustain that condition for a long time. Sustained alarm reaction therefore leads to the second stage of adaptation, which builds certain resistance to stress. Finally, if stress goes on sufficiently long, the body eventually enters a state of exhaustion. A pathological state therefore develops from ongoing, unrelieved stress (Selye 1998). Selye's scientific approach was very strict on the usage of the word stress. He felt that a "stress response" could only be applied if several stressors of a different nature could produce the same response (Szabo et al. 2012).

In addition to describing the overall stress syndrome, Selye was the first to demonstrate the crucial and specific role of the hypothalamic-pituitary-adrenal axis in the stress response. He also presented ideas, seen as radical at that time, including the notion that stress had causal relationships to a number of illnesses, for example heart disease and cancer (Szabo et al. 2012). Selye's breakthrough ideas about stress helped establish an entirely new field of natural science research based on the study of biological stress and its effects. The field has several sub-branches with accompanying terminology, but from a distance the activity

evolves around the same topic, how the human body responds to stressful challenges and how detrimental effects of stress can potentially be prevented or even treated.

2.8.1 Psycho-neuro-immunology

Hans Selye's work on the hypothalamic-pituitary-adrenal (or HPA) axis represents the first modern description of the biomolecular effects of stress on the body. When receiving signals evoked by stressors, the hypothalamus starts a hormonal cascade response (Szabo et al. 2012). The hypothalamus secretes corticotropin-releasing hormone which then stimulates the anterior lobe of the pituitary gland to release adrenocorticotropic hormone which causes the adrenal gland to release cortisol. Cortisol is a glucocorticoid steroid hormone with a primary function to redistribute energy. However, according to Selye's work, cortisol is responsible for most of the morphological manifestations of (di)stress, especially in the later stages of resistance and exhaustion (Szabo et al. 2012). Cannon, the physiologist who coined the term homeostasis, later published findings on the effects of stress on the autonomic nervous system, i.e. the sympathetic and parasympathetic responses. These responses are most prominent in the "fight or flight" mode of the stress response. Cannon described the catecholamines norepinephrine and epinephrine which act in the central nervous system through the sympathetic-adrenal-medullary axis (Szabo et al. 2012). Around the middle of the 20th century, the contemporaries Selye and Cannon had outlined the most central pathways of the stress response.

In 1975, Robert Ader and Nicholas Cohen, at the University of Rochester, demonstrated the classic conditioning of immune function in the stress response. They coined the term *"psychoneuroimmunology"*, thus integrating their own research with the earlier works of Selye and Cannon. They concluded that the brain and the immune system represented a single, integrated system (Ader and Cohen 1993). They found that glucocorticoids, released in the HPA response, suppressed the synthesis of proinflammatory cytokines, such as the interleukins, tumour necrosis factor alpha and interferon-gamma. The cytokines control immune and inflammatory responses. This response stimulates the physiological acute-phase reaction, associated with sickness behaviour and pain (Ader and Cohen 1993). Furthermore, chronic secretion of glucocorticoids and catecholamines may reduce the effect of neurotransmitters, such as serotonin and dopamine, leading to further hormonal dysregulation (Ader and Cohen 1993).

In 1985, neuropharmacologist Candace Pert revealed that neuropeptide-specific receptors are present on the cell walls, both in the brain and the immune system. This indicated that the central nervous system modulates the immune and endocrine systems in a complex multidirectional causal web (Pert 2003).

2.8.2 Allostasis and allostatic load

Around 15 years after psychoneuroimmunology emerged as a concept, Sterling and Eyer proposed the concept of allostatic load (Sterling and Eyer 1988). In contrast to homeostasis, they described allostasis as "stability through change". Thus, instead of holding variables constant (i.e. within a very narrow range) as in homeostasis, allostasis describes mechanisms that change the controlled variable by predicting what level will be needed, and overriding local feedback to meet the anticipated demand (Sterling and Eyer 1988, McEwen and Getz 2013). While homeostatic systems, such as blood oxygen, pH and body temperature, must be maintained within narrow ranges, allostatic systems have much broader boundaries (McEwen 1998). We are evidently speaking about the same physiological system, but the terms homeostasis and allostasis draw attention to quite different aspects of organismic functioning.

Wingfield described allostasis and allostatic load as follows:

> "The concept of allostasis, maintaining stability through change, is a fundamental process through which organisms actively adjust to both predictable and unpredictable events (…) Allostatic load refers to the cumulative cost to the body of allostasis, with allostatic overload (…) being a state in which serious pathophysiology can occur" (Wingfield 2003).

Bruce McEwen, professor in neuroendocrinology at Rockefeller University and contemporary authority in the field of allostasis and allostatic load (as well as co-author on Papers I and II), wrote the following on the subject in 1998:

> "Allostasis, the long-term effect of the physiologic response to stress (…) is critical to survival. Through allostasis, the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, and the cardiovascular, metabolic, and immune systems protect the body by responding to internal and external stress. The price of this accommodation to stress can be allostatic load, which is the wear and tear that results from chronic overactivity or underactivity of allostatic systems" (McEwen 1998).

McEwen proposes four situations associated with increased allostatic load. The first—and, as he states, the most obvious— is frequent stress. He exemplifies this by surges in blood pressure that can trigger myocardial infarction in susceptible persons. The second type is lack of adaptation to repeated stressors of the same type, resulting in prolonged exposure to stress hormones. Inability to shut off allostatic responses after a stress reaction is terminated is the third type, and the fourth type involves inadequate response by an allostatic system that triggers compensatory increases in others (McEwen 1998). In the same article, he also suggests that high allostatic load over a lifetime may cause the allostatic systems to wear out or become exhausted (McEwen 1998).

Allostasis and allostatic load therefore represent a multifaceted mind-body approach to describe the biological response to stress in various forms. In addition, the concepts enable scientific research to articulate dynamic processes that, during acute stress, can have protective effects in the short term (as with positive stress). However, in the long run, they can destabilize into maladaptive processes, indicating that the stress has become toxic in the sense of biologically damaging (Beckie 2012). Within limits, allostatic states represent adaptive responses to fluctuating demands, fully compatible with good health and positive development (meaning that the stress load can be categorized as positive or at least tolerable). However, if additional loads of unpredictable or uncontrollable challenges are added to the burden of stress, be it a viral infection, minor accident, troubled relationships or social difficulties, then the allostatic load can increase dramatically (McEwen and Wingfield 2003). While ‘allostatic load’ neutrally denotes the cumulative impact of strain over time, allostatic overload denotes a “red flag”—a physiological risk scenario—where the organism’s adaptive and restorative capacity is overtaxed to such an extent that adaptability and flexibility are gradually lost (McEwen 2006). The result is physiological dysregulation, at times expressed only in subtle but widespread perturbations. These might nevertheless have a significant cumulative impact on the entire organism. Allostatic overload therefore provides ground for disease development, influenced by individual, genetic susceptibilities, the social environment and eventual maladaptive, unfavourable ways of living (McEwen 1998).

McEwen has thoroughly described the effect of stress on the brain. In his view, the brain is the central organ of stress and adaptation, both a conductor and a target organ of the physiological stress responses described above (McEwen 2009). With chronic stress, the brain itself changes in structure and function in a process called adaptive plasticity. It is thus

a key organ of both adaptive and maladaptive responses to stress because it interprets what is threatening and, therefore, potentially stressful. The brain as well regulates the behavioural responses to stress, including appetite and sleep (McEwen 2009). The effect of stress on the brain is probably most prominent in the hippocampus, which has high concentrations of cortisol receptors. The amygdala and prefrontal cortex, as well as the hippocampus, undergo stress-induced structural remodelling, which further alters behavioural and physiological responses. The amygdala is an essential part of the memory system for fearful and emotionally laden events, while the hippocampus is involved in determination of the context in which such events take place. These two structures are therefore both anatomically and functionally linked (McEwen and Gianaros 2010).

The hippocampus, amygdala and prefrontal cortex coordinate behaviour with neuroendocrine, immune, and autonomic functions in the service of adaptively coping with environmental and psychosocial challenges (McEwen and Gianaros 2010). The hippocampus participates in verbal memory and memory of context. It can both exacerbate stress by preventing access to the information needed to decide that a situation is not really a threat and induce short-term memory loss through inhibition of the HPA axis response and increased cortisol due to acute stress (McEwen 1998). However, repeated or chronic stress can kill hippocampal neurons. In the prefrontal cortex, increased levels of chronic stress are connected to smaller cortex size. Increased functional activity in the amygdala has been related to the development of atherosclerosis (McEwen 2009). Furthermore, long-term stress causes earlier appearance of several biologic markers of aging, possibly accelerating aging of the brain (McEwen 1998). In summary, structural changes to the brain due to chronic stress can increase future stress response, accelerate aging of the brain and induce disease development.

Before proceeding to discuss measurements of allostasis, it may be relevant to emphasise that this model is one among a handful of related models with different names and somewhat differing perspectives. One such term is “centralized sensitization syndrome.” Others include sustained arousal and the Cognitive Activation Theory of Stress (CATS). These concepts all advance similar claims related to the effect of stress on the human biology. They have emerged in different milieus and need not be considered as competing or in contradiction (Stranden et al. 2016). Probably, these models will become more or less unified with time. To

avoid extending this thesis even further, I decided to focus on the model of allostasis and allostatic load.

2.9 Measurements of allostasis

A key feature of the concepts of allostasis and allostatic overload is that multiple mediators of adaptation are involved that are interconnected in a complex, nonlinear network. Many of the mediators produce biphasic effects and are regulated by other mediators, often in reciprocal fashion, leading to effects upon many organ systems of the body (McEwen 1998). Allostatic load differs from the more traditional concepts of biological risk factors in two ways, as described by Seeman et al. in 2010:

> "The first is its focus on the "sum total of physiological dysregulation across systems"—a view closer to the reality of known system interconnections than approaches that focus on the role of one or another regulatory system. And, the second is its inclusion of relatively more modest forms of dysregulation in the accounting of biological risk. This view of biological risk proposes that relatively modest dysregulation when cumulated across multiple systems may have significant impacts on health risks, even if none of the individual effects would be deemed either statistically or clinically significant in and of themselves" (Seeman et al. 2010).

Measuring allostatic load therefore has the goal to tap into many body systems concurrently. The biomarkers associated with allostatic load fall into three different classes, as is shown in Figure 3. The figure shows the state of the art at the time of our analyses. However, more markers have been introduced since, as will be discussed in the *Discussion.*

Primary mediators of allostatic load regulate rapid adjustment to demands of acute stress. They include cortisol, sympathetic and parasympathetic activity, pro- and anti-inflammatory cytokines, metabolic hormones and neurotransmitters and neuromodulators in the nervous system (McEwen 2015). Primary mediators give rise to *secondary mediators*, reflecting the cumulative actions of primary factors in a tissue- or organ-specific manner. These reflect abnormal metabolism and risk for cardiovascular disease, such as waist-hip ratio, blood pressure, glycosylated haemoglobin, cholesterol and HDL cholesterol. Furthermore, McEwen describes how, through neuroimaging, examples of secondary outcomes can be seen through functional changes in hypo- or hyperactivation of a set of brain regions (McEwen 2015).

More recently, telomeres and telomerase functions have been proposed as secondary factors (McEwen 2015), as has also mitochondrial function (Picard et al. 2015).

Tertiary markers of allostatic load are manifest diseases or disorders (often diagnostic entities). Elevated blood pressure and cholesterol are secondary markers, whilst symptomatic heart disease is a tertiary marker. McEwen also gives the example that slightly disturbed cognitive function represents a secondary marker, whilst Alzheimer's disease or vascular dementia could be tertiary. Cancer would also be a tertiary marker, whereas the common cold would be a secondary (McEwen 2015). In saying this, McEwen does not indicate that allostatic load represents the only or ultimate cause of the specific disorders. His point is that cumulative allostatic load decreases the body's resilience and resistance to pathogenetic factors and agents, be they genetic or acquired, and thereby paves the way to disease development.

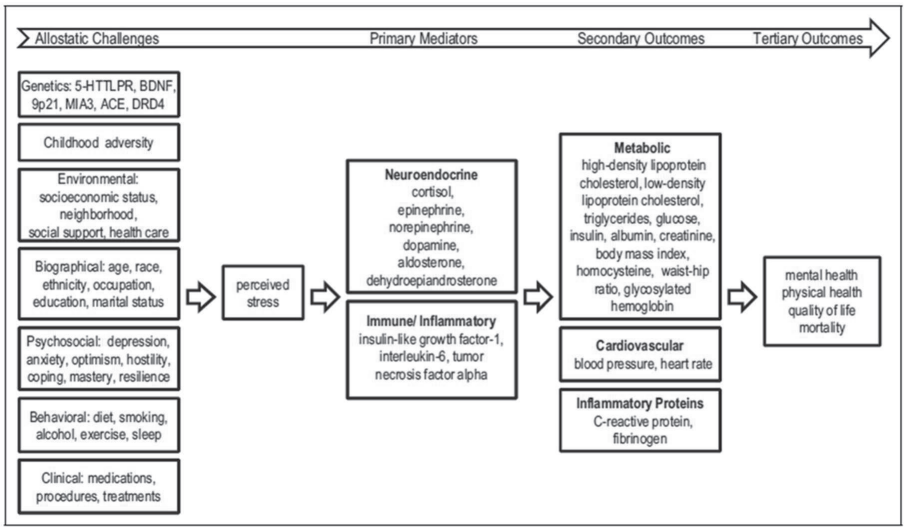

Figure 3. Model showing common makers and mediators of allostatic load. Beckie 2012. (Reprint permission requested May 2017).

The allostatic load model proposes that by measuring the interactions of primary and secondary mediators, biomedical advances can be made in the detection of individuals at high risk for the tertiary outcomes (Juster et al. 2010). However, quantifying allostatic load at a biological level has represented a significant challenge, especially as the markers interact in a

non-linear manner with fluctuations in values (Juster et al. 2010). *Therefore, to date there is no straightforward or accepted gold standard for measuring or quantifying allostatic load.*

The simplest approach presented for predicting outcomes has been to divide values for each marker into quartiles and then give a score to anyone with a marker in the most extreme quartile, be it the highest or lowest, depending on the marker in question (McEwen 2015). The score of 1 is given for each marker in the most extreme quartile and the score summed for each individual. The original approach included 10 markers of multisystem biological dysregulation comprising four primary mediators—dehydroepiandrosterone sulphate (DHEA-S), urinary free cortisol, epinephrine and norepinephrine—plus the secondary outcome measures of systolic blood pressure, diastolic blood pressure, waist-hip ratio, high-density lipoprotein cholesterol, the ratio of total cholesterol to high-density cholesterol and glycosylated haemoglobin (Beckie 2012).

However, as there is no consensus on measurements, many different algorithmic formulations and statistical techniques have been applied, using around 30 different allostatic markers (Juster et al. 2010). The original set of 10 parameters was not meant to be comprehensive or a fixed measure of allostatic load but an attempt to operationalize allostatic load using available data. Subsequent work has therefore included more factors as they have become available. The goal is to optimize assessment by incorporating as many factors as possible, achieving an index as comprehensive as possible, reflecting the cumulative burden of physiological dysregulations across as many regulatory systems as possible (Seeman et al. 2010).

Apart from the quartile approach mentioned above, other models have been proposed, such as a *metafactor model*. It is an aggregate measure of six underlying latent biological sub-factors, with the metafactor capturing 84% of variance of all pair-wise associations among biological subsystems. Another method of analysis involves recursive partitioning to identify a set of pathways, composed of combinations of different biomarkers (McEwen 2015). A recent systematic review of allostatic load by Beckie stated:

> "The results revealed considerable heterogeneity in the operationalization of allostatic load and the measurement of allostatic biomarkers, making interpretations and comparisons across studies challenging" (Beckie 2012).

In a paper from 2015, McEwen also proposes that future work should use a standardized allostatic load battery along the lines of the quartile model described above, to facilitate comparisons across studies (McEwen 2015).

However, although standardization of the allostatic load battery would prove useful to compare studies, integrative research in the fields of medicine, genetics, psychology and sociology has shed new light on the connection between disadvantage or stress and health or health development, starting to dismantle the walls between these different fields of research. The next chapters will further describe this paradigmatic change.

2.10 An intriguing fusion of different scientific perspectives

Allostatic load – the conceptualization of the cumulative effect of stress mediated through complex and multidirectional biological processes - has enabled new and fruitful dialogues between natural scientists, epidemiologists and social scientists, and to an increasing extent, also the medical community. This is facilitated by the fact that the allostatic load can be addressed both from a biological and philosophical perspective, as well as a layman perspective. The basic ideas can be communicated by plain natural language, through the expressions “stress” and “wear and tear” on the body (McEwen and Getz 2013). The concept allostatic load is also very helpful to explain how social conditions “get under the skin” and contribute to the social gradient in health. It invites careful specification of both the social conditions under scrutiny as well as the biological processes by which they might become embodied (Krieger 2005). These social conditions may be manifested in physical, chemical, biological or social exposures/experiences. Their biological impact will in turn depend on the individual characteristics of the body. Exogenous exposures may also have shaped these characteristics in complex manners through the life-course which cannot simply be inferred from gene frequencies (Krieger 2005). In other words, the concept allostasis facilitates discussions about how genes and environment interact, and emphasizes the importance of considering the organism’ (or person’s) developmental *history.* A history which can be spelled out both in natural language (the person’s biography) or the natural scientist’s language of epigenetics.

2.10.1 How childhood adversity fits into the picture

Central to this framework is an increasing interest in the extent to which *early* experiences and exposures are biologically embedded with a potential for *lifelong* consequences. In their 2009 article in *JAMA*, Shonkoff, Boyce and McEwen explored the scientific validity of the proposition that reducing significant disadvantage early in life might be a powerful strategy for reducing the population-level burden of chronic morbidity and premature death (Shonkoff et al. 2009). They state:

> "For much of the 20th century, adult conditions such as coronary heart disease, stroke, diabetes, and cancer were regarded solely as products of adult behaviour and lifestyles. By the century's end, however, an extensive body of evidence linked adult chronic disease to processes and experiences occurring decades before, in some cases as early as intrauterine life, across a wide range of impairments" (Shonkoff et al. 2009).

And further:

> "Investigators have postulated that early experience can affect adult health in at least two ways—by accumulating damage over time or by the biological embedding of adversities during sensitive developmental periods. In both cases, there can be a lag of many years, even decades, before early adverse experiences are expressed in the form of illnesses. If the damage occurs through a cumulative process, chronic diseases can be seen as the products of repeated encounters with both psychologically and physically stressful experiences. When exposures occur during sensitive periods of development, their effects can become permanently incorporated into regulatory physiological processes" (Shonkoff et al. 2009).

As previously outlined, a clear association has been documented between cumulative exposure to stressful experiences and an array of adult health conditions (Felitti et al. 1998) (see section 2.4.2). Examples of such latent effects of adversity during sensitive periods could be the effects of poor living conditions in early life, as Forsdahl discovered (Forsdahl 2002), or the association between low birth weight and several risk factors for heart disease and type 2 diabetes (Shonkoff et al. 2009).

In 2008, Bruce McEwen stated that early life physical and sexual abuse carried a life-long burden of behavioural and pathophysiological problems, including an increased proinflammatory tone 20 years later. Changes can as well be seen in the brain structure of people growing up in cold and uncaring families (McEwen 2008). In 2011, McEwen published a review article with Andrea Danese, a scientist in psychobiology at King's College in London, on childhood adversity and allostatic load. There they described the

biological embedding of adverse experiences through allostasis. They stated that the most consistent neurobiological and behavioural findings in children exposed to adverse experiences seem to be linked to impaired prefrontal cortex functioning, causing deficits in executive function and behavioural problems with rapidly shifting attention, impulsiveness, and increased motor activity. Neuroendocrine findings suggest that maltreated children exhibit chronic activation of the HPA axis and blunted response to psychosocial stressors. Again, they stated that abused individuals tend to exhibit elevated inflammation levels. Similar changes could be found in adults with a history of childhood maltreatment. However, the response to psychosocial stressors through the HPA axis was either blunted in those with no current psychiatric disorder or heightened in those with current psychiatric disorder (Danese and McEwen 2012).

A further updated, detailed discussion about the relationship between adversity-induced alterations in brain structure and connectivity on the one hand and diagnosed psychopathology on the other, is beyond this thesis. However, I note that Harvard scientist Martin Teicher and co-workers recently wrote in detail about what is currently known on the subject (Ohashi et al. 2017). In short, the relationship between adversity, brain changes and psychopathology appears to be very complex (or complicated) and currently defies individual, clinical prediction. However, Teicher's group does not hesitate in saying that:

> "Maltreatment is an important factor that needs to be taken into account in studies examining the relationship between network differences and psychopathology" (Ohashi et al. 2017).

To date, there are not many empirical studies on the association between childhood adversity and allostatic load. In a prospective study from 2015, Widom et al. examined whether child abuse and neglect predicted allostatic load. For this purpose, they used nine physical health indicators. In a 30-year follow-up, they found that abuse and neglect in childhood predicted allostatic load in middle adulthood (Widom et al. 2015). Even though allostatic load is still an unknown subject to many if not most medical professionals, the knowledge seems to be gaining rapid momentum.

In 2012, the American Academy of Paediatrics issued a policy statement on early childhood adversity and toxic stress. It stated the following:

> "Advances in a wide range of biological, behavioural, and social sciences are expanding our understanding of how early environmental influences and genetic predispositions affect learning capacities, adaptive behaviour, lifelong physical and mental health, and adult productivity…Paediatricians are now armed with new information about the adverse effects of toxic stress on brain development, as well as a deeper understanding of the early life origins of many adult diseases. As trusted authorities in child health and development, paediatric providers must now complement the early identification of developmental concerns with a greater focus on those interventions and community investments that reduce external threats to healthy brain growth" (Garner and Shonkoff 2012).

2.10.2 An overarching concept: The biology of disadvantage

Beyond childhood adverse experiences, the wider environment of socioeconomic disadvantage has been a key theme in research on allostasis, recently termed "the biology of disadvantage" (Adler and Stewart 2010). Earlier epidemiological work, such as the Whitehall Studies, has shown that the association between socioeconomic position and future disease is strong, even after adjusting for measurable behavioural factors (Marmot et al. 2001). Regarding the biology of disadvantage, Nancy Krieger says the following, regarding embodiment:

> "Embodiment reminds us we cannot neatly parse our social experience and their cumulative impacts on any one or several disease processes. In particular, it highlights the strong likelihood of socially patterned confounding affecting study of exposure-outcome associations in observational studies. For example, considering the public health problem of increased risk of hypertension in African Americans compared with white Americans, "embodiment" reminds us that a person is not one day African American, another day born low birth weight, another day raised in a home bearing remnants of lead paint, another day subjected to racial discrimination at work, and still another day living in a racially segregated neighbourhood without a supermarket but with many fast food restaurants. The body does not neatly partition these experiences—all of which may serve to increase risk of uncontrolled hypertension, and some of which may likewise lead to comorbidity, for example, diabetes, thereby further worsening health status" (Krieger 2005).

In 2012 Gruenewald et al. published an article on the association between socioeconomic disadvantage and allostatic load later in life. They measured socioeconomic disadvantage in childhood and twice in adulthood and found the highest level of allostatic load in those with persistent socioeconomic adversity both in childhood and adulthood. However, childhood socioeconomic adversity was found to have an independent association with adult allostatic load as well (Gruenewald et al. 2012). Through the biology of allostatic overload, McEwen has described how low socioeconomic position has correlated with smaller hippocampal volumes and a reduction in prefrontal grey matter (McEwen 2012).

In 2010, Kiecolt-Glaser et al. summarized existing evidence linking the quality and quantity of relationships with gene expression, intracellular signalling mechanisms and inflammatory biomarkers. They stated that a close link between personal relationships and immune function is one of the most robust findings in the literature on psychoneuroimmunology (Kiecolt-Glaser et al. 2010). Troubled early relationships have been linked to attachment insecurity, dysregulated autonomic and HPA function, poor adult relationships, more depressive symptoms, poor health behaviours, and a proinflammatory epigenetic phenotype (Fagundes et al. 2011).

The science of epigenetics is becoming ever more prominent relative to allostatic load and the biology of disadvantage (McEwen 2015, Naess and Kirkengen 2015). Furthermore, it has been shown that cortisol reduces the activity of telomerase, causing increased shortening of the telomeres (Blackburn and Epel 2012). In a commentary in *Nature* in 2012, Epel and Blackburn state:

> "We now have three pairwise links involving three factors: stress with telomere shortening; stress with disease risks; and telomere shortness with risks for these diseases. It is hard to avoid the interface that at least one of the ways stress causes chronic diseases is by shortening telomeres" (Blackburn and Epel 2012).

They furthermore say:

> "…what is new is the wealth of evidence demonstrating that telomeres powerfully quantify life's insults. They are shorter in people who were exposed to adversity as children, and shorter still for each year a person spends depressed, caring for a sick child, being abused and so on. Telomeres send one more signal—from the tips of our chromosomes—that unmanageable social and physiological stress, especially during early life, is as insidious as smoking or too much fast food" (Blackburn and Epel 2012).

2.10.3 On "gains and drains"

Based on the "wear and tear" metaphor, the concept of allostatic load, as seen above, can effectively accommodate knowledge pertaining to the pathogenic impact of socioeconomic disadvantage, adverse childhood experiences and existential hardships. However, if looking at the concept from the perspectives of adaptation and resilience, evidence of restorative (or *salutogenic*) factors can also be encompassed (Getz et al. 2011). Allostatic load could therefore, in plain language, be described as a measure of balance or imbalance between what

constitutes *gains* and *drains* for a given individual, as Anna Luise Kirkengen so elegantly put it (Kirkengen 2010).

Salutogenic factors, or *gains*, could be factors such as trust, belonging, respect, nourishment, care, honour and pride, described as the healing physiology of meaning, belonging and trust (Kirkengen 2010) (see section 2.6). These factors serve as important counteraction to stress, possibly making what might have been toxic stress to the individual more tolerable. On the other side of the scale are factors inducing pathogenesis, or *drains,* such as threat, betrayal, isolation, neglect, humiliation, guilt and shame—factors described above as parts of the biology of disadvantage.

The balance between these groups of factors is delicate, and the strength of the arms of the scale differs widely between individuals. What strongly shifts the balance for one person might not do so for another. I mentioned earlier how resilience affects this balance, but other effects stem from the basic definition of stress as environmental demands exceeding people's *perception* of their ability to cope. This brings us to the next chapter. How can we best approach and evaluate the effects of stress, trauma and disadvantage for the individual patient in a daily clinical setting?

2.11 Objective and subjective evaluation of health, stress and disease

In this chapter, I will gradually zoom in on previous research with direct or indirect relevance to my empirical work in papers II and III. Both papers involve survey questions which address very personal and subjective experiences; the respondent's global view of her or his own childhood (Paper II) and a sense of 'existential unease' in everyday life (Paper III). Both these approaches are new, and thereby in need of justification. In the following, I will present other strands of research which I believe have considerable relevance to the approaches we applied.

The traditional biomedical approach primarily rests on a (presumably) objective evaluation of health and disease. It grants subjective experience only a supplementary status. Likewise, measurements of stressors deemed possibly harmful to health have mainly been objectively measured in terms of categorical exposures, describing adversity, violence, abuse, and other

types of stressful events. However, calculating the impact of predefined *events* as deviations from the epidemiological norm does not capture the potentially wide range of subjective and sociocultural meanings inherent in human experience (Mjolstad et al. 2013). As Mjølstad et al. described in 2013:

> "The approach provides no explanation of how experiences may be categorized as having equal impact and yet affect individuals differently, which can limit healthcare professionals' capacity to identify, appraise and address the health impact of existential experience and may ultimately lead them to employ medical interventions that prove ineffective, counterproductive or even harmful. An experience is always about something, for a specific person situated in a given context, inextricably linked to a subject, each experience is informed by and integrated with previous experiences" (Mjolstad et al. 2013).

As McEwen had already described in 1998, and as discussed here in earlier chapters, how a person *perceives* a given situation as a threat, be it physical or psychological, is foremost what determines a person's physiological and behavioural responses. In a highly simplified version, the response can be fleeing, fighting or cowering in fear (McEwen 1998). Subjective stress, as opposed to objectively measurable environmental stress, has likewise been correlated with higher allostatic load (Clark et al. 2007). In an article from 2007, Clark et al. compared caregivers' environmental and psychological stress in a two-year longitudinal study. They found that the respondents' psychological stress (subjectively determined) was a better predictor of primary mediators of allostatic load than environmental stress (presumably objectively assessed). Furthermore, the primary mediators related to allostatic load rose with time for caregivers, but not for non-caregivers (Clark et al. 2007).

In an article in 2010, McEwen describes the effect of perceived stress as follows:

> "For example, chronic experience of low SES at the individual level could involve enduring financial hardships, a sense of insecurity regarding future prosperity, and the possible demoralizing feelings of marginalization or social exclusion attributable to comparative social, occupational, or maternal disadvantage. Further, an individual's perception of her or his relative standing or ranking in a social hierarchy, formally termed subjective social status, may affect an individual's pattern of emotional, behavioural and physiological reactivity to and recovery from life stressors, consequently impacting risk for ill health" (McEwen and Gianaros 2010).

Accumulating evidence is showing ever more clearly that subjective experience and perception are of fundamental biological relevance (McEwen and Gianaros 2010, Ulvestad

2012). This seems to hold true in many contexts, as will be further described in the following sections.

2.11.1 Subjectivity in research: The predictive power of Self-rated health

Health and illness are subjective experiences. To the extent such experience can be mapped on a scale, it must be interpreted in a different manner than a scale pertaining to a well-defined and thereby more "objectifiable" disease. In addition, philosophers remind us that people can experience good health in the presence of even major diseases, just as much as they can feel illness in the absence of any biomedically acknowledged disease (Nordenfelt 2006). Health and illness are in other words relative states, defined by each person, as a result of his or her evaluation of physical, emotional, social and cognitive domains (Sturmberg 2012).

Early in the 1990s the value of self-rated health as an independent factor predicting mortality became clear (Waller 2015). Since then, the independence of self-rated health as a powerful predictor for disease and mortality has been extensively documented. A substantial body of international research has reported the item to be significantly and independently associated with specific health problems, such as cardiovascular disease, diabetes and psychiatric disorders, use of health care services, changes in functional status, recovery from episodes of ill health, mortality, and respondents' sociodemographic characteristics (Bowling 2005). Furthermore, the relationship between self-rated health and mortality persists even when adjusting for more objective indicators of health, such as multimorbidity biomarkers or functional abilities (Schnittker and Bacak 2014). Schnittker and Bacak thus stated in 2014:

> "This unusually robust relationship is surprising if one believes self-rated health is based on individual perception rather than objective assessment or that individuals systematically misreport their health in ways that dilute its value" (Schnittker and Bacak 2014).

In the same article the authors speculate whether the reason could be, at least partly, that when asked to rate their health, individuals consider a more inclusive set of factors than they would do in a questionnaire with more fixed questions regarding health, or during a routine medical examination (Schnittker and Bacak 2014). Their study aimed to show the change in the correlation between self-rated health and mortality over 22 years, from 1980 to 2002. I find their reasoning very relevant to this introduction:

> "If the validity of self-rated health is premised on accurately evaluating the many relevant dimensions of health, it is likely that the relationship between self-rated health and mortality has changed over time. If so, however, it is not entirely clear how the relationship has changed (…) Some scholars fear, for example, a growing contamination of self-rated health by the widespread medicalization of seemingly superficial conditions or by potential overdiagnosis more generally. Expectations for health have generally increased over time, meaning individuals set a lower bar for reporting "poor" health. Furthermore, it is increasingly difficult to reach a cultural consensus regarding what is or is not disease, potentially allowing assessments of poor health to include a variety of symptoms only weakly related to disease and mortality. In this light, individuals may be objectively healthier than before but feel sicker and deflate their self-rated health accordingly" (Schnittker and Bacak 2014).

However, the authors found the marker self-rated health to be a stronger predictor of mortality in 2002 than in 1980, leading to a *wider gap* in survival between those reporting good health and those reporting poor health. They conclude that the reasons for discounting individuals' subjective assessments when it comes to health are getting weaker (Schnittker and Bacak 2014).

In 1983, Kaplan and Camacho published an article proposing that self-rated poor health could be an encompassing concept explaining the possible links of social isolation, negative life events, job stress and other psychosocial stressors to mortality (Kaplan and Camacho 1983). This has since been much debated. Current literature points more strongly toward it being independent of other psychosocial factors (Waller 2015). Studies have however linked self-rated health to social capital, low education and working conditions (Waller 2015). Furthermore, low self-rated health has been associated with higher allostatic load (Hasson et al. 2009, Vie et al. 2014). A Norwegian study from the HUNT material measured self-rated health in adolescence and again 11 years later in young adulthood. The results showed that self-rated health was relatively stable through this period, and poorer self-rated health in adolescence was related to higher allostatic load at follow up (Vie et al. 2014).

Research on the theme of self-rated health has documented an apparent contradiction in people with "objectively" defined poor health reporting good self-rated health or quality of life. Researchers have termed this *the well-being paradox* and have at least partially attributed it to resilience (Netuveli and Blane 2008).

2.11.2 Stress as a subjective experience

As previously explained, the concept of allostatic load has been used to categorize stress according to its toxicity (Shonkoff et al. 2009). Exposure to chronic stress is deemed to possibly have the most toxic effects as it is most likely to result in long-term or permanent emotional, physiological, and behavioural dysregulation. These, in turn, influence susceptibility to disease and its course. This holds true for stressful events persisting over a long period (such as caring for a sick spouse) or brief focal events that some people continue experiencing as overwhelming, long after they have ended (such as sexual violation) (Cohen et al. 2007). However, much less is known about the exact types of stressors that can cause this type of toxicity—or, on a philosophical note, whether there are any exact types.

As previous sections have repeatedly stated, the strongest predictors are those most extensively researched as being detrimental to health: childhood violence, death of a close relative (child or spouse) or sudden threats to life (Felitti et al. 1998, Chen et al. 2015a, Chen et al. 2015b, Shen et al. 2016). However, far less is known about the effect of subtle, yet long-standing, challenges impacting human physiology and its predisposition to disease, although researchers have increasingly examined these factors in recent years (Damjanovic et al. 2007, Gallagher et al. 2009, Steptoe et al. 2009, Berger and Sarnyai 2015). In the following, I will mention some studies that imply a certain relevance for our idea that subtle "existential unease" might represent a pathogenic factor over time:

Recent studies show, for example, the pathogenic impact of low self-esteem (Trzesniewski et al. 2006), unfairness (De Vogli et al. 2007), lack of well-being (Steptoe et al. 2009, Keyes and Simoes 2012), work dissatisfaction (Faragher et al. 2005), loneliness (Holt-Lunstad et al. 2015), lack of social relationships (Holt-Lunstad et al. 2010), subjective social-evaluative threat (Lehman et al. 2015) and anger (Tsenkova et al. 2014) on impairing health. A perceived lack of purpose in life has recently been connected to allostatic load (Zilioli et al. 2015, Cohen et al. 2016), as has compromised sleep quality (Zisapel 2007, Juster and McEwen 2015, McEwen and Karatsoreos 2015).

An increasing amount of literature has emerged on so-called perseverative cognition (i.e. continuous thinking about negative events) and worries (Ottaviani et al. 2016) as well as *ruminations* (i.e., "repeatedly going over the same events in your mind") which is a behavioural mechanism linked to worries and anxiety. Studies have shown that ruminations,

even about moderately painful but non-traumatic life events, are connected to biological changes (McCullough et al. 2007). Post-stress rumination has also been connected to HPA axis responses to repeated acute stress, possibly mediating maladaptive stress response patterns (Zoccola et al. 2011, Gianferante et al. 2014, Zoccola and Dickerson 2015).

Subjective social status is a concept referring to an individual's *perception* of his or her own position in the social hierarchy. It is related to objective socioeconomic status in as much as the socioeconomic resources people possess form the basis for their judgement about their social standing in a given society or community (Demakakos et al. 2008). It has been shown that subjective social status is significantly related to many health outcomes, and that sociodemographic characteristics or objective socioeconomic status indicators could only partially account for this relationship (Prag et al. 2016). It has therefore been suggested that subjective social status might capture dimensions of social status that objective indicators of socioeconomic status do not (Demakakos et al. 2008).

What the evidence suggests, then, is that whether stress becomes toxic does not necessarily depend on the "objective" *type and intensity* of the stressors present but, as described above, just as much on the individual's perception of those stressors in relation to her or his complex human existence. This notion is important to the clinical setting, pointing out once more the importance of the patients' own perspective and the clinician's ability to connect with the individual in front of her. By comparison, an evaluation based on pre-defined categories might be less valid.

2.12 Gathering the strands and formulating the research hypotheses

The introduction to this thesis has been quite long. At the same time, it covers major, comprehensive and important concepts and theories upon which the research hypotheses are built. Beyond justifying my own research project, I find the material to be of fundamental relevance for general practice and medicine in general.

As outlined in the chapter on the origins and focus of the thesis, the extensive literature on multimorbidity published in the last few years slightly changed my original view of the problem. It has been documented beyond any doubt that multimorbidity is extremely

prevalent, in fact "the new norm," especially in the primary health care setting. Optimising and managing care of multimorbid patients, as well as reducing fragmentation, increasing personal contact and improving health care utilisation are enormous tasks. These tasks will mostly be the family physician's responsibility. It is therefore particularly important to document and – ultimately – understand this phenomenon sufficiently. At the start of the PhD process, no literature existed on the prevalence or patterns of multimorbidity in a Nordic setting. Since then a handful of papers have appeared.

However, as mentioned briefly at the end of the chapter on multimorbidity, as a quantitative, disease-oriented measure, multimorbidity at least partially mirrors the reductionist, biomedical approach to disease (Boeckxstaens et al. 2016). One could therefore speculate that multimorbidity is, to some extent, an artefact of this same fragmentation. When describing the peculiar increase in the prevalence of multimorbidity from 2003-2009 in Canada, the authors did not take this possibility into account when discussing their results (Pefoyo et al. 2015). We can also see that this speculation has not been researched or documented in the literature up to this point.

I argue that the artefact could be twofold. First, in line with literature on medicalization and overdiagnosis, the extensive focus on neatly defined risk factors and objectively approachable disease accounts for part of the problem: More testing leads to more findings. Lowering of thresholds leads to more people defined with pathology.

Second, symptom-based disorders and illnesses, in line with medically unexplained symptoms, are often divided by organs or muscle groups. Thus, for example diffuse, widespread pain could be diagnosed as many different diseases in one person.

When examining the literature on the disease patterns of multimorbidity, this becomes even clearer. The most prominent patterns are cardio-metabolic (mainly risk factors) and musculoskeletal (mainly symptom-based diagnoses). The third prominent pattern is psychiatric. We could therefore be crystalizing most of the problems of the Knidian biomedical approach to disease in the phenomenon of multimorbidity.

I am definitely not suggesting that the problem of multimorbidity does not exist. Far from it. It is very real. Based on experience from primary health care, as I mentioned earlier, most of

the patients I see on a regular basis do have multimorbidity in one form or another. Furthermore, they are very often dealing with difficult life situations as well. Therefore, in the Koan—or general practice—approach to the problem, the main reflections at the beginning of the PhD process were to see whether these difficult life situations could possibly play a part in the development of multimorbidity.

When moving away from the fragmented approach and looking generally at the wider picture of a phenomenon, it is important to look at the aetiology. To date, this step has seldom been taken regarding multimorbidity. Basic science researchers like McEwen had suggested that adversity might lead to multimorbidity before our research group started this project. Medical multimorbidity researchers, however, have paid far less attention to this link. One exception is a very recent discussion paper by Australian GP researcher Joachim Sturmberg and colleagues who conceptualize multimorbidity as the manifestation of network disturbances (Sturmberg et al. 2017).

Based on personal clinical experiences from myself and co-workers, in combination with existing literature at the start of the PhD, the main question of this project has since its beginning addressed potential common causal roots of multimorbidity. Could difficult and demanding life situations, through their effects on the physiological adaptation systems and human brain and body, represent a common causal pathway to development of multimorbidity? Is it relevant to add a new metaphor beside the fragmented "silo" approach to disease, *a boiling volcano of biological perturbations related to overtaxation of the stress response systems?* A volcano erupting in the form of seemingly different but nevertheless linked diseases, in accordance with the individual's inherited or acquired biological vulnerabilities, and statistically speaking earlier than the person's chronological age would otherwise suggest?

2.12.1 A note on the development of the literature in parallel with this thesis

In this introduction, I have presented an array of research from a wide range of milieus which I believe strengthen the main hypothesis of this thesis. Much of the research is however quite recent, published later than the start of this project. As explained in the opening of the thesis, none of the reported literature has led to changes in the overall design and methodology of this project. It has simply strengthened the rationale for the hypothesis. I therefore decided to

present it here in the background section. Alternatively, all the supportive material could have looked impressive as part of the discussion of the project results, but I decided to devote the discussion part of this thesis to more critical matters.

When this is said, I find it of interest to reflect on the chronological development of the literature upon which this thesis is based (i.e. literature published before 2010), or by which it is supported (more recent literature). First, I became aware of the major epidemiological research, set out in section 2.4, mainly by Marmot, Felitti and Kirkengen. It describes how adverse childhood experiences, on the one hand, and socioeconomic adversity and work-related social influences, on the other, could detrimentally affect future health. Second, as described in sections 2.7 and 2.9, there is the concept of allostatic overload as a means of inscribing this adversity into human biology through embodiment.

The references in section 2.9 show that the connection between the epidemiology of adversity and allostatic load was just beginning to emerge in 2010. McEwen's publication on stressful early life experiences on the human brain and body function was published in 2008 and the JAMA publication which viewed childhood adversity in a public health perspective by Shonkoff, Boyce and McEwen had come in 2009. Since then, an increasing volume of relevant literature on the subject has been published, in parallel with my research.

Furthermore, it has been of great interest to observe how the research literature has evolved during recent years, moving from adversities in childhood in direction towards adulthood, and from explicit adversity to more subtle stress factors. Finally, as discussed in the last chapter, the focus has also moved from objective measures in direction of subjective self-reports. However, to my knowledge, no research has so far addressed subjective and subtle stress in combination, and certainly not from the perspective of multimorbidity.

From a contemporary perspective, it can be said that our hypothesis represents an example of what has more recently become a scientific buzz term, namely a *life course approach* to health and disease development. As explained in a glossary by Kuh et al., life course epidemiology is the study of "long-term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood and later adult life" (Kuh et al. 2003). The aim of a life course approach is to elucidate biological,

behavioural, and psychosocial processes that operate across an individual's life course, or across generations, to influence the development of disease risk (Kuh et al. 2003).

This approach harmonizes well with my theories. However, the approach required simplification in this thesis because of the database I have been working with, as explained in *Methods* and *Discussion*.

As shown in Figure 4, the *main hypothesis* in this thesis is that existentially demanding life circumstances, whether in childhood or adulthood, would lead to allostatic overload that would then lead to the development of multimorbidity. However, as we know, life is not so simple. These circumstances, likely through allostatic overload firing back on the brain, but possibly also through other mechanisms, can lead to destructive behavioural and relational patterns, such as overeating, smoking, less physical activity and social isolation. These factors can both increase the allostatic overload, thus increasing the likelihood of multimorbidity—or they can directly influence disease development, such as through the carcinogenic effects of smoking. Finally, multimorbidity, which causes morbidity burden on the patient, increases allostatic load and leads as well to destructive behavioural patterns—which can be described as existentially demanding circumstances.

However, for simplification in this thesis, we will be focusing on the first and main pathway through the model.

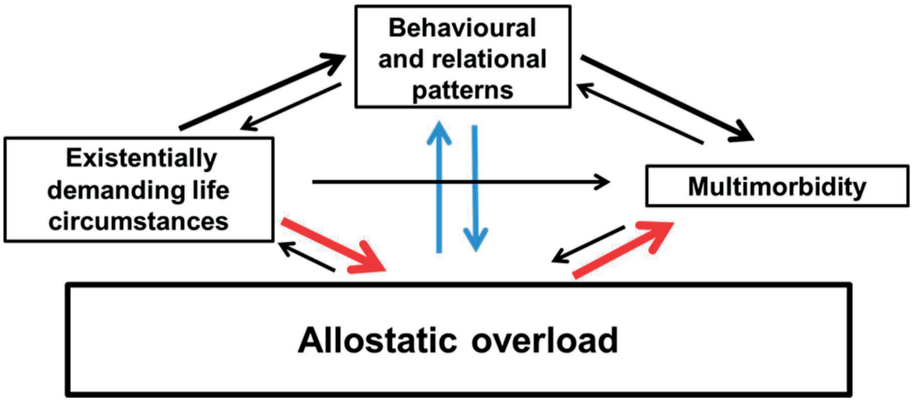

Figure 4. Theoretical model of disease development as hypothesized in this thesis. The main hypothesis is that existentially demanding life circumstances, lead to multimorbidity through the process of allostatic overload.

3 Aims of the study

While the theoretical reflections and research hypothesis for the thesis are quite broad, the research questions and aims were more tightly defined and concrete. They reflect the knowledge level and possibilities deemed available at the start of the project, relative to the database I would be working with. The paramount objectives were to contribute new knowledge about multimorbidity prevalence and disease clustering, and to investigate the phenomenon of multimorbidity from an innovative perspective, based on the concept allostasis and the impact of life-course adversity. To formulate my research questions, I drew on theories and evidence from several different fields of science. I thereby hoped to be able to shed new scientific light on some of the most challenging clinical scenarios of general practice, i.e., complex disease clustering. My clinical experience, as well as the rapidly evolving literature on the links between life experiences and health, highly motivated me to investigate potential links between patients' biographies and biology, based on a comprehensive population database.

To sum up, the general aims of the project were to analyse and describe the prevalence and patterns of multimorbidity in a general Norwegian population and explore possible associations between multimorbidity and challenging or adverse life circumstances, both in childhood and adulthood, in light of the concept of allostatic load.

More specifically the aims were to:

- document the prevalence and potential clustering patterns of multimorbidity in a general Norwegian population (Paper 1)
- estimate the association between subjective childhood difficulties and adult multimorbidity (Paper 2)
- explore possible prospective associations between stressful or existentially demanding circumstances in healthy adults and development of multimorbidity later in life (Paper 3)
- evaluate signs of allostatic overload in adults with regard to self-rated experiences of childhood (Paper 2)

To meet these objectives, three papers were written. The aims for each were as follows:

Paper I:

The aim of this paper was to describe epidemiologically the prevalence of multimorbidity and complex disease clustering in a general population, looking specifically at different patterns of diseases. Theoretical reflections on allostatic overload as a possible underlying mechanism in complex disease development were formulated.

Paper II:

The aim was to explore the association between subjective global experience of childhood and multimorbidity in adult life, taking into account the possible effect of behavioural factors as well as markers of allostatic overload in adulthood.

Paper III:

The aim of this paper was to explore prospectively associations between subjective subtle stress factors or demanding circumstances (which we termed *existential unease*) in healthy adults and development of multimorbidity 11 years later, both with regard to individual items indicating unease and a cumulative score of items, as a proxy for greater allostatic load.

4 Material and methods

4.1 The Nord-Trøndelag Health Study

The data underlying this thesis are derived from the *HUNT Study* (Helseundersøkelsen i Nord-Trøndelag). It is a renowned population database for medical and health-related research (Krokstad et al. 2013). To date, three phases of the study have been completed, HUNT1 in 1984-86, HUNT2 in 1995-97 and HUNT3 in 2006-2008. Originally, the study was set up primarily to address hypertension, diabetes, screening of tuberculosis and quality of life (Krokstad et al. 2013). However, the scope has expanded greatly over time, and a biobank has been established. The database now contributes knowledge regarding health-related lifestyle, prevalence of somatic and mental illness and disease, health determinants and associations between disease phenotypes and genotypes (Krokstad et al. 2013).

Data collection in the HUNT study consists of questionnaires, interviews, clinical examinations and non-fasting blood samples. The information involves demographic factors, habits, personal and family histories and social environment in addition to symptom- and disease-focused questions. Furthermore, sub-populations have gone through more thorough testing, such as spirometry, bone density measures, etc. Participants may be grouped into families, followed up longitudinally between surveys or linked to several national health registers, if given approval from the Norwegian Data Inspectorate (Krokstad et al. 2013).

Every adult (over age 20) living in the county of Nord-Trøndelag, Norway, was invited to participate in each phase, with 89.4% participation in HUNT1 (77 212 participants), 69.5% in HUNT2 (65 237 participants) and 54.1% participation in HUNT3 (50 807 participants). The decline in participation rate between studies is in accordance with most other population-based studies (Krokstad et al. 2013). In total, 37 071 individuals took part both in HUNT2 and HUNT3, that is 73% of the HUNT3 population (Krokstad et al. 2013). Further information on the HUNT Study can be found at: http://www.ntnu.edu/hunt.

4.2 Study population applied in this thesis

Papers I and II in this project are based on participants in the HUNT3 study. Paper III is a follow-up study, based on individuals who took part in both HUNT2 and HUNT3. In general, the HUNT population has been described as ethnically homogenous, dominated by

individuals of Nordic origin, and has been regarded as being fairly representative of the Norwegian population regarding demography, morbidity and mortality (Vikum et al. 2012). However, being a rural area and lacking large cities, educational levels and mean income are somewhat lower and the population more homogenous than in urban areas, in terms of ethnicity and social gradients (Krokstad and Knudtsen 2011). Regarding health care utilisation, no social gradient is found for primary health care or inpatient care, but inequity appears regarding use of private medical specialists and hospital outpatient care (Vikum et al. 2012).

In all three HUNT surveys, a higher percentage of women than men participated. In HUNT3 it was 49.5% of invited men and 58.7% of invited women. The highest participation in HUNT3 was in the middle-aged and elderly groups (50-79 years)—over 60% for men and around 70% for women. There was lower participation in the oldest (80+) and youngest (20-29) age groups (Krokstad et al. 2013). Regarding questionnaire answers, 95-99% of the questions in questionnaire 1 were answered, with the highest rate of missing answers for life style questions. For questionnaire 2 response rates varied from 73-80% (Langhammer et al. 2012).

Due to possible selection bias in open invitation studies, and especially considering the decreasing participation rate in HUNT3, a nonparticipation study was done. The nonparticipation questionnaire was answered by 6.9% of the men and 7.9% of the women originally invited to participate in HUNT3 (Langhammer et al. 2012). The most common reason given for nonparticipation was lack of time or not receiving the invitation. In the oldest age group, many reported being too ill to participate. In general, nonparticipants had higher prevalence of common chronic diseases, such as cardiovascular disease, diabetes and psychiatric disorders (a pattern confirmed by primary health care records). Registry data showed that nonparticipants had lower socioeconomic status and higher mortality than participants (Langhammer et al. 2012).

For the present study, different eligibility criteria were applied in each of the papers, based on the group of focus each time, especially regarding age. Details regarding inclusion are found in each paper separately, but Table 1 presents a summary, along with the variables examined and statistical analyses made.

4.3 Definition of multimorbidity

In accordance with international consensus (WHO 2008, Mercer et al. 2009), multimorbidity was defined as two or more coinciding chronic diseases or conditions in the same individual. The analyses for papers I and II included 21 chronic diseases or conditions in the definition, while paper III, on grounds of comparison between HUNT2 and HUNT3, included 17. There has not been a consensus regarding the number of conditions needed for a good evaluation of multimorbidity, as discussed earlier.

The conditions included are listed in Appendix 1 along with the questions in the HUNT questionnaire from which they were drawn. Of the 21 conditions, 12 were self-reported in response to the question: "Have you had or do you have the following medical condition?" Cardiovascular disease was combined in one group and included the following: a history of myocardial infarction, angina pectoris, heart failure, other heart disease and/or stroke. Hypertension was defined as a positive answer to the question. "Do you take or have you taken antihypertensive medicine?" and/or severe hypertension (systole ≥180mmHg and/or diastole ≥110mmHg) as a mean of measurements 2 and 3 at clinical examination if both were present, otherwise, measurement 2 was used. To avoid overestimation or double registration, the presence of self-reported CVD was used as an exclusion criterion, as the definition was mainly based on use of medication. Hyperlipidaemia was defined as total cholesterol above 7.0 mmol/L and/or triglycerides above 3.0 mmol/L. Chronic back pain was based on a report of having pain in the back or neck that had lasted more than 3 months during the last year. Thyroidal disease was defined as either hyper- or hypothyroidism; dental health problems as when the participant defined dental health as bad or very bad; gastro-oesophageal reflux as much heartburn/acid regurgitation during the last year and, finally, clinically relevant mental problems were defined as a positive answer to the global question: "Have you had or do you have mental health problems for which you have sought help?"

The four diseases that were not found in the HUNT2 questionnaire, compared to HUNT3, and were therefore not included in the definition of multimorbidity in paper III were: renal disease, COPD, psoriasis and dental health problems.

4.4 Allostatic parameters

As outlined in section 2.8, allostatic parameters have been classified as *primary* (biochemical mediators that regulate rapid adjustment), *secondary* (reflecting cumulative actions of primary parameters in a tissue/organ specific manner) and *tertiary* (emerging as clinical diseases or disorders) (Beckie 2012, McEwen 2015). The allostatic analyses in paper II included 12 secondary allostatic parameters; Height, waist circumference, waist-hip ratio, BMI, systolic and diastolic blood pressure, heart rate, pulse pressure, CRP, cholesterol, glucose and creatinine.

For the estimation of systolic and diastolic blood pressure, heart rate and pulse pressure, HUNT3 participants using antihypertensive medication or diagnosed with cardiovascular disease were excluded to avoid medication bias. Likewise, participants reporting diabetes were excluded from estimation of serum glucose. Similar precautions were not possible for cholesterol, as information on cholesterol-lowering medication was unavailable. The variables were presented as estimated means for each parameter individually but an allostatic load score for combined variables was not calculated.

In paper III, disease development in general and multimorbidity development in particular were considered relevant as tertiary indicators of allostatic overload with regard to the classification discussed above. While some of the conditions accounted for in the estimation of multimorbidity, such as hypertension and hyperlipidaemia, are more often classified as risk factors or secondary allostatic mediators, the global concept of complex disease clustering would be more relevantly defined as a tertiary parameter.

4.5 Self-reported experience of childhood

HUNT3 addressed the overall quality of the respondents' childhood with one single question, designed by members of our research team. It had not been applied before. It had five fixed response alternatives, referring to the respondent's subjective global perception of his/her childhood. The childhood question was phrased (in English translation): "*When you think about your childhood, would you describe it as: 'Very good-good-average-difficult-very difficult'*?" In the questionnaire, the question appeared after questions related to everyday topics, such as intake of dairy products and living with pets in childhood. It was not connected to any predefined adverse events during childhood. The question was worded with

respect to the local linguistic and cultural context, but it had not been through rigorous validation. Our research group therefore awaited the analyses with anticipation.

4.6 The concept of existential unease

Increasing number of publications are currently emerging which describe the effect of subtle, yet longstanding, challenges to human physiology and predisposition to disease. Furthermore, it is increasingly acknowledged that it is *subjective experience* or *perceived* stress that becomes biologically embodied, as discussed in section 2.11. However, the topic is challenging to explore in a scientifically valid manner.

Paper III represents an attempt to examine the impact of subtle, subjective stress, with a follow-up study from HUNT2 to HUNT3. Questions were selected from the HUNT2 questionnaires that were deemed to shed light on the respondents' evaluations of self, experienced purpose in life, well-being, and significant social relations. As noted by the US Centres of Disease Control and Prevention (CDC Homepage), the scientific literature contains a wide range of concepts related to the notion of health-related quality of life, such as well-being, flourishing, life satisfaction and happiness.

The HUNT2 survey was informed by contemporary theoretical frameworks from various domains, especially sociologist Pierre Bourdieu's theories concerning social and cultural capital (Bourdieu 1990, Rocco and Suhrcke 2012, Mackenbach et al. 2016), sociologist Aron Antonovsky's concept Sense of Coherence (Antonovsky 1993, Eriksson and Lindstrom 2006), and the psychological notions of self-esteem and well-being (Dobson et al. 1979, Robins et al. 2001, Pressman and Cohen 2005). The questions we included in Paper III were purposefully selected as being particularly indicative of an existentially, and thereby also biologically, demanding lifeworld. However, an established term that accommodated the research questions and the applied data set was not found.

Therefore, a new term, *existential unease,* was introduced to describe lack of self-esteem, well-being, meaning and/or social interrelatedness. The word "existential" points to Maurice Merleau-Ponty, an existential philosopher mentioned earlier, when describing the concept embodiment (section 2.6). My main hypothesis became that over time, *existential unease* in

the above-mentioned realms might contribute substantially to allostatic load and thereby to the development of complex, medical *disease.*

In total, 11 items were included in the analysis. Together they cover thematically related, but nevertheless distinct, perspectives. Two of the items, "being satisfied with life" and "having a positive opinion of oneself" stem from Rosenberg's Self-esteem Questionnaire, validated and predominantly applied in sociological studies (Dobson et al. 1979, Robins et al. 2001). The remaining nine questions were single-item questions. The list of questions is presented in Appendix 2 as they appeared in the HUNT2 questionnaire.

The response options for these questions were rearranged to have the reference group of the least stressful or most positive outcome presented at the top. For further analyses, response options were collapsed and binary variables were constructed when relevant. Three of the 11 items were originally binary with yes/no answers, but for the others, the two most unfavourable response options were combined to indicate existential unease. Finally, a summation of the binary variables was used as to indicate more distress or unease, and thus, hypothetically higher allostatic load.

4.7 Behavioural factors

Papers II and III described common behavioural factors, classically seen as potential confounding factors in epidemiological research. The factors were smoking, physical activity, and adult education. Smoking was defined as use of cigarettes, cigars and/or pipes daily. Physical activity was measured as a combination of light and hard exercise during the last year, measured in hours as no activity, less than three hours of light activity, more than three hours of light but less than one hour of hard activity and finally more than one hour of hard activity per week.

The HUNT database lacks direct data on socioeconomic status, so adult education was used as a proxy, defined as primary school, secondary education or university. In paper II, sleep problems were included as a possibly confounding behavioural factor, defined as difficulty falling asleep, waking up repeatedly during the night or waking too early and not being able to fall asleep again, several times per week for the last month.

To address possible confounding or recall bias by current undiagnosed depression at time of answering the questionnaires, the results in papers II and III were adjusted for possible depressive symptoms. Current depressive symptoms were defined as eight or more points for depression on the Hospital Anxiety or Depression Scale (HADS).

4.8 Missing data

Regarding the definition of multimorbidity, missing data on individual diseases was defined as negative for the condition in question. In paper II, participants with missing data on individual allostatic parameters were excluded in all logistic regression models. In paper III, missing data on individual unease factors, were defined as a neutral answer for the factor in question when doing analysis regarding summation of the binary factors. In papers II and III, missing data on behavioural factors were coded as an additional group for precise comparison between logistic models.

4.9 Statistical analyses

The SPSS statistical program was used for all analyses. Version 20 was used in paper I and II and version 22 for paper III. Thorough discussions of the statistical analyses performed in each paper follow below:

4.9.1 Paper I

Paper I was a cross-sectional analysis on prevalence and patterns of multimorbidity, mainly based on descriptive analyses. Participants aged 20-79 were included. The upper limit of 79 years was chosen due to lower participation rate in older age groups, and due to the extremely high prevalence of multimorbidity in the oldest age groups. The lower level reflects the youngest age at invitation to the HUNT Study. The age group 40-59 years was then selected specifically for further analyses on multimorbidity as participation rates were high in that age group but especially as this is the age group where prevalence of multimorbidity starts to increase significantly, without having the possible explanation of old age.

The prevalence of multimorbidity was estimated as described above and presented as age-specific as well as age-standardized according to the European standard (Petursson et al. 2009). Age standardized prevalence is presented to enable comparison between countries and

account for under-or overrepresentation for certain age groups in the study. Prevalence numbers of mental health problems were estimated in relation to somatic health problems and odds ratios (ORs) were generated for the association.

Simple association analyses were done on different patterns of multimorbidity for descriptive information. Associations were tested with Chi-square tests and odds ratios, with 95% confidence intervals generated.

4.9.2 Paper II

Paper II was a cross-sectional analysis evaluating the possible association between self-reported childhood experience on one hand, and adult multimorbidity and allostatic load, on the other. The age group 30-69 year was chosen for this paper. The lower limit was set at 30 due to underrepresentation of the youngest age group, with only 31% participation. The upper limit was set due to very high prevalence of multimorbidity in the oldest age groups that could possibly have confounding effects.

Descriptive analyses were stratified according to childhood experience. The categorical variables were expressed as frequencies with percentages and continuous variables as means with standard deviations. Differences between childhood groups with p-trends were estimated with the Mantel-Haenszel test for linear association and ANOVA test for linearity, as appropriate. The Mantel-Haenszel test for linear association was used as well to test if prevalence of multimorbidity followed a gradient from very good to very difficult childhood. Prevalence ratios (PR) of multimorbidity, with 95% CI, were calculated for each category of childhood experience with participants reporting a very good childhood as a reference group.

To assess odds ratios of multimorbidity according to childhood experience, binomial logistic regressions were used due to the binary nature of the multimorbidity concept. Different models were generated, adjusting for behavioural factors and allostatic factors, both individually and in combination.

Finally, parameters pertaining to allostatic load were analysed according to childhood experience for each gender. Means were estimated, with participants reporting a very good childhood as the reference group. Deviances from the mean according to each group of

childhood experience, as well as p-trend, were subsequently estimated with linear regression after adjusting for age.

To address possible recall bias associated with depression, multimorbidity analyses were also performed after adjusting for current depressive symptoms as discussed above. Multimorbidity and experience of childhood were also compared between depressed and non-depressed groups.

4.9.3 Paper III

Paper III was a prospective study with 11-year follow up between HUNT2 and HUNT3, examining the possible associations between existential unease and multimorbidity. Included participants had completed both phases of the study and were without multimorbidity at baseline (less than 2 chronic conditions). The age group 20-59 years at baseline was chosen, being then 31-70 years at HUNT3 when multimorbidity was assessed. This is at follow up same age group as in paper II.

Descriptive analyses were stratified according to the development of multimorbidity between the two phases of the study, with categorical variables expressed as frequencies and continuous variables as means with standard deviations. Assessment was made for possible multicollinearity between different unease variables, which appeared not to occur.
Poisson logistic regression for prospective data was used to estimate the relative risk of multimorbidity associated with each of the variables expressing unease. 95% confidence intervals were generated. The variables were analysed independently. All associations were adjusted for age and gender, the second model also adjusted for behavioural factors, and model 3 adjusted for current depressive symptoms as well.

The same method for Poisson regression was used when assessing the relative risk for binary variables, as well as for the variable summing all the binary factors of existential unease. Age, gender, smoking, physical activity, and education were adjusted for. Finally, the sum of binary variables for existential unease was grouped as 0, 1-2, 3-4 and 5+ and assessed with regard to developing increasing numbers of diseases as well as self-reported experience of childhood.

4.10 Ethics statement

Each participant in the HUNT Study signed a written consent regarding the screening and the use of data for research purposes. The study was approved by the Norwegian Data Inspectorate and the Regional Committee for Ethics in Medical Research (2010/2627-3).

Table 1.

Overview of methods for each paper.

	Paper I	**Paper II**	**Paper III**
Type of study	Cohort Cross-sectional Descriptive	Cohort Cross-sectional Associations	Cohort Prospective Associations
HUNT database	HUNT3	HUNT3	HUNT2-HUNT3
No. of participants	47 959	37 612	20 365
Inclusion criteria	20-79 years	30-69 years	20-59 years Non-multimorbid Participate in HUNT2+HUNT3
Variables	Multimorbidity Individual diseases	Multimorbidity Self-reported childhood Allostatic parameters	Multimorbidity Existential unease Self-reported childhood
Statistical methods	Descriptive Odds ratio Chi-square	Descriptive Mantel-Haenszel for linear association ANOVA Binominal logistic regression Linear regression	Descriptive Poisson regression

5 Results

The general aims of the project were to analyse and describe the prevalence and patterns of multimorbidity in a general Norwegian population and explore possible associations between multimorbidity and challenging or adverse life circumstances, both in childhood and adulthood, in light of the concept of allostatic load. This was done with the methods described in the previous chapter. Each paper had a different theme, and I therefore start by describing the results according to aims for each paper, followed by additional results. A more global summary of the results will be given in the next chapter on key findings.

5.1 Results according to aims, paper I

Paper I was a cross-sectional, descriptive analysis of the prevalence and patterns of multimorbidity.

First aim: *To document the prevalence of multimorbidity in a general Norwegian population.*

Data were analysed from 47 959 HUNT3 participants, aged 20-79 years. The prevalence of multimorbidity increased steadily from 14% among people aged 20, to 33% for people aged 40, 62% for those 60 years, and up to 77% for participants 79 years old. The overall age-standardized prevalence of multimorbidity in the age group, 20-79 years, was 42%, with 19% having two chronic conditions and 23% having three or more chronic conditions (see Figure 1 in paper I). Twenty-nine percent of this population had no chronic condition. There was a significant ($p<0.001$) gender difference, the total prevalence for men was 39%, compared to 46% for women.

Second aim: *To document potential clustering patterns of multimorbidity.*

The first step in this analysis was to document the prevalence of individual diseases. This was done for the selected age group 40-59 years, as explained in the methods section. The most common condition was chronic back pain, with a prevalence of 37.1%, followed by obesity 23%; hyperlipidaemia 20.2%; mental health problems 15.0%; hypertension 13.0%, and osteoarthritis 10.6%. The gender difference was most prominent in musculoskeletal

conditions and mental health problems being far more common among women, and cardiovascular disease and hyperlipidaemia being more common in men.

The next step was to examine the association of mental health problems to somatic health conditions. The results showed the association to be strongest in the youngest age group (20-39 years), where the OR increased from 1.5 (95% CI 1.3-1.7) in the presence of one somatic condition to 6.9 (95% CI 4.5-10.6) in the presence of 5 or more somatic health conditions. The results were similar in the age group 40-59 years. There OR went from 1.4 (95% CI 1.3-1.6) to 5.1 (95% CI 4.3-6.0). The association was much weaker in the oldest age group (60-79 years), where the OR rose from 1.0 for one disease to 1.3 (95% CI 1.1-1.6) for two diseases up to 2.8 (95% CI 2.3-3.5) in the presence of 5 or more diseases.

Finally, prevalence of multimorbidity was analysed in the age group 40-59 years with respect to single diseases. There the prevalence of multimorbidity was highest if musculoskeletal disease was already present. Index conditions were selected as representing diverse aspects of disease presentation and the degree of overlap illustrated by Venn diagrams. The overlap between any two of the selected diseases was significantly greater than expected by chance ($p<0.01$), the odds ratios ranging from 1.3 (95% CI 1.2-1.4) for the well-documented association of mental health problems and metabolic diseases (obesity and diabetes) to 3.5 (95% CI 3.1-4.1) for mental health problems and fibromyalgia.

5.2 Results according to aims, paper II

Paper II was a cross-sectional analysis evaluating possible associations between self-reported experience of childhood, on one hand, and adult multimorbidity and allostatic load, on the other.

First aim: *To estimate the association between subjective childhood difficulties and adult multimorbidity.*

Data from 37 612 HUNT3 participants, aged 30-69, were analysed according to self-reported experience of childhood. In total, 85.4% of the respondents characterised their childhood as very good or good, 3.3% as difficult and 0.8% as very difficult. In general, individuals

reporting a difficult or very difficult childhood were younger, more often female, smokers, with more sleep problems, less physical activity and lower educational level.

Respondents characterising their childhood as very good had a lower number of diseases, with 26.3% reporting no disease, compared to 9.5% and 4.2% for those reporting a difficult and very difficult childhood, respectively. The total prevalence of multimorbidity increased from 44.8% among respondents reporting a very good childhood to 77.1% among those with a very difficult childhood, with an age-adjusted prevalence ratio of 1.9 when compared to those reporting a very good childhood.

When looking at prevalence of individual diseases, the prevalence increased significantly with increasing degrees of childhood difficulty for all diseases, except hypertension and cancer. The increase was sevenfold for mental health problems, fourfold for chronic obstructive pulmonary disease and dental health problems, and more than double for fibromyalgia, gastro-oesophageal reflux disease, rheumatic arthritis and asthma.

Binominal logistic regression was done to model the OR of multimorbidity with regard to childhood experience, with 'very good childhood' as the reference. The crude model showed increased OR from 1.20, for those with a good childhood, to 5.08 (95% CI 3.63-7.11), for individuals reporting a very difficult childhood. Different models were made, adjusting for different possible confounding or mediating factors. When all twelve allostatic parameters were introduced to the model, the OR associated with a very difficult childhood declined from 5.08 to 4.73 (95% CI 3.30-7.68), with no effect on OR for the other groups of childhood experience. Behavioural factors combined had a stronger impact on OR than the allostatic factors, but when all factors were introduced into the model, the OR declined to 3.78 (95% CI 2.61-5.47) for the very difficult childhood group. This is further explained in paper II, especially *Table 2* and *Supplementary Table 2.*

Second aim: *To evaluate signs of allostatic overload in adults with regard to self-rated experience of childhood.*

The mean values of 8 of the 12 analysed allostatic parameters differed according to the participants' description of their childhood ($p<0.05$). Those reporting a difficult or very difficult childhood had, on average, shorter stature, larger waist circumference, higher waist

hip ratio and BMI, higher resting heart rate, lower systolic blood pressure, and lower pulse pressure, compared to the other groups. Females reporting a difficult childhood had significantly higher non-fasting blood glucose. Correspondingly, males had a statistically significant trend towards lower diastolic blood pressure.

5.3 Results according to aims, paper III

Paper III was a prospective study, with an 11-year follow up between HUNT2 and HUNT3 examining the possible association between existential unease and multimorbidity.

First aim: *To prospectively explore associations between existential unease, on one hand, and indications of general biological disruption, expressed through development of multimorbidity, on the other.*

Prospective data on 20 365 individuals that participated in HUNT2 and HUNT3 were analysed with respect to the development of multimorbidity between surveys. In total, 6 277 persons (30.8%) acquired multimorbidity during these 11 years. Those becoming multimorbid were on average older, more likely to be women and smokers, less physically active and had lower education.

Relative risks of developing multimorbidity were generated according to each of the eleven items indicating existential unease. The factors with the strongest association were “being dissatisfied with life”, “having a negative opinion of self”, “having financial worries”, “not feeling calm and good” and “poor self-rated health”, all having RRs above 1.4 for the subgroups, indicating the most distress when adjusted for behavioural factors.

The relative risks changed slightly after constructing binary factors from the unease items. In the binary model, “being dissatisfied with life”, “having sleep problems affecting work”, “not feeling calm and good” and “having financial worries”, all had a RR above 1.3.

When assessing by gender, the results were quite similar, except for “not having enough friends”, which was a stronger predictor for women and “boiling with anger but not showing it”, which was a stronger predictor for men.

Second aim: *To examine the same associations with a cumulative score of unease items as a proxy for greater allostatic load.*

Next, the relative risk of developing multimorbidity was evaluated in association with increasing numbers of unease factors. There was a dose-response association in RR from having one factor, RR being 1.18 (95% CI 1.11 to 1.25) up to RR 1.81 (95% CI 1.50 to 2.18) for six or more factors, the prevalence of multimorbidity being 26.7% for those with zero factors at baseline and linearly increasing up to 49.2% for those with six or more. Those with no unease factor were more likely to remain free from multimorbidity during follow-up, compared to those reporting unease. With an increasing number of unease factors, the prevalence of 2, 3 or 4+ diseases at follow-up became higher, with 2.8% among those with no unease factor having 4+ diseases, compared to 8.8% among those with five or more unease factors.

Finally, the number of unease factors was examined in relation to self-reported childhood experiences, with the purpose to link the themes of papers III and II. However, with the inclusion criteria for paper III being not multimorbid at baseline, more than half of all respondents who reported a difficult or a very difficult childhood were excluded, as they were already multimorbid. Those reporting a very good childhood in HUNT3 reported less unease factors in adult life, while the prevalence for higher numbers of unease factors in adulthood increased with the presence of reported childhood difficulties. Altogether 57.9% of those reporting a very good childhood reported no unease factor in adult life, compared to 28.1% of those with a very difficult childhood. Furthermore, 1.3% with a very good childhood had 5 or more unease factors, compared to 17.2% of those with a very difficult childhood. These results were published as Supplementary material to paper III.

5.4 Additional results

In the fall of 2014, I had a poster presentation at the conference *Preventing Overdiagnosis* in Oxford. The poster presentation was named *"Too many diagnoses – multimorbidity as a medical artefact?"*. It was based on HUNT3 material, the same population as described regarding paper I. The aim was to evaluate the prevalence of multimorbidity in relation to self-rated health. The results showed that most people with two or three diseases still identified their health as good, with around 60% of participants with 3 diseases reporting

their health as very good or good. With four or more chronic conditions, over 50% of participants reported their health being not so good, but still only around 6% reported their health as poor. The poster is presented in Appendix 3.

6 Key findings

In this study of a general Norwegian population, we found that multimorbidity is very common, with nearly half the population over 20 years of age having multimorbidity, according to the formal definition. The finding verifies earlier statements on multimorbidity becoming the norm for the adult population, with more people having multimorbidity than having no disease. The connection between somatic and mental health problems was strong, especially for the younger population. This association became stronger as the number of somatic health conditions increased.

Regarding patterns of complex disease clusters, the most common diseases made the most common combinations. When looking at the combinations of selected index diseases, all examined combinations occurred more often than expected by chance. The disease patterns transgressed the more conventional biomedical dichotomies, such as somatic/mental and organic/functional division, as well as the diagnostic categories within the specialized medical domains. This could pose a fundamental challenge to biomedicine's current way of conceptualizing risk, disease and treatment strategies.

When widening the scope from prevalence descriptions to considerations regarding possible aetiology, we found a clear association between self-reported childhood difficulties and adult disease burden. With increasing childhood difficulties, the prevalence of multimorbidity, as well as most of the eligible diseases and disorders, increased in a dose-response manner. Sleep problems, physical activity and smoking habits followed a similar trend. However, the cross-sectional study design did not permit direct, causal inferences.

When looking prospectively at the risk of developing multimorbidity with regard to existential unease 11 years earlier, a similar dose-response effect was found. There was a significant correlation between most of the individual unease factors and the risk of developing multimorbidity. The dose-response effect emerged when looking at the relative risk associated with an increasing number of unease indicators.

Finally, allostatic load was examined from the perspective of biomarkers. Looking at 12 allostatic parameters with regard to difficult experience of childhood, we could see a partial

mediating effect on the odds ratio of multimorbidity for those reporting a very difficult childhood. Individual assessment of the parameters with regard to childhood experience found those with a difficult or very difficult childhood to be shorter, have a larger waist and higher BMI, higher resting heart rate and lower systolic blood-pressure. In the prospective study, looking at existential unease as a predictor for multimorbidity 11 years later, we saw this complex disease development as tertiary markers of allostatic load, mediated through subtle, long-term biological perturbations. The dose-response effect found for the development of multimorbidity with increasing existential unease strengthened this theory.

In total: Although multimorbidity is highly prevalent in the general population, and might (as previously explained) partly represent an artefact of our Cartesian, fragmented way of defining and counting diseases, our empirical studies document a clear association between existential hardship (self-reported difficulties, both in childhood and adulthood) and development of multimorbidity. Our original hypothesis is thereby strengthened. Demanding life circumstances can, through the process of allostatic load, lead to multimorbidity.

7 Discussion of the methods

7.1 The HUNT study

The main strength of the analyses in this thesis lies in the generally high quality of the HUNT database (Krokstad and Knudtsen 2011). The experience of the staff organizing and carrying out the comprehensive data collections, as well as re-evaluated and standardized methods due to earlier phases of the study, are great strengths. The HUNT population is large, compared to other population studies, even when taking lower participation rates into consideration. The fact that the HUNT population is ethnically quite homogenous, stable and relatively affluent, with good and equitable access to primary healthcare (Vikum et al. 2012), can also be seen as a strength in relation to our research questions, as it lowers the potential for confounding by socioeconomic factors that could not be fully accounted for in the analyses.

Despite the homogeneity and lack of large cities, the HUNT population has been regarded as fairly representative of the Norwegian population regarding demography, morbidity and mortality (Krokstad et al. 2013). The similarities of the Nordic nations regarding life-expectancy, social structure and health (Petursson 2012) suggest a certain transferability of the results in a Nordic context, while greater uncertainty may be associated with application to more diverse populations and other sociocultural settings.

A general weakness of the HUNT3 study is the limited participation rate. It must nevertheless be seen as acceptable in the contemporary context (Krokstad et al. 2013), especially regarding the age groups included in our analyses. However, when comparing participants to non-participants (Langhammer et al. 2012), the limited participation might result in underestimating the multimorbidity count in the population. Underestimation might also be the case for difficult childhood experiences, as they were more commonly reported among younger participants (with lower participation rates than older). The lack of comprehensive data on socioeconomic position represent a clear weakness as well, as it is a well documented mediator regarding adversity in all its forms.

The HUNT Study was conceived in accordance with the conventional biomedical disease and risk factor definitions. Therefore, both the researchers designing the survey and the questionnaire respondents could be said to have been “blinded” to the research questions of

our study. Consequently, expectation bias can be ruled out. However, the questions available for analysis were not always optimal with respect to the research questions, as will be discussed below.

7.2 The definition of multimorbidity

As discussed earlier, there is no consensus regarding the number of conditions needed for a good evaluation of multimorbidity. A recent systematic review by Fortin et al. concluded that twelve or more of the most common chronic conditions would account for a fair evaluation (Fortin et al. 2012) and a study by Harrison et al. showed that less than ten of the most common diseases made up the largest part of disease combinations (Harrison et al. 2016). However, Harrison et al. concluded in 2014 that using 12 of the most common conditions identified only about 80% of multimorbid patients, compared to using a larger number of conditions (Harrison et al. 2014). It appears clear, though, that our count of 21 and 17 (Paper III) common chronic conditions should be sufficient for an evaluation of the prevalence of multimorbidity.

However, not having the same number of diseases defining multimorbidity in paper III as in the earlier papers is a certain weakness. Regarding conditions and diseases included, most were presented with a simple self-reported question regarding diagnoses given by a doctor. Some were symptom-based and therefore might be less reliable, such as chronic back pain or gastro-oesophageal reflux disease. Finally, we lumped cardiovascular disease into one disease group in order to minimize double registration. The same was done by excluding hypertension for those already reporting cardiovascular disease, as the diagnosis of hypertension was based on a question regarding medication use. In hindsight, more symptom-based diagnoses might have been gathered from the HUNT3 questionnaire, such as frequent headaches and indications of alcohol abuse.

The heterogeneity of questions from which diseases or conditions were inferred might be seen as a weakness. Furthermore, some discrepancies were found in reporting between questionnaires when comparing disease reporting in HUNT2 and HUNT3. A recent paper validating self-reported psoriasis in the HUNT3 questionnaire found a degree of *underreporting* of the disease, compared to clinical examination (Modalsli et al. 2016). On the opposite side, a new study indicates that rheumatoid diseases might be *overreported* in

HUNT (Videm et al. 2017). Self-reporting of disease might thereby give less reliable descriptions of diagnoses than medical records do. However, self-reporting might better reflect the individual's quality of life (Bayliss et al. 2005) and provide a more person-centred view of the experienced burden of disease.

7.3 Measures of allostatic load

Twelve biological parameters were included for evaluating allostatic load in paper II. They were all defined as secondary markers. Four of these were anthropometric, 4 related to heart rate and blood pressure, and 4 were drawn from blood samples. The blood values were not from fasting blood samples, so the accuracy of measurments was not optimal. Only one factor indicating inflammation, CRP, was available and the database did not include cortisol, one of the most commonly measured factors regarding allostatic load.

To my knowledge, only one other study to date has been published on HUNT data and allostatic load (Vie et al. 2014). In that study 11 parameters were chosen, very similar to those used in this study. It could therefore be stated that from the data available, a closer look at allostatic markers was not possible, without running additional, costly analyses (for instance telomere length). As was described in section 2.8, the goal of allostatic measurements is to incorporate as many allostatic factors as possible each time, and a gold standard for measurements has not been developed (Seeman et al. 2010).

The allostatic parameters were evaluated individually with regard to experienced difficulty of childhood and adjusted for in logistic models. Therefore, we made no attempt to assess allostatic load as a combined measure. The above mentioned paper by Vie et al. handled allostatic measures in the HUNT population by assessing allostatic scores as deviations from the mean. They reported not attempting more common ways of acquiring allostatic scores due to the limited precision of recording and low variance in allostatic load markers in the HUNT population (Vie et al. 2014). However, they concluded that the relationship found was stronger with a combined allostatic score than when assessing individual markers. It can therefore be seen as a weakness of our analyses that no allostatic score was made. At the time of the study, the decision was made not to generate an allostatic score, due to the similar nature of the parameters available that could possibly cause a bias when estimating associations.

7.4 Measures of subjective experience of childhood and existential unease

The single item question about subjective childhood experience has not been posed in earlier research regarding adversities in childhood. The theme is usually approached through predifined events, sometimes gathered to acquire a score of adverse events. The fact that our question could yield such results, is a new and interesting finding. The approach needs further validation in other contexts, but might ultimately prove to have certain qualities in common with the single item question about self-rated health (Schnittker and Bacak 2014). Further validation could be done through qualitative studies on the theme, and through repeating the question in the upcoming HUNT4 Study.

Since the study on childhood experience was cross-sectional, recall bias connected to the respondents' childhood cannot be ruled out. Theoretically, a heavy disease burden might be blamed on childhood adversities. However, previous studies comparing retrospective and prospective data on childhood adversity have not found evidence of recall bias (Hardt et al. 2010, Rich-Edwards et al. 2010, Rich-Edwards et al. 2012). In our study, we believe that adjustments regarding current depressive symptoms by HADS score further diminished the possibility of recall bias.

A similar problem regarding validity arose when defining "existential unease". Here, we introduced a new concept based on questions from several different fields. The questions were purposefully collected due to their particular relevance for our hypothesis, on the basis of clinical experience and existing evidence, allowing for reflection on empirical data in light of theoretical or experiential pre-knowledge. Although being a new concept, existential unease is based on established and often validated psychosocial concepts and theories. Being a new concept it has clear methodological weaknesses, but from the perspective of innovation and theory building, it can be said to have strengths.

In assessing existential unease, current depressive symptoms could be seen as a possible confounding factor. Therefore, we also did analyses adjusting for current depressive symptoms according to HADS scores.

7.5 Reflections on study design and statistical methods

The first two papers were cross-sectional and the third paper prospective. The cross-sectional design for the first paper was quite acceptable although a prospective analysis would have opened up an opportunity for incidence analyses as well as examining the change in multimorbidity prevalence and patterns in the 11 years between phases of the HUNT study, especially with regard to the possibility of it being an artefact.

The pattern analyses in paper 1 were descriptive, based on the state of knowledge at the time. Venn diagrams were made and odd ratios estimated for only a few chosen patterns of disease or conditions. Factor analyses would have more elegantly described the possible patterns. However, the approach taken was simple and transparent. It was thus easily understood. As the results are in accord with the literature on multimorbidity patterns, the approach can be described as adequate.

The cross-sectional design of paper II had some weaknesses. A prospective design would have made it possible to estimate the experience of childhood and allostatic markers in adults without multimorbidity, reducing the likelihood of recall bias or confounding of allostatic load by morbidity burden. However, as was seen in paper III, more than half of respondents reporting their childhood as difficult or very difficult had already developed multimorbidity when answering HUNT2, and the statistical power of the results would therefore have been much weaker, especially for those reporting a very difficult childhood. Furthermore, the question regarding childhood, as well as some allostatic parameters, such as CRP, were not included in HUNT2. These prospective analyses would therefore not have been possible until after completing HUNT4 in approximately 4 years from now.

The design and statistical analyses for paper III were adequate for the data available. The combined score of existential unease factors was developed in line with the combined score made for adverse childhood experiences (Felitti et al. 1998). In 2010, Seeman et al. discussed how earlier research showed that simple summative indices appear to capture the essential cumulative nature of such childhood risk factors, and the cumulative number appears to predict outcomes more strongly than specific risk factors or combinations of such factors (Seeman et al. 2010).

For papers II and III, more detailed information on socioeconomic status would have been optimal. For both papers II and III, true comparison between subjective and objective experience might have been helpful for further validation of the subjective approach.

7.6 If starting the project today

In hindsight, as would be expected, I see issues that could perhaps have been better addressed during the data analysis. The definition basis of our multimorbidity counts could have been developed more thoroughly—for example, by basing the definition of multimorbidity on both HUNT2 and HUNT3 questionnaires; by determining the cut-off points for measurements in a more homogenous way and by a somewhat clearer policy on including single diseases or disease groups.

Factor analyses on multimorbidity patterns would have been elegant, as well as making an allostatic load score in paper II in relation to childhood experience. However, as I have explained above, I feel that the methods were adequately suited for the overall hypothesis and aims I had for this project.

8 Discussion of the results

In the introduction, I described a vast amount of literature to document the foundation for the hypotheses in this thesis. In this section, I will elaborate further on some of the themes, but now with direct regard to the results of the three empirical studies. I will also present theories and further thoughts that have developed during the PhD process. I will move from descriptive perspectives on multimorbidity to analytic considerations and from epidemiologic assesment of adversity to biological considerations pertaining to allostatic overload. In addition I will move from discussing major adversities to more subtle stress factors; from childhood to adulthood; from objective measures to more subjective measures, and finally from a fragmented to a holistic perspective.

Most importantly, this thesis indicates that challenging life circumstances and the stress they entail for the individual can represent important risk factors for developing complex disease clustering and poor health in general. Statistically, stressful life circumstances appear just as important for health as many of the more conventional medical risk factors. This finding is in full concordance with previous reseach that has linked life stress to pahogenesis. What this thesis adds, is an explicit focus on the relatisonship between stressful life circumstances and the phenomenon of multimorbidity, seen in a life-course perspective.

Before moving on, I want to emphasise that difficult life circumstances are *risk factors*. A stressful life is not the cause of all complex disease. Our data suggest that illness, even to the extent of complex multimorbidity, might well develop in the absence of particularly difficult life circumstances. From both the literature and clinical experience it is also evident that individuals can go through much hardship without losing their health.

8.1 The concept of multimorbidity revisited

The introduction started with a comprehensive description of the concept of multimorbidity, based on the literature published to date. However, it ended by stating that my view of the problem had changed and that, to some extent, multimorbidity might represent an artefact of our way of looking at disease(s). Simply counting diseases the way we currently do might lead us into a scientific blind alley. I started out with the idea that multimorbidity was something that would always be associated with substantial illness and suffering, but found

the phenomenon to be more common in the general Norwegian population than having no disease. I therfore conclude that the concept of multimorbidity—as currently defined—does not capture what it was probably meant to capture in a clinically meaningful way (see section 2.1.1). As Jackson et al. described in 2016, there is:

> "…the need for a more holistic definition that is not restricted by a disease-focused medical label and which encompasses wellbeing and severity of problems that people face" (Jackson et al. 2016).

To meet this challenge, some research groups have recommended *more inclusive* definitions, adding acute diseases and biopsychosocial factors to the defining list of multimorbidity (Le Reste et al. 2013). Others are, on the contrary, in favour of a *stricter* approach and argue that *complex multimorbidity,* defined as three or more chronic diseases in three or more body systems, will help identify the most burdened individuals (Harrison et al. 2016). From the perspective of my main hypothesis and findings, I find the latter, strict approach most promising.

For the analyses in my papers, the established, disease-oriented approach to morbidity was used. Therefore, it is relevant to first compare our results with studies based on similar definitions. In paper I, the age-standardized prevalence of multimorbidity was 42% for the age group 20-79 years. At the time of publication, no other Nordic data were available, but since then, a handful of publications have appeared. A registry study of all Norwegians aged 15 years and older was published in 2015. There, the prevalence of multimorbidity for Norwegian-born people was only 16% for the age group 45-64 years and 34% for those aged 65 and older (Diaz et al. 2015). An Icelandic study based on a medical record database found a general prevalence of multimorbidity in the population to be 35%; 47% for the age group 40-49 and 62% for 60 to 69 year-olds (Linnet et al. 2016). This is comparable to our findings. Similar results were also found in a Danish registry study (Prior et al. 2016). A cohort over the age of 50 years from Finland had a self-reported prevalence of 68% (Garin et al. 2016). Our results are thereby quite compatible with other Nordic studies.

The fact that the prevalence of multimorbidity proved to be so high, even in younger age groups, in this relatively affluent population with only moderate differences in socioeconomic status, shows that it is not only a phenomenon related to high age and/or social deprivation. And while multimorbidity in the elderly might simply reflect normal aging, the growing

burden of multimorbidity among younger and middle-aged adults has raised concern internationally (Jackson et al. 2016). As outlined in the introduction, a study by Pefoyo et al. showed a substantial increase in multimorbidity prevalence between 2003 and 2009 in Canada, most evident in the middle-aged population (Pefoyo et al. 2015). According to Prados-Torres et al., the main disease patterns for this age group were established organ disorders, while risk factors were more prominent in the younger age groups (Prados-Torres et al. 2012). In our paper I, risk factors such as hypertension and hyperlipidaemia were most common in middle-age, along with pain conditions and mental health problems. It was however evident, as has been shown in other papers, that the biggest risk factor for multimorbidity is to have one disease already present (Harrison et al. 2014).

Harrison et al. found that some patterns of *complex* multimorbidity are more prevalent than several single conditions that receive much clinical attention. For example, the specific cluster of hypertension+hyperlipidaemia+osteoarthritis is more prevalent at the GP office than each of the conditions: congestive heart failure, rheumatoid arthritis or chronic obstructive pulmonary disease (Harrison et al. 2016).

Van den Akker stated already in 1998 that "the clinical rule to reduce all signs and symptoms to a single diagnosis does not hold for gerontology – is not exclusively true for gerontology*"* (van den Akker et al. 1998). Furthermore, several researchers have found that when examining possible patterns of diseases, most, if not all, clusters appeared more than expected by chance, based on the individual disease prevalences (van den Akker et al. 1998, Fortin et al. 2012). In 2011, Starfield argued that for patients with multimorbidity, the burden was more than the sum of their individual conditions, and that by using a single-disease approach, one would fail to grasp the true nature of the patient's health status, leading to inadequate management (Starfield and Kinder 2011). Guthrie et al. agreed to this and stated that it would never be possible to have good evidence for management of every possible combination of conditions (Guthrie et al. 2012).

Once a patient has been diagnosed with one chronic condition, the clinical contact as such increases the chance of identifying and diagnosing other conditions (Harrison et al. 2016). In 2009, Valderas et al. formulated three main reasons why diseases would be diagnosed in the same individual: by *chance*; by *selection bias* (due to established clinical contact), or due to one or more types of *causal association* (Valderas et al. 2009).

In summary, it seems that multimorbidity is a phenomenon so common that the currently used definition as two or more co-occuring diseases/conditions fails to sort out the burdened patients we aim to find– and with possible cluster patterns so diverse that categorising them much further appears futile. In order to move closer to the core of the problem of complex disease clustering, with or without subjective loss of health, we apparently need to understand better both the biological nature and aetiological pathways to the phenomenon. Earlier medical literature has contributed remarkably little here, as described in section 2.11.

8.2 Moving from a descriptive to an analytic approach

Intuitively, diseases would be expected to cluster in an individual if they share common causal pathways, i.e. if the resilience or vulnerability of the individual was altered (Valderas et al. 2009). In this thesis, I ask whether unbuffered stress and allostatic overload might represent one important and unifying, causal pathway to complex disease clustering, influenced by the genetic vulnerabilities, environmental exposures and experiences of the individual in question. The next section will discuss this further.

8.3 The biology of disadvantage – allostatic overload

As outlined in the introduction, the body's allostatic processes involve a range of biological markers which interact in a complex manner. As noted earlier, allostatic overload denotes the price the body will ultimately pay for having to adapt to challenges that exceed the person's capacities, resulting in physiological dysregulation and increased disease risk (McEwen 1998).

Figure 1 (page 29) shows the rapidly increasing number of publications on allostasis and allostatic load in recent years. Allostatic processes have by now been causally connected (empirically or theoretically) to many common health problems: metabolic diseases like obesity and diabetes; vascular diseases; autoimmune disorders; cognitive decline (McEwen 1998), Alzheimer's disease, sleep deprivation (McEwen and Karatsoreos 2015), fibromyalgia (Martinez-Lavin and Vargas 2009), pain severity (Sibille et al. 2017) and cancer (Delpierre et al. 2016). Allostatic overload has also been explicitly connected to adversity in childhood (Shonkoff et al. 2009, Danese and McEwen 2012), low socioeconomic status (Gruenewald et

al. 2012), lack of close relationships (Kiecolt-Glaser et al. 2010) and low subjective social status (McEwen and Gianaros 2010). Our reseach hypothesis thereby rests on a far stronger empirical foundation today than when the project was conceived in 2010.

As described in section 2.8, the rule of thumb in allostasis research has been to include as many and diverse factors as possible each time (Seeman et al. 2010), resulting in different algorithms and scales. On the physiological level, the list of potential allostatic variables has recently been expanded to involve shortened telomere length (Tomiyama et al. 2012), mitochondrial energetics (Picard et al. 2015) and epigenetic processes (Juster et al. 2016). In 2016, Juster and co-workers summarized the allostasis literature to date and proposed a detailed, causal chain from stress via allostatic load to comorbidities and multimorbidity in an evolutionary perspective, with specific reference to childhood conditions and personality development. Paper 2 in this thesis is included in the reference base. Juster et al.'s suggested pathway leads from *chronic stress* to *primary allostatic mediators* (neuroendocrine and metabolic), followed by diverse *effects on mitochondrial function, cellular dysfunction, telomere shortening* and *epigenetic re-programming.* Together, these complex processes predispose for *secondary and tertiary allostatic outcomes* such as hypertension, diabetes, neurodegeneration, cognitive decline, comorbidities and multimorbidity (Juster et al. 2016).

In addition to research which explicity applies the allostasis model, advances in other milieus add valuable, new insight. In January 2017, Tawakol et al. showed that amygdala regulates bone-marrow activity in response to stress, and that this can lead to arterial inflammation and cardiovascular disease (Tawakol et al. 2017). Thus, a new neural-haemopoietic-arterial axis was described, in full coherence with pre-existing literature on the brain, inflammation and allostasis. As an umbrella term, the allostasis concept can accomodate multiple knowledge bases and facilitate innovative, scientific descriptions of *how everything in the human body is essentially connected to everything else, and how subjective experience matters, in a very literal sense.*

Application of a wide range of allostatic variables may be important in relation to studies of multimorbidity, because few and homogenic factors might be sronger predictors for certain diseases than others. In relation to paper II, most of the included factors were anthropometric or related to blood pressure. These variables have known relevance for cardiovascular disease

but perhaps less for other disease categories. This renders support to the decision we made not to construct a combined allostatic score for the purpose of our study.

When considering the individual allostatic parameters in paper II, it is of particular interest to look at *height differences* according to the categories of childhood experience (see tables 3 and 4 in paper II). Individuals reporting a very difficult childhood were on average just under 2 cm shorter than those reporting a very good childhood (1.71cm for women and 1.87cm for men, $p<0.001$). This finding is in line with historical epidemiological data from the French population, by Villermé, in 1817-1821. His results showed the poorest male population to be about 1cm shorter than the wealthiest male population (Krieger and Davey Smith 2004). A similar difference in height (1.2cm for adult men) was found in a British birth cohort from 1958 with regard to adverse childhood experiences (Denholm et al. 2013).

In total, although we refrained from attempts to define an allostatic load score in our empirical analyses, the results appear compatible with our main hypothesis. Juster et al.'s relatively detailed outline of paper 2 in their overall argument (Juster et al. 2016) further validates this impression. The question then arises whether it is really necessary to establish ever more complex measurements of allostasis for everyday clinical purposes. Linn Getz and I wrote a commentary on this theme in 2016 (see Appendix 4). It is, of course, important to consolidate and advance the research field. Data on individual biological markers accumulate quickly in various biobanks, and measurements become cheaper. We find it likely that in a few years, the list of factors included in allostatic load models will merge with the ongoing "omics" development in the basic sciences (Vogt et al. 2014, Delpierre et al. 2016). This will be further discussed in section 8.6.1.

Whatever will happen to the empirical measurements of allostatic load, we find the concept allostasis interesting for other reasons as well. We argue that it should be tended to as a *philosophical* concept, and as such a potential cornerstone of coherent, non-fragmented thinking in future medicine (Delpierre et al. 2016). In our experience, the concept allostatic load can be addressed both in *everyday language with explanatory metaphors* (excessive "wear and tear" of the body through an imbalance between "gains and drains") and as an *ever-expanding natural science construct* (Heath 2013). As our commentary paper states:

> "Already in 1992, Cassell pointed out that (personal) human agency must necessarily involve the whole human being, all the way down to the mitochondria. Today the basic sciences have reached a point where we can view both Cassell's argument and the mitochondria in terms of allostatic load. This convergence of philosophical and physiological perspectives opens new perspectives on narrative in medicine and the medical relevance of attending to human stories in the clinical encounter" (Delpierre et al. 2016).

Progressing further with the importance of human stories and perceptions regarding allostatic load, Getz et al. stated in 2008:

> "Allostatic load (…) invalidates the traditional methodological assumption that events categorized as "the same" (i.e. divorce or death of a spouse) will affect the studied subjects in the "same" way. It is not the event as such, but the experiencing person who interprets the event in light of previous experience who will ultimately determine its individual impact" (Getz et al. 2008).

We could therefore say that its quite logical to further explore the relationship between *subjective experience,* health and disease.

8.4 Subjective experience and allostasis

Inherent to the definition of stress, both as advanced by neuroendocrinologist Bruce McEwen and more phenomenological definitions, is subjective experience, or *perceived* stress (see section 2.10). It has been of great interest for me to move away from measures related to predefined stressful *events* in direction of more open measures of *subjective experience.* If well constructed, subjective measures might elicit the individual patient's/person's perspectives in a more open but still meaningful manner.

The childhood experience question we developed and applied in paper 2 was deliberately simple and open-ended. And we think it yielded quite striking results. To our knowledge, no similar studies have previously been published. However, compatible results have been shown repeatedly through studies on predefined childhood experiences, linking them to a myriad of health problems in adulthood (Felitti et al. 1998, Felitti 2002, Kirkengen 2010, Danese and McEwen 2012), potentially mediated through allostatic load (Danese and McEwen 2012, Drury et al. 2014), of which telomere shortening might represent one aspect, as said (Naess and Kirkengen 2015).

In the same month as paper II was published, a paper by Sinnott et al. on an Irish population was published in *Family Practice* (Sinnott et al. 2015). They examined a population-based cohort from primary care, with 2047 participants, 50-69 years old. The prevalence of multimorbidity was 45%. It was found that multimorbid participants reported predefined adverse childhood experiences significantly more often (28%) than participants with no chronic disease (16%), with an OR of 1.6 (95% CI 1.3-1.9) (Sinnott et al. 2015). The comparison was between those reporting ACEs in general and those that did not. The study contained no ACE score. To date, I have found no other comparable empirical studies on the association between childhood experiences and multimorbidity.

As discussed in section 2.11, little is currently known about the effect of subtle, yet long-standing challenges on allostatic load and disease development. However, in recent years, subtle stress has become an expanding field of research. It seems that even (presumably) moderately straining life events might have clinical significance (McCullough et al. 2007, Zoccola and Dickerson 2015). One particular strand of research explores so-called *ruminations.* Ruminations describe a maladaptive form of self-focused attention, characterized by recurrent thinking about perceived threats, losses, and injustices to the self, associated with feelings of anxiety, depression, and anger (Smart et al. 2016). Ruminations have been linked to increased stress responses and non-habituation of the HPA axis (Gianferante et al. 2014).

Ruminative tendencies have also been linked to changes in amygdala and prefrontal cortex functions, which in turn affect heart rate variability through changes in the parasympathetic nervous system via the vagal nerve which modulates inflammation (Williams et al. 2015). Ruminations have thereby been linked to several parameters of allostatic load. Furthermore, a recent meta-analysis has shown that ruminations are associated with unhealty behaviours (Clancy et al. 2016). This has also been found for more conventional measures of perceived stress (Prior et al. 2016). Finally, research suggests that ruminations and other maladaptive emotional regulations are linked to the individual's family environment in childhood and youth, including parental psychiatric problems and maternal internalizing emotions (De Witte et al. 2016).

Rumination has been divided into different types; general rumination, depressive rumination, anger rumination and self-critical rumination. Self-criticism is a form of negative self-

evaluation in which judgemental, condemning and attacking thoughts are directed to the self, especially in the context of perceived mistakes, failures, and inability to live up to one's own or others' standards (Smart et al. 2016). It has been shown to mediate relationships between childhood maltreatment and many problems in adulthood, including body dissatisfaction, impaired romantic relationships and depression (Smart et al. 2016).

In total, recent research on ruminations fit well with our hypothesis in paper III. The questions regarding negative self-opinion, not experiencing a meaningful life, boiling with anger but not showing it, as well as not feeling inner calm, might as I see it, be interpreted as tendencies to ruminate.

Furthermore, low self-esteem (Trzesniewski et al. 2006), unfairness (De Vogli et al. 2007), lack of well-being (Steptoe et al. 2009, Keyes and Simoes 2012), work dissatisfaction (Faragher et al. 2005), loneliness (Holt-Lunstad et al. 2015), lack of social relationships (Holt-Lunstad et al. 2010), subjective-evaluative threat (for example, manifesting in distrusting neighbours) (Lehman et al. 2015) and anger (Tsenkova et al. 2014) have all been related to some form of impaired health. A perceived lack of purpose in life has recently been connected to allostatic load (Zilioli et al. 2015, Cohen et al. 2016), as has compromised sleep-quality (Zisapel 2007, Juster and McEwen 2015, McEwen and Karatsoreos 2015).

It is not evident to what extent all questions explored in paper III represent precursors to chronically impaired biological function. Some of them might tap directly into an early pathogenic process not yet manifested as overt, clinical disease. Recent evidence has suggested a relationship between self-rated health and allostatic load (Vie et al. 2014, Waller 2015). A subjective perception of poor health might well develop concomitantly with, and not prior to, allostatic overload. The same might pertain to impaired sleep. However, existing evidence (Friedman et al. 2005) as well as clinical experience give reason to consider impaired sleep also as a primary indicator of experienced stress.

As mentioned in the Methods section, our questions on existential unease were selected from the HUNT2 survey. Some of them reflect Bourdieu's theories on social capital and Antonovsky's concept *Sense of Coherence (SOC)*. Sense of coherence, as described by Antonovsky, is:

> "…a global orientation, that expresses the extent to which one has pervasive, enduring though dynamic feeling of confidence that (1) the stimuli deriving from one's internal and external environments in the course of living are structured, predictable and explicable; (2) the resources are available to her/him to meet the demands posed by these stimuli; and (3) these demands are challenges, worthy of investment and engagement" (Antonovsky 1993).

The SOC concept thereby contains three major components: comprehensibility, manageability and meaningfulness. A strong sense of coherence has been associated with lower levels of perceived stress, and some evidence indicates that sense of coherence increases health-related quality of life in patients with chronic conditions (Lundman and Norberg 1993, Ekman et al. 2002, Zirke et al. 2007). A study on the impact of sense of coherence on health-related quality of life showed that sense of coherence is a potential resource for increased health-related quality of life in multimorbid patients (Vogel et al. 2012).

In Paper III, self-rated health was chosen as one of the questions included in the concept of "existential unease". As described in section 2.10.1, an extensive literature connects self-rated health to disease development and mortality, even after adjusting for measurable signs of established pathology at baseline. The strong association between self-rated health and multimorbidity found in paper III is therefore no surprise. As said, self-rated health has been connected to allostatic load (Vie et al. 2014). However, theoretically, self-rated health could, to some extent, reflect other processes of existential unease, thus complicating the interpretation. Multicollinearity analyses did not show too much overlap between the included questions.

As we defined it, the concept 'existential unease' included questions that earlier studies have not examined in combination. Very few studies have in fact analyzed the combined effects of stress pertaining to different aspects of everyday life. A study by Dich et al. in 2015 on the Whitehall II cohort is one exception. It prospectively explored the interactive effects of job strain and family stress from informal caregiving on allostatic load. High caregiving burden predicted higher allostatic load. The effects were strongest in individuals who *also* reported job strain (Dich et al. 2015). This study thereby points in the same direction as paper III regarding a potential dose-response effect of stress in different domains.

I have now discussed the empirical elements of this thesis in view of the rapidly evolving literature. The next sections will involve more theoretical reflections on the thesis' main topics.

8.5 Weaknesses of the Knidian biomedical approach

Only a few decades ago, feeling ill was the legitimate reason for seeking medical care. Surveillance of risk factors amenable to medico-technical interventions represent a more recent reason for legitimate contact. Subjective, symptom-based illness like chronic pain and sadness have lower status and typically evoke clinical frustration rather than much interest. According to Eriksen and co-workers, "medical method, criteria, observations and requirements of evidence, together with disproportional focus on medical diagnostic naming, represents a possible barrier to understanding such symptoms" (Eriksen et al. 2013). This dynamic has been said to add a new dimension to the *inverse care law* (Mercer et al. 2012). That is, the dynamic makes less and less room for people who suffer, whilst medicine dedicates ever more time and resources to subjectively healthy people. It could be argued that medico-technical knowledge overshadows patients' symptoms or opinions regarding their own health.

This hierarchy of diseases and risk factors has become so evident that symptom-based disorders, although they have been shown to be among the most common causes of contact in general practice, get limited and half-hearted attention in medical schools as I know them. The conditions get some attention in medical research, however with more focus on classifying the problems and measuring effects of standardized treatment protocols (e.g., drug regimens or cognitive therapies) than on actually exploring what might be going on at the suffering person's level (Starfield 2011).

Philosopher Miranda Fricker has named problems of this kind "*epistemic injustice*" (Fricker 2007, Carel and Kidd 2014). Anna Luise Kirkengen introduced this term into Norwegian primary care (Kirkengen 2010). The prioritisation of risk factors and preventive medicine above patients' own perceived problems might spark a renewed debate over the moral aims of medicine and the mandate of the medical profession in general.

Why have doctors become so techno-scientific and detached from the patients' reality? Part of the answer lies in the biomedical approach. Although this approach has unequivocal benefits, it merits some criticism as well.

8.5.1 Fragmentation and silo-medicine

As discussed in section 2.3, the Knidian biomedical approach directs researchers to increasingly smaller fractions of the human body, in hope of break-through answers to fundamental questions of health and disease. At the same time, it has led to a system of nearly 16,000 different diagnoses and increasing (sub-)specialisation of medical doctors. As discussed in the 2010 article by Parekh and Barton, this process has inadvertently created individual disease *silos* (Parekh and Barton 2010) which mandate doctors to focus on their specialty's domain with only limited, if any, responsibility for attending to the total of the patients' health problems.

As previolsy mentioned, this paves the way to "collusion of anonymity", and that is not a health-promoting situation. It increases the risks of polypharmacy, side effects, drug-drug and drug-disease interactions, as well as contradictory and possibly wrong medical advice. It also gives clinicians legitimate routes of escape from issues that really matter to the patient ("You should talk to someone else about that, I'm only here for your heart").

8.5.2 Neglect of the social context

The dominating biomedical model has been widely criticized for not taking people's social context into consideration. Embodiment of distress and disadvantage has been ignored by biomedically minded doctors and researchers, despite the extensive literature now available, both epidemiological, biological and clinical. According to Sturmberg, issues related to the patient's social context can represent more important triggers for hospitalization than actual deterioration in the patient's underlying disease (Sturmberg 2012). This might be reflected, at least in part, in the inadequate implementation of new person-related knowledge, as described by Mjølstad and discussed below (Mjolstad 2015).

I also wonder whether 'lack of implementation' describes the problem clearly enough. Relevant new knowledge can be implemented very rapidly in medical practice if it is a question of a promising new drug (e.g. a painkiller) or a new theory associated with mendable, molecular disease mechanisms (e.g. vitamine D deficiency). Could lack of

implementation in our case have more to do with the fundamentally non-medical nature of the knowledge involved? Doctors have hardly learnt to address (or respond to) sensitive, existential issues, and lack of standardized treatment options might push us away from addressing the problem.

It is clear to me that although the bio-psycho-social model has been described as the ideal medical model in medical schools in Scandinavia for years, it is still overshadowed by the biomedical model, both in theory and practice. Furthermore, the bio-psycho-social model has received substantial critique (see 2.4.3). It is said to invite a new kind of fragmentation by dividing the person into biological, psychological and social domains, without explaing the interactions suggested by the two hyphens (Ghaemi 2009, Tavakoli 2009).

8.5.3 Weaknesses of evidence based medicine and clinical guidelines

Since its emergence in mainstream medicine in the 1990s, *evidence-based medicine*, or EBM, has become the basis for all health care services, and the framework for all clinical guidelines by which clinicians should structure their work. According to Gordon Guyatt (a key figure in the development of EBM) in his book *User's guides to the medical literature,* EBM represented a medical paradigm shift:

> "In contrast to the traditional paradigm of medical practice, EBM places lower value on unsystematic clinical experience and pathophysiologic rationale, stresses the examination of evidence from clinical research, suggests that interpreting the results of clinical research requires a formal set of rules, and places a lower value on authority than the traditional medical paradigm" (Guyatt et al. 2008).

The methodology of EBM was primarily designed to evaluate standardized actions and interventions. The founders came to acknowledge a paradoxical danger of replacing the old-style authoritarian clinical expert with a new authoritarian scientific regimen (see more on this below) and modified their description of EBM accordingly (Sackett et al. 1996). As formulated by Guyatt:

> "Decision makers must always trade off the benefits and risks, inconvenience, and costs associated with alternative management strategies and, in doing so, consider their patient's *values and preferences*" (Guyatt et al. 2008).

However, this modified EBM approach which explicitly gives room for clinical expertise and the patient's values and preferences, somehow tends to get lost in the translation from theory

to practice. Furthermore, the founders of EBM to my knowledge never explicitly focused on the massive evidence which shows the health impact of societal conditions and human relationships, for better or worse. The authoritative methodological toolkit of EBM might have lead to downgrading of scientifically "messy" but causally important aspects of human life.

The dilemmas associated with EBM are closely linked to pitfalls in the making of *clinical guidelines,* as introduced in section 2.1.7. Clinical guidelines aim to summarize available evidence on well-defined medical topics to support the practicing clinician's considerations and advice. They have become mainstays for clinicians as the increase in scientific publications has become such that it is out of reach for doctors to keep up with new evidence relevant to everyday clinical work. Research has shown that practicing clinicians deem guidelines to be generally important, but at the same time they complain that the guidelines fit poorly with their own patients, especially those with multimorbidity (Austad 2017).

The methodological limitations and clinical dilemmas associated with clinical guidelines have been discussed thoroughly in the PhD theses of my GP colleagues Halfdan Petursson (Petursson 2012) and Bjarne Austad (Austad 2017). From different perspectives, they question how guidelines are made, and whether the evidence they are based upon is adequate in the clinical setting. Petursson specifically discusses that authors of guidelines sometimes have unstated conflicts of interest, and give excessive importance to the authors' own values and preferences. The strength of the scientific data on which EBM guidelines are based is often insufficiently stated and sometimes of questionable quality, i.e. paradoxially low in the hierarchy of scientific evidence posed by EBM itself.

Petursson specifically mentions five possible explanations for the lack of quality of the evidence that clinical guidelines are made by. He mentions *pharmaceutical bias,* where publication bias of positive results, drug-sponsored trials and down-grading of non-pharmacological interventions are parts of the problem. Next comes reliance on "soft" *surrogate end-points,* assuming a corresponding "hard" effect on mortality, *combination of fragmented knowledge* in ways that might lack relevance in daily clinical practice, *evidence gaps in important areas,* and finally so-called *"Vulgar Cochranism"*-- a term launched by Norwegian professor in medicine Torgeir Bruun Wyller (Wyller 2011), described by Petursson as follows:

> "Vulgar Cochranism does not refer to inadequate evidence as such, but rather to presumptuous and erroneous use of evidence. First, available evidence may be applied beyond the range of its validity. Second, there is excessive emphasis on randomized controlled trials and pharmaceutically biased evidence, downgrading non-pharmacological interventions and evidence involving structural, societal phenomena and psychosocial risk factors. The evidence gap discussed above is exaggerated and ignored at the same time by overlooking the available evidence in the field as well as the research opportunities. Third, the role of clinical expertise of (general) practitioners (for whom the guidelines are intended) is devaluated and, with aggressive assertiveness, attempts to adjust the guidelines to clinical reality are met with labels such as clinical inertia" (Petursson 2012).

Petursson notes that the 2007 European guidelines for management of arterial hypertension included 825 references, none of which discussed psycho-social risk factors or social determinants, despite considerable documentation of their relevance to development of cardiovascular disease (Petursson 2012). Furthermore, when clinical guidelines do take the reality of social circumstances into account, they often do so vaguely or unspecifically, thereby downplaying their relevance in the clinical encounter.

In her PhD thesis, general practitioner Bente Prytz Mjølstad further discusses the lack of implementation of new, relevant knowledge pertaining to the close interrelatedness of biology and biography. She interviewed both frail patients and health professionals and found that *not even the patients themselves* were surpised that their most personal concerns were deemed irrelevant (or rather, beyond the scope of the institution's professional mandate) as they were admitted to a rehabilitation institution (Mjolstad 2015). This shows how rooted conventional biomedical thinking has become in the wider society.

To sum up, despite the best intentions, evidence-based medicine and clinical practice guidelines have significant shortcomings, even in settings where the problem might be one specific disease. In the presence of clinically significant multimorbidity, the problems might potentially increase quite dramatically.

8.5.4 Multimorbidity as a medical artefact

In section 2.2.4, I wrote how multimorbidity can to some extent represent an artefact of the fragmented, biomedical way of defining disease, suffering and risk. Research indicates that although the prevalence of chronic disease in general has increased, the prevalence of multimorbidity has increased more. An article by Uijen et al. from 2008 showed that the

prevalence of chronic diseases in the Netherlands doubled between 1985 and 2005 (Uijen and van de Lisdonk 2008). However, in this period, the proportion of patients with one or two diseases remained stable while the proportion with three chronic diseases increased by 60%, and those with four or more chronic diseases increased by approximately 300% (Uijen and van de Lisdonk 2008).

Furthermore, Starfield et al. showed that among elderly people in the United States, the percentage of people with five or more diagnosed conditions who reported being in excellent or good health increased from 10% to 30% between 1987 and 2002 (Starfield and Kinder 2011). It can thus be said that self-reported morbidity burden does not follow the number of new diagnoses (Starfield and Kinder 2011). From this it seems that the current notion of multimorbidity adds to the so-called *well-being paradox* (Netuveli and Blane 2008). Starfield's results are in line with the results in Appendix 3 in this thesis, which shows that around 40% of participants in the HUNT study claimed to have good or very good health, despite reporting four or more chronic medical conditions. Only around 6% of the same group reported poor health.

Concluding the section above, it is possible to argue that the multimorbidity epidemic challenges *all the weaknesses* of the biomedical model discussed above. Multimorbidity might not simply mirror a genuine deterioration in population health, but to a large extent emerge as a result of increased fragmentation of existing problems, combined with the ongoing move toward preventive, risk-factor-focused medicine. Medical-silos *complicate* rather than ease the approach to treatment and prevention. Evidence-based medicine and clinical guidelines as we know them today *do not apply* adequately to multimorbid patients. Furthermore, the patient's social context seems to be strongly associated with the development of multimorbidity. In total, the state of affairs in multimorbidity research indicates that it is time for new thinking about the problem.

8.6 Are we medicalizing life?

As discussed in section 2.2.3, the on-going move in direction of preventive medicine entails increasing medicalization, for better or worse. Great advances in research, technology and treatment options have brought this on, but increased longevity of western populations also facilitates it, combined with enhanced expectations regarding health. At the same time, ever

widening disease definitions and lower cut-off points contribute (i.e. for hypertension, cholesterol and diabetes), along with increasing use of sensitive imaging technologies such as MRI which result in more incidental findings of unknown significance. Emotional reactions previously considered as normal, like grief, are added to the diagnosis list of DSM-5 (Frances 2013). All this is done with intentions to benefit the patient. However, stretching the borders ever wider diminishes the potential for benefit and increases the risk of unintended harm as soon as we start to intervene (Moynihan 2011).

The expanding indications for medical surveillance and interventions have already blurred the lines between health and disease, as previolsy discussed. And what is currently happening, is a move involving new distinctions between "normal" and "optimal" health (Vogt et al. 2016). This movement is about to spread to the wider culture, and it will pose demands on the medical profession as well. It prompts the question: *Have we started to medicalize life itself?* I will dig a bit further into that topic, as my own scientific approach to multimorbidity might by some be seen as medicalization of human life, and I want to explain why I disagree.

8.6.1 On biomedicine and systems medicine

As discussed in section 2.3.2, biomedicine's most recent approach to the complexity of our biological functioning is called *systems medicine.* As stated by Bousquet et al. in 2011, systems medicine views health and disease in a presumably holistic manner with the aim to address *all* the complexity of non-communicable diseases, both at the individual and societal level (Bousquet et al. 2011). In light of the critique I have presented of biomedicine, this can at first sight look like a timely and positive development. A holistic view is exactly what has been missing. The question, however, is to what extent a systems medicine approach might lead to genuine progress, and at what costs and with what down-sides, direct and indirect.

The above mentioned systems medicine approach is based on high-throughput analyses of "big data" involving *billions of data points* for each individual, elicited at all conceivable "omics levels" of the human organism, from genomics via transcriptomics and metabolomics "upwards" in the direction of clinical and even behavioural data (Delpierre et al. 2016). The data will constitute a virtual cloud for each person, and complex computational models allow early discovery of deviations from the individual's presumed optimum, thus empowering the person to take control (Hood et al. 2015).

In some areas of medicine, an "omics" approach might become highly useful. A discussion of that is however beyond the scope of this thesis. And at least from the perspective of primary health care, the vision brings up many practical and ethical questions, as discussed by my GP colleague Henrik Vogt (Vogt et al. 2014, Vogt et al. 2016). For the coherence of my own argument, I will briefly mention some of the considerations here.

First, the aim to accurately calculate and predict changes in health through billions of data points might prove to be utopian. For many years to come, the outputs will be challenging to interpret and translate into meaningful, clinical action. Seen in light of Petursson's analysis on much simpler cardiovascular risk-algorithms (Petursson 2012), it is reasonable to question whether a dramatic increase in included parameters, combined with mathemathical algorithms that medical doctors can hardly comprehend, will yield reliable risk estimates. The estimates might come out directly misleading, and they may also represent irrelevant but resource-consuming false alarmes.

Is the "omics development" gradually colonizing life itself? Already in 2006, Norwegian medical professor Per Fugelli expressed deep concern with a development where he felt that the human being is being reduced to what he calls *a statistical clone.* In face of the doctor, the person's identity might change from a free human being to a restrained manager of health risks. Fugelli stated:

> "We must acknowledge the individual as the one and only right master builder of own health. Our mission as health professionals is to provide the box of bricks (knowledge), not the architectural drawing of peoples' life" (Fugelli 2006).

Third, it will be interesting to see if these massive means to address the health of individuals will truly improve public health and increase human flourishing and well-being. Will this change the advice provided, or will the most common diseases still remain common? Will the general means to improve health still be a healthy diet, doing the right amount of physical activity and aiming for life-satisfaction?

And finally, will we possibly be medicalizing life itself, making everything we do a risk factor for possible deterioration?

8.6.2 Allostatic load – medicalizing life or facilitating genuine understanding?

In a corresponding manner to my "omics critique", I expect that questions of unfavourable medicalization may arise as I suggest that a patient's childhood, relationships and even subtle feelings of existential (un)ease have relevance for evaluation of their health profile.

To my defence, I might evidently point to WHO's definition of health as a "state of complete physical, mental and social well-being" (WHO 1978). But beyond this, I think that potential down-sides of holistic medical thinking will depend on how the topic is approached. In *Medical Nemesis,* Ivan Illich warns us how medical practice, by transforming pain, illness and death from a personal challenge to a technical problem, can expropriate the potential of people to deal with their human condition in an autonomous way and make it a source of disease or unhealth (Illich 2003).

With regard to allostatic load and patients' biographies*,* the aim I personally strive for is the exact opposite. *My aim is not to medicalize the biography, but to demedicalize those aspects of suffering that are best dealt with in a relatively low-tech manner*. The simple act of asking and listening can start a health-promoting process and move the locus of control from the doctors to the patient and the wider society. By giving the patient sufficient insight, acceptance and recognition, the suffering could be moved to another level, where the patient him- or herself has more control over their own health, instead of relying completely on biomedicine's decontextualized view of their suffering. Vincent Felitti and co-workers found that by acknowledging personal life histories and the suffering they may have caused, and discussing them in context of the person's health problems, lead to a 35% reduction in doctors' visits the following year (Felitti 2017). Such a working style might also gradually contribute to demedicalization by teaching people how good relationships and a safe upbringing can keep people out of the healthcare system.

To sum up, I argue that by paying attention to people's life histories and existential circumstances, *we are first and foremost humanizing medicine, not medicalizing life.* We are admitting what matters to the paient and empowering people to take control over the imperfect reality of being.

8.7 Leaving fragmentation behind and connecting the pieces

When putting forward his original definition of biological stress in 1955, Selye stated:

> "Life is largely a process of adaptation to the circumstances in which we exist…[and]…the secret of health and happiness lies in successful adjustment to the ever-changing conditions on this globe; the penalties of failure in this great process of adaptation are disease and unhappiness" (Selye 1955).

These words come very close to the essence of this thesis. We are now finally able to show biologically, all the way down to the mitochondriae and the genomic level, how true the words of this endocrinologist were. Thereby, biomedicine can no longer escape what philosophers, artists, sociologists and humanistic doctors have known for centuries: The social context matters. The coming years are bound to bring a lot more evidence on this, but we already know enough to demand change. To quote Sir William Bragg, winner of the 1915 Nobel Prize in Physics:

> "The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them".

8.7.1 The importance of understanding and addressing 'gains' and 'drains'

From the statement made by Selye it could be said that health is a matter of adaptation, or being able to juggle both the health-promoting and pathogenic factors in life, as outlined in the *salutogenic model* of health, stress and coping introduced in section 8.4 (Lindström and Eriksson 2005). I argue that the medical doctor has an important function as a companion and advisor in this process. And to be the observant co-thinker and advisor for another person, the doctor needs words that convey the right meanings.

As previously described, professor in general practice Anna Luise Kirkengen uses the metaphorical terms *gains* and *drains (*Norwegian: *det som nærer* og *det som tærer)* to explain the model of allostatic load in ordinary language (Kirkengen 2010). But in order to understand what it is that drains, and what it is that gains a person, we must first understand what it is *to be* a person. This is one more philosophical concept that is difficult to comprehend in depth although most of us think we understand the concept pretty well beforehand. As described by physician and philosopher Eric Casell:

> "A person is an embodied, purposeful, thinking, feeling, emotional, reflective, relational, very complex human individual of a certain personality and temperament, existing through time in a narrative sense, whose life in all spheres points both outward and

> inward. Each of these terms is a dynamic function, constantly changing, and requiring action on the part of the person to be maintained" (Cassell 2013 p28).

From the perspective of embodiment, it is not possible to imagine feelings and experiences without appreciating that it all happens in the body. Unbuffered feelings of purposelessness, lack of meaning, social isolation, humiliation, lack of necessary control, i.e. feelings that undermine the very essence and integrity of the person, are associated with biological vulnerability and represent a threat to health, as I have described earlier in this thesis.

Fortunately, however, it works both ways: recent studies have shown how positive psychological states, such as hopefulness and life satisfaction, can lower cortisol output and be favourably associated with variables such as heart rate, blood pressure and inflammatory markers, leading to reduced cardiovascular disease and increased resistance to infections (Steptoe et al. 2009). A recent meta-analysis showed that positive affect, optimism and hopefulness were associated with reduced mortality (Chida and Steptoe 2008). Spiritual peace has been shown to lower mortality risk among patients with congestive heart failure (Park et al. 2016). A recent study comparing health outcomes, such as the number of health conditions, better health behaviour, and better health-related quality of life in light of adverse childhood experiences, showed that dispositional mindfulness, i.e. a general awareness of sensations, thoughts, and feelings in the present moment while suspending judgements, was associated with better health outcomes at each quantified level of adversity (Whitaker et al. 2014).

The above findings bring us back to the previously introduced concept resilience (see section 2.6.2). Beyond pure biological sturdiness, it draws attention to salutogenic processes and positive individual traits that help buffer stress (Ungar 2011). Here, physicians can play a positive and supportive role. In the presence of chronic disease and multimorbidity, this becomes of utmost importance (Ghanei Gheshlagh et al. 2016, Wister et al. 2016). Studies among patients with chronic conditions have shown that resilience is positively associated with self-care, treatment adherence, health-related quality of life, pain perception, physical activity, self-empowerment, self-sufficiency, reduced stress and anxiety, as well as accelerated recovery (Ghanei Gheshlagh et al. 2016).

It is however important to realize that resilience is not a static trait. A person may have different capacity for adaptation, depending on the challenge at hand, context and culture (Ghanei Gheshlagh et al. 2016). In line with the model of allostatic overload, a (previously) resilient person's capacity for further adaptation might become exhausted after years of tackling challenges. This might explain some of the social inequities in health (Brody et al. 2016).

8.7.2 The person in the medical encounter

Looking at disease and suffering from the person's perspective, Casell states:

> "Almost nothing about persons is unaffected by sickness. What sickness does is impair function, but the functions that it limits are found in every sphere of a person's life as it is lived. The knowledge of this provides an opportunity to understand sickness, but it also creates therapeutic opportunities that are far greater than are usually considered. The fundamental understanding that must not be forgotten diagnostically or therapeutically is that whatever happens to one part of a person happens to the entire person. Also, however, whatever is done for one part of a person has an impact on the whole person" (Cassell 2013 p50).

In light of the resilience concept, I find this passage very relevant. And as Mjølstad discussed in ther thesis, we are just in the beginning of *"reintroducing the person in medicine"*. She also points to two trends indicative of this. One is *"person-focused care,"* the other is "*narrative medicine"* (Mjolstad 2015).

The term *person-focused care* was introduced by Barbara Starfield in 2011. In the context of chronic, complex health problems, she states:

> "Care is better when it recognizes what the patient's problems are rather than what the diagnosis is (Starfield 2011)".

Person-focused care considers consultation episodes as part of a life-course experience with health, and it views diseases and body systems as interrelated phenomena. Compared to conventional patient-centred care, person-focused care builds on long-term relationships between doctors and patients (instead of episode based). It also focuses more on the evolution of people's experienced health problems. Starfield argues that a long-term clinical relationship provides a better basis for understanding the person's health problems and identifying the medical needs in the context of other needs (Starfield 2011).

Starfield explicitly states that a person-focused (rather than disease-focused) view of multimorbidity, where multiple illnesses can interact in a myriad ways, can more accurately depict the possibly greater impact of illness for those experiencing disadvantage. It furthermore represents interventions that take into account this possible vulnerability to, and interactions among, diseases (Starfield 2011).

To most scholars, *narrative medicine* focuses on the patient's narrative or story in order to understand the meaning of the illness for the person and enhance empathy in the clinician. In other words, it sees the narrative as a tool to promote more rewarding and healing encounters, both for patients and doctors. Its aim is to restore humanity in medicine (Mjolstad 2015).

Person-focused care and narrative medicine thus both aim to introduce a personal level into the clinical relationship. They pose compatible approaches, based on doctor-patient relationships and an intimate, broad knowledgebase of the patient as a person through his or her biography, experiences and needs. In the research group I belong to in Trondheim, we are now considering how the concept of allostasis and the links between biography and biology might relate to narrative medicine. A discussion of that topic is however beyond the scope of this thesis.

I would like to end this discussion by a proposal from Sir William Osler, as he attempted to modernise Hippocrates – or the *Koan way* to approach medicine. Osler argued that the physician's role was to treat disease in the body (biomedical reductionism) while attending to the human being, the person, who has the disease. He aimed to apply the medical model non-reductionistically. Where overt and curable disease is present, one can treat the disease; where disease is ameliorable but not curable, one might try to control the disease but with increased attention to the potential risks involved and the needs of the person. Where suffering is diffuse and hard to define, one attends primarily to the human being as a person (Ghaemi 2009). In total, this can be seen as a contemporary version of the Hippocratic vision *To cure sometimes, treat often, comfort always.*

9 Implications

The potential implications of this thesis are many. I will roughly divide them in three categories: A need for change in biomedical theory and practice; implications for politics and public health; and finally, implications for clinical medicine with a focus on primary care - both at the organisational and clinical level.

9.1 Biomedicine challenged

Both in the *Introduction* and *Discussion*, I described how I have come to see a link between the increasing challenges of multimorbidity and fundamental short-comings in the biomedical paradigm, as mirrored in everyday research and practice. I have criticized mainstream medical thinking for being too reductionistic and discussed how evidence-based medicine has come to marginalize the health impact of social conditions and life experiences. I have noted how I see human suffering as down-graded in the medical hierarchy of health problems and pointed to the term "epistemic injustice" in that connection. I have discussed how a disease (or organ) specific organisation of health services, clinical guidelines, and risk-factor driven research represent fundamental premises for the highly challenging situation in contemporary primary care. As a consequence of this all, I allow myself to ask: perhaps these accumulated challenges reflect problems so fundamental that we need a medical paradigm shift, in the sense of Kuhn (Kuhn 1970)? I will not expand my argument further in that radical direction. I will instead turn to more concrete and immediate implications.

9.2 Political and public health challenges

The political and public health implications of the subject of this thesis are profound. However, the general connections between social disadvantage and poor health have been described and discussed by several scholars and professional societies. One might in fact ask why this effort is hardly traceable in contemporary public policies around the world. Even in a social democratic country such as Norway, the social gradient is on the increase, with deleterious effects for children (Oppvekstrapporten 2017). But the increasingly clear gap between scientific knowledge and political action is not a major theme in this thesis. I will only mention a few examples of evidence-based, policy statements that are in full accord with the findings of my research:

In the report *Fair Society, Healthy Lives,* Michael Marmot states that social inequalities are a matter of life and death and that "reducing health inequalities is a matter of fairness and social justice" (Marmot 2010). Furthermore, he states that "creating a fairer society is fundamental to improving the health of the whole population and ensuring a fairer distribution of good health" (Marmot 2010).

Adversity and associated toxic stress levels have shown the strongest effect in childhood. In 2011, the American Academy of Paediatrics issued a policy statement on the subject where they advise development of innovative strategies to reduce the precipitants of toxic stress in young children and to mitigate their negative effects on the course of development and health across the life span (Garner and Shonkoff 2012).

There is growing international recognition of the vast implications of early childhood for a nation's economy, for example creating better health, social-, educative- and economic outcomes for society. A pioneer in this field is Nobel Laureate James Heckman (Heckman 2013). On the same note, the Nordic Federation of General Practice issued a policy paper in 2013 on the role of the GP in preventing disease:

> "One of the most significant preventive measures is to ensure that every child grows up in a secure environment in the presence of responsible adults" (Nordic Federation of General Practice 2013).

From this point on, I will focus on more proximate implications of my work. These involve medical education, healthcare organisation, and clinical work in general practice.

9.3 Biography impacts on biology: a challenge for medical education

A popular phrase from hospital physician and pioneer in medical education Sir William Osler comes to mind:

> "It is more important to know what type of person has the disease than to know what type of disease the person has".

This statement can evidently be interpreted in various ways. But it surely applies to persons suffering from complex health problems and multimorbidity. Although it might be misleading to conceptualise types of persons in analogy to types of diseases, it seems wise to

consider the impact of experience on people's health. Consequently, one interpretation of Osler would be: It is crucial for a physician to acknowledge that their patients have incorporated their lifetime experiences not only as verbal memories and stories, but also as physiological inscriptions. These embodied stories inform their very being, affecting their general health and also the particularities of their symptoms and ailments (Kirkengen 2010).

This implication conveys a major message to medicine as a whole, not only to primary health care where patients and doctors have the chance to get to know each other on the basis of several encounters over time. Acknowledgement of the fact that many patients have embodied stories of adversity, by some experienced GPs metaphorically referred to as "carrying heavy backpacks", is important in all clinical encounters. It may in fact be especially important when *not* knowing the patient as a person, for instance in an out-of-hours encounter late at night. In most instances, that is not the right time to elicit people's life-stories. But it is still possible to act professionally, respecting that people who seek medical help/attention in awkward ways, and typically at unsuitable times, are often people who would have a tough story to tell, if ever asked.

Quite radical changes in medicine must evidently be accompanied by corresponding changes in the basic education of doctors. Medical education is still to a high degree focused on the provision of evidence-based care for specified diseases. Very little focus is on understanding whole persons in illness and health, and most young doctors are thereby far better prepared for specialist-driven than generalist-based medicine. Consequently, work in the medical frontline in general, and general practice in particular, can be very frustrating and fear-provoking for a novice who becomes overwhelmed and mistakes (potentially intriguing) clinical complexity for (unmanageable) chaos. In my own experience, it is in most instances possible to navigate the labyrinths of primary care in a rewarding manner. But in order to do so, you must be able to acknowledge the person in front of you.

9.4 Time in the first-line clinical encounter

As said, I see Osler's statement in a new light after writing this thesis. And I think it might be even more relevant in general practice than in the hospital setting where Osler formulated it. I have already introduced the concept person-focused (or person-centred) care, and stated that it builds on long-term relationship and mutual recognition of both the patient and the doctors

as persons, in the sense of doctor and philosopher Eric Cassell (see 8.7.1). But what does it take to implement person-focused care, beyond understanding what it is all about?

To do a good job, especially with multimorbid persons, the GP needs sufficient *time*. Time to listen, ask and think. To sort out and prioritize the person's problems and risk factors, key biographical information, values and preferences. And due to the current state of affairs in EBM and clinical guidelines (see section 8.5.3), the GP will need additional time to consider, compare and, to the extent possible, accomodate recommendations from different disease-specific guidelines. And these processes and negotiations should take place in a transparent and including manner, to establish and maintain mutual trust and respect.

Asking for more time, one might soon encounter the argument that person-focused care sounds like waste of limited resources, despite the arguments listed above. I will argue against this and state that on the contrary, if the doctor can invest sufficient time when needed, time and resources can be saved in the long run. This is in line with Michael Balint's term "*doctor as a drug"* (Balint 1968) which refers to the clinical impact of asking, listening, accepting, and being there for the patient, something that appears especially vital in the presence of complex health problems and social disadvantage. Young doctors have often confessed to being afraid of not having enough experience or resources to deal with all the complex and painful human stories. But I am convinced that just being there, asking and accepting, has clinical impact. If both doctor and patient are able to create a shared understanding of what is going on in the person's life, they create coherence, a cornerstone of salutogenesis. Influenced by sociologist Arthur Frank (Frank 2007), Linn Getz has stated:

> "The process of establishing a sense of meaning, where a person could previously see only apparently fragmented and meaningless events or experiences, involves healing potential" (Getz 2006 p 42).

In line with the above argument, recent evidence indicates that longer consultations in general practice result in more appropriate health advice, less prescribing and increased patient satisfaction (Wallace et al. 2015). Despite this fact, time is a very limited resource for most GPs I know, and lack of time thereby presents a modifiable hindrance to effective clinical work. The last years have seen increasing focus on "productivity", "pay for performance" or "pay per visit"; systems which encourage quick throughput of patients. Treatment outcomes are often evaluated on the basis of easy-to-measure parameters that may not give a valid

picture of the overall outcome for the patient. In other words, the prevailing situation is at odds with what is most needed in the face of medical complexity. As Mangin et al. wrote in 2012 when discussing person-centred medicine:

> "However, all these attributes are being rapidly eroded in face of payment by results and a system that evaluates the quality of care and doctors on the basis of siloed adherence to evidence based guidelines for single diseases. This move carries the potential to disempower doctors and patients and prevent them from using their observation of individual responses and needs (Mangin et al. 2012)".

9.5 The need to invest more resources in primary health care

As previously explained, multimorbidity has become the new norm in the Western world. To avoid unfavourable and potentially risky fragmentation of care, patients need doctors with broad, generalist knowledge. Furthermore, this thesis indicates that good care for multimorbid patients also presupposes knowledge about each patient's life history and current circumstances. Consequently, one may argue that general practice is needed now, more than ever. One might even argue that multimorbidity constitutes *the core challenge* of primary health care as a discipline today.

It has been shown that healthcare systems underpinned by strong generalist primary care produce better health outcomes for patients with chronic illness, at lower cost and with less health inequality than systems without this foundation (Starfield et al. 2005, Mangin et al. 2012). And, as I have also explained, expert generalist care is not just the sum of competent care for a number of independent conditions. It crucially combines the biotechnical with the biographical and tailors interventions to each patient's circumstances and preferences (Moffat and Mercer 2015).

The mandate of general practice (family medicine) is to cover the human lifecourse *"from the cradle to the grave"*, attending to the whole family and thereby knowing the patients' background, history and social context. The GP profession is often emphasized in political vision papers and strategy plans. However, in many countries (including Iceland and Norway) GPs still have to fight for their discipline, as national authorities are still often disregarding it and underfunding it.

Despite overwhelming, new knowledge pertaining to the relationship between social life conditions and health, little has changed in everyday medical life as I know it. The fragmentation of care is still continuing at the expence of developing primary health care further, engaging increasing numbers of subspecialists who apply ever more advanced and costly diagnostic technologies. Until someone is able to prove the opposite, I see the development of systems medicine as part of that hyper-reductionistic wave, despite its explicit aim to promote medical "holism". Before further fragmentation is allowed to happen, all patients should at least have secured access to a coordinating generalist physician they know and trust.

It is also of interest to contemplate, in light of the literature on subjective experience, whether primary care doctors could in general rely a bit less on technical and often expensive approaches, and more on a relationship-based, person-oriented approach. How often could a well-trained GP succesfully reduce the focus on clinical measurements and pay more attention to good dialogues about that, which really matters to the patient? And when encountering someone who feels and looks genuinely healthy, the good GP should not undermine this positive perception unless for a very clear reason. Futhermore, when looking at the literature on self-rated health as a strong indipendent risk factor, one might consider the patient's own perceptions equally relevant as measuring blood-pressure or weight. This becomes a particularly interesting speculation with regard to the vision of systems medicine and life-long, personal monitoring of every imaginable variable in the person's body and life. Can that be combined with an effective, personal clinical relationship?

At the level of health care organization, it is important not to confuse an interdisciplinary, disease-oriented approach with a genuinely person-centered approach. Within organ-specialized health care, we currently witness establishment of new competence centres, with the aim of looking at a given medical problem/diagnosis (e.g. chronic pain, fatigue or obesity) from several professional angles, including psychosocial assessment. This approach can obviously lead to valuable new insight, both for the patient and the health care providers. But as I see it, it can not replace the GP's person-perspective. A genuine person-perspective puts the *person first*, before the symptom or disease in question. I argue that it is not a wise and sustainable move to establish an interdisciplinary team at the tip of ever more sub-specialized, medical branches.

9.6 Core tasks of family physicians/GPs

Through the discussion, we saw how multimorbidity demands a shift in focus away from the biomedical reductionist approach. We saw how subjective experiences of hardship, through biological disruption, can pave the way to complex disease development. We have furthermore seen the importance of the person-perspective when managing such complex health problems. With these themes in mind, I will mention four tasks that I see as essential to the work of family physicians /GPs, and that highlight the importance of the profession:

Consider the complete picture: It is an essential GP task to take a wider look at the person's symptoms and diseases. It is the core of the family physician's profession to work outside medical silos, with the focus on the person, trying to understand and manage the whole spectrum of a person's health problems.

Work with person's biography and narrative: It is an essential GP task to look at the patient or person towards the background of his or her biography. It is an old truth for family physicians that biography shapes health. However, we are now finally able to show scientifically how subjective experience affects the complex interactions of human biology. It is the family physician that stands at the bridge between biography and biology when interpreting the person's symptoms and ways of dealing with them.

Give weight to the person's values and preferences: It is an essential GP task to incorporate the person's values and preferences when managing different diseases. Today, the family physician still stands in a heap of clinical guidelines, sorting through and customizing different treatment options to fit the individual patient. Strict followers of evidence-based medicine and clinical guidelines have sometimes talked about *clinical inertia*, blaming family physicians for not adhering well enough to guidelines, when it is in fact obvious that the guidelines have never fitted the average patient. The new NICE guidelines for multimorbidity (mentioned in section 2.1.9) are therefore a breakthrough in the history of clinical guidelines, as they finally introduce a person-perspective. They are in other words the first guidelines I have read that truly have a primary health care focus.

Seek new knowledge where it can be found: Finally, since it is the GP's task is to understand health and disease in whole human beings and in a wider context, one may ask what the knowledge base of general practice should look like. The typical, medical curriculum

provides a strong base, but far from all that is needed. It is therefore an essential task (and privilege) for a GP to maintain a desire to investigate and learn from many different sources, be it scientific or humanistic; epidemiology, biology, psychology, sociology, philosophy, artistic expressions and – not the least – the every-day encounter in clinical practice. It is the family physician who stands there in the light of diverse information, with the ambition to take in that, which is likely to benefit the person seeking help.

9.7 Some ideas for future research

Before I finish this project, it is time to ask: what research would I like to engage in next, at a relatively concrete level? With regard to both multimorbidity and the biology of disadvantage, the increasingly more often mentioned *life-course approach* suggests that new and relevant evidence will be provided in the field I have been working. The life-course approach is the study of the long-term impact of physical or social exposures during different stages of life (Kuh et al. 2003). The approach focuses on critical and sensitive periods of life with regard to health risks and development and sets up a conceptual framework for exposures acting across the life course (Ben-Shlomo and Kuh 2002). This approach is currently gaining increased recognition and popularity with the medical profession, having deeper roots in other fields, such as psychology and sociology.

With regard to more specific research options, I see many possibilities. Looking at multimorbidity as partly a medical artefact, it would be interesting to compare the association of multimorbidity on one hand, and self-rated health on the other, with mortality, frailty, hospitalization, etc. Further validation of the childhood question is also needed. It will be included again in the next HUNT Study (HUNT4). Digging deeper in the field of subtle subjective stress factors, and even more so into different combinations of stress in different aspects of life, would also be intriguing. It is furthermore of great interest to dig deeper into the possible chronology of disease development in multimorbidity, could there be a difference in chronology based on adversity and difficulties in earlier life?

The empirical studies on which this thesis is based do not prove causality in any strict sense. But the results are in fine concordance with our hypothesis, which encourages both me and my co-authors to keep exploring the meaning and relevance of the allostasis concept in

primary care. And we would like to further explore how a GP can work sensibly and effectively in a person-focused manner.

Many other research options could also be mentioned, but I will end my list with a quote which is posted on the door to professor Bruce McEwen's research laboratory in New York City:

> "The greatest obstacle to discovery is not ignorance: - it is the illusion of knowledge"
>
> Daniel J. Boorstin

10 Closing remarks

The writer and social reformer Frederick Douglass once stated:

> "It is easier to build strong children than to repair broken men".

It is a powerful sentence, especially in light of his background as an African-American slave in the 19th century.

For a privileged female doctor in the 21st century, the years of PhD studies have brought many surprising discoveries. I still wonder which came as more of a surprise: reading the ACE study by Felitti and Anda, realizing that over 50% of middle-aged, middle-class Americans reported at least one adverse childhood experience, with 22% reporting sexual abuse and over 10% psychological abuse in childhood (Felitti et al. 1998); or that, at the end of the 20th century, this was still almost unknown – or at least hardly talked about by the medical profession – and is maybe just starting to sink in now, 20 years later.

The same can be said regarding the strong relationship Felitti and Anda have found between ACE and many of the leading health problems we are facing, as well as the results of the Whitehall studies, or the studies by Anna Luise Kirkengen. When we know so much about the relationship between cholesterol and cardiovascular risk, being relatively modest in relation to the impact of violence and abuse, it feels like professional neglect to realize that none of the medical students I teach in their final year in Reykjavik have heard about the ACE Study until I tell them about it.

It surprises me even more how new this insight seems to be for the medical profession when I tell my patients about my PhD project, and they smile and say (and this has happened repeatedly): "Oh, you're writing a thesis about me!" For me this means that mainstream medicine still has a big, blind spot, as I have repeatedly pointed out in this thesis.

I have thought extensively about this contradictory situation and in this thesis, I have mainly discussed it as based on flaws in the Knidian biomedical model. However, this is not the only idea that has come to mind. I find it just as likely to be a consequence of the medical profession having been led by male doctors throughout history (like most other professions). I

most likely find it to be a consequence of culture, be it male or female driven. Up until very recent years, Western culture has leant heavily on rationality as the way to progress and not deemed it civil to talk about such messy things as abuse, let alone imagine that more subtle factors, such as job-insecurity, loneliness or a cold shoulder from your spouse could lead to ill health (except in the case of hysteria…).

Therefore, if I were to make one main conclusion from this thesis, it would be about the importance of subjective experience regarding complex disease development. Despite the fact that the data presented can only be approximated to associations but not to causal relationships, I believe the extensive literature paints a clear picture.

When examining multimorbidity, termed one of the biggest medical challenges of the 21st century, it is evident that negative subjective experience is a very important risk factor regarding its development. It is therefore of utmost importance that the medical profession as a whole reinstates and further refines the generalist perspective, focusing on the person, not the disease.

Epilogue

Last year, after a lecture I held on the topic of this thesis, a woman approached me. It was an elegant, successful woman just under the age of seventy. She told me she had heard me speak before, and that she felt a need to tell me just how important this subject of adversity and violence was. She told me further about how she had gone from doctor to doctor, seen psychologists, psychiatrists, social workers, nurses, family physicians. But up until last year nobody had taken notice of her history of abuse in relation to her health problems. Yes, I said, a bit flustered, it is true, this matters a lot.

> No, Margrét, she said. My whole life. My health, my relationships, my work, everything. It is *all* that matters.

It left me speechless. And I have thought about it profoundly. Mostly I have thought down this road: Can I put this in my thesis? Isn't it a bit too much? Can I state this, as a doctor? Certainly, other things matter as well, of course it is not *all* that matters, what if she had appendicitis, then this wouldn't really matter. Just get the surgeon in and the appendix out. And what about others that have had similar things happening to them, do they feel the same? Is it too much of a generalisation?

But I have changed my mind. This *must* be written here. We are reasonable beings, we know all the other things; the orchid children, the risk factors being just risk factors. But my experience tells me that when I argue for the fundamental clinical relevance of violence, a debate will follow that certainly adverse experiences matter, *but..."* And then the debate would travel into scientific explorations of pros and cons, away from the naked essence of my statement. And if I now choose to reason this woman's powerful sentence into nothingness, I would be falling into the same pit I am suggesting we move away from as a profession.

For this elegant woman, this was *all that mattered.*

To write this thesis has often been a struggle, in a life led by busy schedules and many responsibilities. And sometimes I've not been so sure why I am going through all this trouble.

A few weeks ago, my daughter Sigrún, recently turned five, asked me innocently during dinner:

> Mom, are you writing this thesis because you want to or because you have to?

It shook me back to where I belong. I am doing this because I want to and because I feel it must be done. I do it for her future.

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Paper I

European Journal for Person Centered Healthcare Vol 2 Issue 3 pp 335-345

ARTICLE

Co- and multi-morbidity patterns in an unselected Norwegian population: cross-sectional analysis based on the HUNT Study and theoretical reflections concerning basic medical models

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Abstract

Rationale and aims: Accumulating evidence shows that diseases tend to cluster in diseased individuals, so-called multimorbidity. The aim of this study was to analyze multimorbidity patterns, empirically and theoretically, to better understand the phenomenon.

Population and methods: The Norwegian population-based Nord-Trøndelag Health Study HUNT 3 (2006-8), with 47,959 individuals aged 20-79 years. A total of 21 relevant, longstanding diseases/malfunctions were eligible for counting in each participant. Multimorbidity was defined as two or more chronic conditions.

Results: Multimorbidity was found in 18% of individuals aged 20 years. The prevalence increased with age in both sexes. The overall age-standardized prevalence was 42% (39% for men, 46% for women). 'Musculoskeletal disorders' was the disease-group most frequently associated with multimorbidity. Three conditions, strategically selected to represent different diagnostic domains according to biomedical tradition; gastro-esophageal reflux, thyroid disease and dental problems, were all associated with both mental and somatic comorbid conditions.

Conclusions and implications: Multimorbidity appears to be prevalent in both genders and across age-groups, even in the affluent and relatively equitable Norwegian society. The disease clusters typically transcend biomedicine's traditional demarcations between mental and somatic diseases and between diagnostic categories within each of these domains. A new theoretical approach to disease development and recovery is warranted, in order to adequately tackle 'the challenge of multimorbidity', both empirically and clinically. We think the concept allostatic load can be systematically developed to "capture" the interrelatedness of biography and biology and to address the fundamental significance of "that, which gains" *versus* "that, which drains" any given human being.

Keywords

Adverse life events, allostatic load, disease classification, disease clustering, multimorbidity, person-centered care, theory of science

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Accepted for publication: 30 May 2013

Introduction

By biomedical convention, most diseases are conceptualized, diagnosed and treated as single and independent entities [1-5]. Recently, however, we have witnessed rapidly increasing interest in co- and multimorbid disease patterns [1-4,6-12]. Many, even most, consultations in primary care involve patients with multimorbidity [13]. Primary care providers typically carry the main clinical responsibility for multimorbid patients, except when uncommon conditions are involved [7]. Patients with a relatively low socio-economic status and a correspondingly high disease burden have been shown to use a comparable amount of primary care services, but less specialized out-patient care, compared to patients from higher socioeconomic strata [14,15].

Valid information about the frequency and nature of disease co-occurrence and clustering in individual persons is crucial for organizing effective healthcare, ranging from disease classification and reimbursement systems *via* training of personnel to development of clinical guidelines and preventive programs. Gathering reliable evidence is, however, demanding [16,17]. There is a well-documented association with age, but multimorbidity has been shown to be prevalent even in younger age groups [13,18]. A recent Scottish study, based on a comprehensive primary care database, found that, numerically, more than half of the individuals with multimorbidity were younger than 65 years [19]. Some co-morbid disease associations are particularly well-documented, such as the co-occurrence of depression and metabolic syndrome/cardiovascular disease [20–23]. Until now, prevalence estimates, organizational and therapeutical implications, as well as the general health impact of co-and multimorbidity, have received most scientific attention, but there is also rising interest in causal mechanisms and pathways, ranging from the genetic to the environmental level [24]. Research from various contexts documents that multimorbidity is increased by low socioeconomic status [19,25-29]. Job strain is also associated with worse health and increased disease burden [25,30-32]. Concerning biomolecular mechanisms, some researchers focus on specific pathways, such as systemic inflammation [22,33] or autonomic imbalance [34], while others apply a systems-oriented, life-course perspective [24,35,36]. The US Adverse Childhood Experiences study found a dose-response relationship between adverse childhood circumstances and the number of diseases in adult life, both in the somatic and mental domains [37,38]. Scientific explanations of how adversity gets "under the skin" have been developing and converging over the last decade [39-43].

To sum up, the scientific knowledge pertaining to multimorbidity is rapidly advancing, but still incomplete at every level [44], ranging from prevalence data and cluster descriptions across populations and subgroups (gender, ethnicity, social class), down to precise conceptualization of what - and how - lifetime experience become embodied [45] in a life-course perspective. The aim of the present study was to deepen existing knowledge about the distribution and nature of disease clustering and multimorbidity. We present and discuss data from a Norwegian population study which, by international comparison, represents an affluent, stable and ethnically homogenous society with only moderate degrees of social inequality.

Study population and methods

Our data come from the Nord-Trøndelag Health Study (HUNT), a renowned, longitudinal, total adult population-based study [46]. The third wave, HUNT 3, was carried out 2006-2008. All adults 20 years and above were invited to participate. In total 27,779 women and 23,060 men participated; the participation rate was 54% [46]. Our study group is shown in Table 1. An analysis of non-participants showed that the oldest and youngest groups were somewhat underrepresented, along with people of lower socioeconomic status [47]. The HUNT population has been considered fairly representative for Norway, but since Nord-Trøndelag lacks large cities, the social gradient in the HUNT population might be smaller than for Norway as a whole [15,46].

Table 1 Participants and participation rates according to age groups and gender

Age	Number	% of invited	Females	Males
20-29	4, 276	30.0	2, 517	1, 759
30-39	6, 906	43.9	4, 024	2, 882
40-49	9, 982	56.3	5, 440	4,542
50-59	11, 391	65.8	5, 981	5, 410
60-69	9,741	70.6	5, 112	4, 629
70-79	5,663	65.9	3, 036	2, 627
Total	47, 959	54.8	26,110	21, 849

The HUNT 3 data were collected by means of questionnaires, interviews, clinical examinations and blood and urine samples. For the present analysis, we included participants aged 20-79 years. We selected 21 relevant disease conditions for an analysis of multimorbidity (Table 2). Twelve of these conditions were self-reported in response to the question "Have you had or do you have the following medical condition?" Regarding cardiovascular disease (CVD), we included the following conditions: a history of myocardial infarction, angina pectoris, heart failure, other heart disease and/or stroke. Hypertension was defined as a positive answer to the question "Do you take or have you taken antihypertensive medicine?" and/or severe hypertension (systole ≥180 mmHg and/or diastole ≥110) [48] at the clinical examination. To avoid double registration, the presence of self-reported CVD was used as an exclusion criterion, as the definition was based on use of medication. Hyperlipidemia was defined as fasting total cholesterol above 7.0 mmol/L and/or fasting triglycerides above 3.0 mmol/L. Chronic back pain was based on a report of having pain/stiffness in the back or neck that had

Table 2 Disease prevalences (%) in the age-group 40-59 years (absolute numbers within brackets)

Disease	Total		Females		Males	
Cardiovascular disease	5.3	(1,126/21,379)	3.6	(406/11,423)	7.2	(720/9,956)
Renal disease	2.3	(4,90/21,378)	2.5	(291/11,422)	2.2	(199/9,956)
Hypertension	13.0	(2,356/18,151)	13.2	(1,280/9,662)	12.7	(1,076/8,489)
Hyperlipidemia	20.2	(3,236/16,002)	17.2	(1,462/8,513)	23.7	(1,774/7,489)
Diabetes	2.8	(6,07/21,379)	2.3	(264/11,423)	3.4	(343/9,956)
Obesity	23.0	(4,901/21,324)	22.1	(2,522/11,393)	24.0	(2,379/9,931)
COPD	2.5	(5,24/21,378)	2.6	(302/11,422)	2.2	(222/9,956)
Asthma	9.2	(1,971/21,379)	9.5	(1,083/11,423)	8.9	(888/9,956)
Chronic back pain	37.1	(7,927/21,380)	42.2	(4,819/11,424)	31.2	(3,108/9,956)
Mental health problems	15.0	(3,128/20,799)	18.5	(2,051/11,094)	11.1	(1,077/9,705)
Cancer	3.2	(682/21,379)	4.0	(460/11,423)	2.2	(222/9,956)
Psoriasis	6.4	(1,370/21,379)	6.4	(733/11,423)	6.4	(637/9,956)
Gastro-esophageal reflux	7.2	(1,176/16,310)	6.7	(595/8,921)	7.9	(581/7,389)
Thyroidal diseases	6.7	(1,125/16,814)	10.1	(935/9,277)	2.5	(190/7,537)
Dental health problems	7.5	(1,300/17,227)	7.1	(668/9,462)	8.1	(632/7,765)
Osteoarthritis	10.6	(2,192/20,702)	13.7	(1507/11,028)	7.1	(685/9,674)
Fibromyalgia	4.1	(843/20,798)	6.9	(764/11,095)	0.8	(79/9,703)
Rheumatoid arthritis	3.2	(671/20,843)	3.7	(411/1,125)	2.7	(260/9,781)
Ankylosing spondylitis	2.0	(416/20,880)	1.9	(217/11,148)	2.0	(199/9,732)
Osteoporosis	1.1	(240/20,885)	1.8	(204/11,139)	0.4	(36/9,746)
Epilepsy	1.3	(275/20,933)	1.4	(153/11,177)	1.3	(122/9,756)

lasted more than 3 months during the last year. Thyroidal disease was defined as either hyper- or hypothyroidism; dental health problems when the participant defined dental health as bad or very bad; gastro-esophageal reflux as much heartburn/acid regurgitation during the last year and, finally, clinically relevant mental problems were defined as a positive answer to the global question: "Have you had or do you have mental health problems for which you have sought help?"

We estimated the prevalence of multimorbidity as a simple count of 2 or more co-inciding diseases and/or relevant conditions in the same person [9], age-specific as well as age-standardized (European standard) [49]. Prevalence numbers of mental health problems were estimated in relation to somatic health and odds ratios (ORs) were generated for the association of mental health problems with the number of somatic health problems. In our analyses of multimorbidity, missing values for independent diseases were defined as negative.

Regarding specific diseases and their associations, we focused on the group 40-59 years, where disease prevalences are typically higher than in younger age groups and multimorbidity prevalences lower than in older age groups. We excluded participants with missing data about the disease in question (Table 2). Associations of selected diseases were tested with Chi-square test and odds ratios, with 95% confidence intervals (CI) generated. We decided to look more closely at disease clustering around 3 strategically selected conditions which, according to biomedical tradition, would be regarded as relatively different and distinct: that is, gastro-esophageal reflux, thyroid disease and dental health problems (including periodontal disease). SPSS statistical program (version 20) was used for calculations.

Ethical approval

Each participant in the HUNT Study signed a written consent regarding the screening and the use of data for research purposes. The study was approved by the Norwegian Data Inspectorate and the Regional Committee for Ethics in Medical Research.

Results

We analyzed data from 47,959 eligible HUNT 3 participants, aged 20-79 years. Figure 1 shows the prevalence of multimorbidity and how it steadily increases from 14% among people aged 20, to 33% for people aged 40 to 62% for people aged 60 and to 77% for people aged 79 years. The overall age-standardized prevalence of multimorbidity in the age group 20-79 years was 42%. Bold numbers in the figure add information regarding the age-standardized prevalences of multimorbidity, with reference to the number of diseases/conditions. The data show a significant difference ($p<0.001$) in prevalence

Figure 1 Age distribution and prevalence of multimorbid diseases/conditions among participants aged 20-79 years in the HUNT 3 Study. Bold prevalence numbers are age standardized

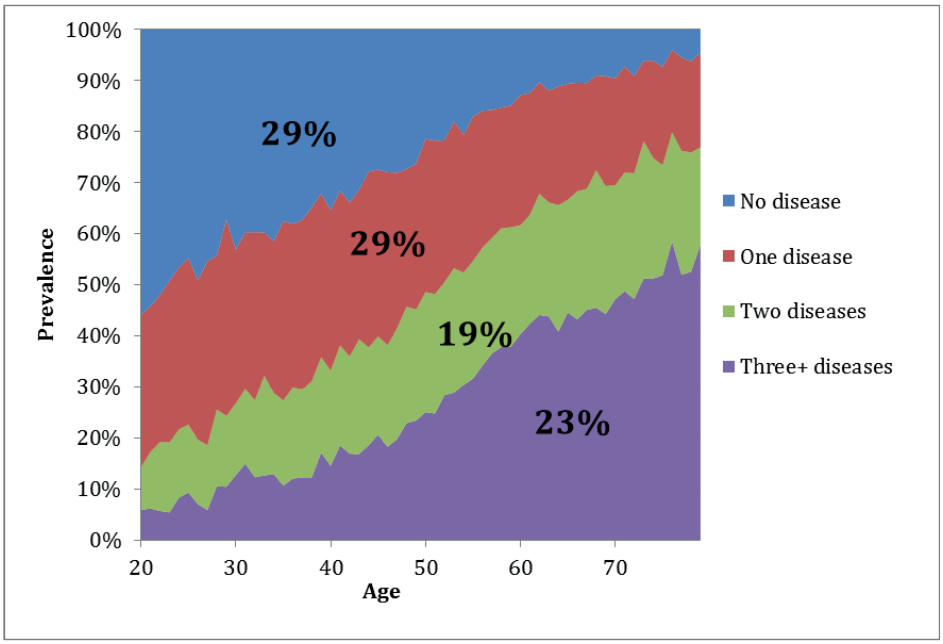
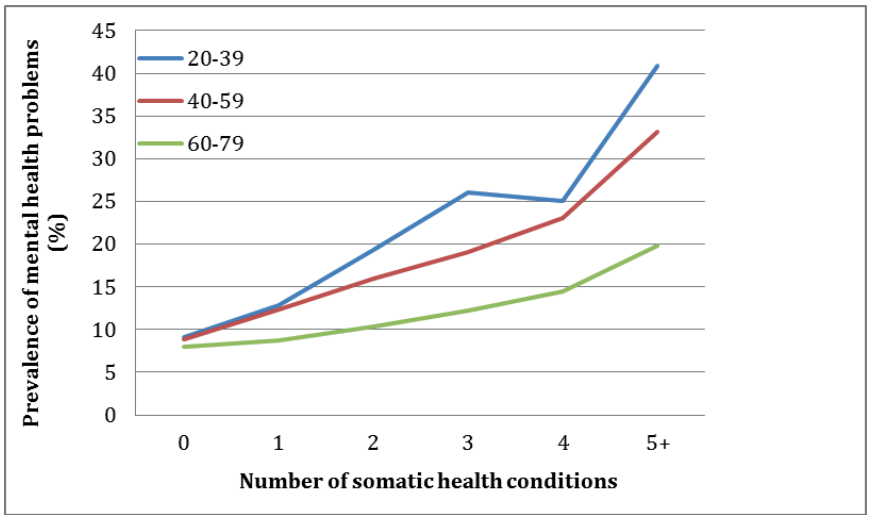


Figure 2 Prevalence of mental health problems in relation to increasing number of somatic health conditions in the age groups 20-39 years; 40-59 years; and 60-79 years in the HUNT 3 study



between genders; males had a total prevalence of 39%, compared to 46% among women.

The gender differences are further detailed in Table 2. They were most prominent for the most common diseases, with musculoskeletal conditions and mental health problems being far more common among women, whilst CVD and hyperlipidemia were more common in men (Table 2). In the age group 40-59 years, however, the most common diseases were equally prevalent for both genders;

chronic back pain, obesity, hyperlipidemia and mental health problems.

Figure 2 shows how the prevalence of mental health problems increased with the number of somatic health conditions. The association was greatest in the youngest group (20-39 years), with an OR increasing from 1.5 (95% CI 1.3-1.7) in the presence of one somatic disease to 6.9 (95% CI 4.5-10.6) in the presence of 5 or more somatic diseases. The results were similar for the 40-59 year group, where OR = 1.4 (95% CI 1.3-1.6) for one disease and OR = 5.1 (95% CI 4.3-6.0) for 5 or more diseases. The association was much weaker in the oldest age group (60-79 years), where the odds ratio did not differ significantly from 1.0 for one disease, but increased steadily from 1.3 (95% CI 1.1-1.6), with 2 diseases to 2.8 (95% CI 2.3-3.5) in the presence of 5 or more diseases.

We also analyzed the prevalence of multimorbidity with respect to single diseases among participants, aged 40-59 (Figure 3). Multimorbidity prevalence was highest in association with musculoskeletal diseases (fibromyalgia, ankylosing spondylitis, rheumatoid arthritis, osteoarthritis). A striking morbidity load was observed in association with gastro-esophageal reflux, thyroid disease and dental health problems. Consequently, we selected these "index" conditions and specifically addressed their degree of "overlap", as illustrated by Venn diagrams in Figure 4. The degree of overlap between diseases ranged from 13% to 32%. The overlap between any 2 of the selected diseases (Table 3) had odds ratios ranging from 1.3 (95% CI 1.2-1.4) for the well-documented combination mental health problems/metabolic diseases (obesity or diabetes) to 3.5 (95% CI 3.1-4.1) for mental health problems/fibromyalgia. All overlaps shown in Figure 4 were significantly greater than expected by chance ($p<0.01$).

Discussion

In this unselected and general Norwegian population with only moderate degrees of social inequity, multimorbidity proved to be common in all adult age-groups. The prevalences of the most common diseases were comparable in both genders, while multimorbidity as such was more common among women. An overall age-standardized multimorbidity prevalence of 42% is in accordance with some earlier reports [6,17].

The dose-response association between the number of somatic and mental disorders was prominent in all but the oldest age group. This finding is in accordance with previous research [19]. Beyond this, our study provides additional documentation of disease clustering, indicating identifiable patterns linked to the selected index conditions gastro-esophageal reflux, thyroidal disease and dental/periodontal health, again in accordance with previous observations [50-60]. Our findings add to the accumulating documentation that patterns of morbidity are ubiquitous and transcend the biomedical dichotomies somatic/mental and organic/functional and also the diagnostic categories within the specialized medical domains. This can be seen as posing a fundamental challenge to biomedicine's current way of conceptualizing risk, disease and recovery [24,61-63].

Looking for ways to deepen our scientific understanding of disease clustering and multimorbidity, we think it might be fruitful to study multimorbidity from the perspective of *allostasis* and *allostatic load.* The concept allostasis was introduced by Sterling and Eyer in the 1980s [64] and has subsequently been nuanced, developed and debated, see for instance [26,35,36,40,41,65-74]. Allostasis essentially refers to the body's (including the brain's) dynamic adaptation to challenges across multiple physiological systems, through which the organism actively adjusts to predictable and unpredictable experiences and stressors, small and big, 'physical' and 'mental', over time. Allostatic load neutrally denotes the cumulative impact of strain over time, while allostatic *over*load denotes a "red flag" physiological risk scenario, where the organism's adaptive and restorative capacity is overtaxed to such an extent that adaptability and flexibility is gradually lost [75]. The result is physiological dysregulation, at times expressed only in subtle but widespread perturbations. These might, in accordance with complexity theory, nevertheless have a significant cumulative impact on the entire organism. Allostatic overload provides 'soil' for disease development, influenced by individual, genetic susceptibilities, eventual maladaptive, non-favorable ways of living (unhealthy lifestyle) and even the microbiome [76,77]. With reference to a booming scientific interest in systems biology in general and systems medicine in particular [24], the allostasis concept might be compatible with a theoretical framework of *the lived body*, the lifelong embodiment of personal experience [78].

The main repository of the lived experience is the person's brain, with its capacity for decoding and memory and its paramount regulatory monitoring of systemic mediators of the autonomic, neuroendocrine, metabolic and immune systems that can promote allostatic overload. Moreover, in a situation of allostatic overload, these systemic mediators affect not only peripheral targets, such as organs, tissues and cells, but also "fire back on" the brain itself, including regions involved in cognitive, emotional and self-regulatory functions and result in remodeling of neural architecture that alters these functions as well as epigenetic changes that alter DNA methylation and patterns of gene expression [79,80]. The principally inevitable wear and tear on the body and brain take a toll on every individual, but the more efficiently allostasis is "buffered" or "counterweighted", the longer the ravages of cellular aging and disease development can in principle be delayed. Fortunately, the healthy brain has a considerable potential for reactivation of plasticity, providing new possibilities in the treatment of conditions previously believed to be very difficult, if not impossible, to change [36,81].

Grounded in the natural sciences, the concept allostasis can accommodate advancing scientific knowledge about biomolecular mechanisms and pathways. It is already an established framework for conceptualization of the detrimental impact of socioeconomic disadvantage and adverse lifetime experiences [26,36,41,57,58].

Figure 3 Number and distribution of disease clustering / multimorbidity by index diseases in the age-group 40-59 years. COPD = Chronic obstructive pulmonary disease

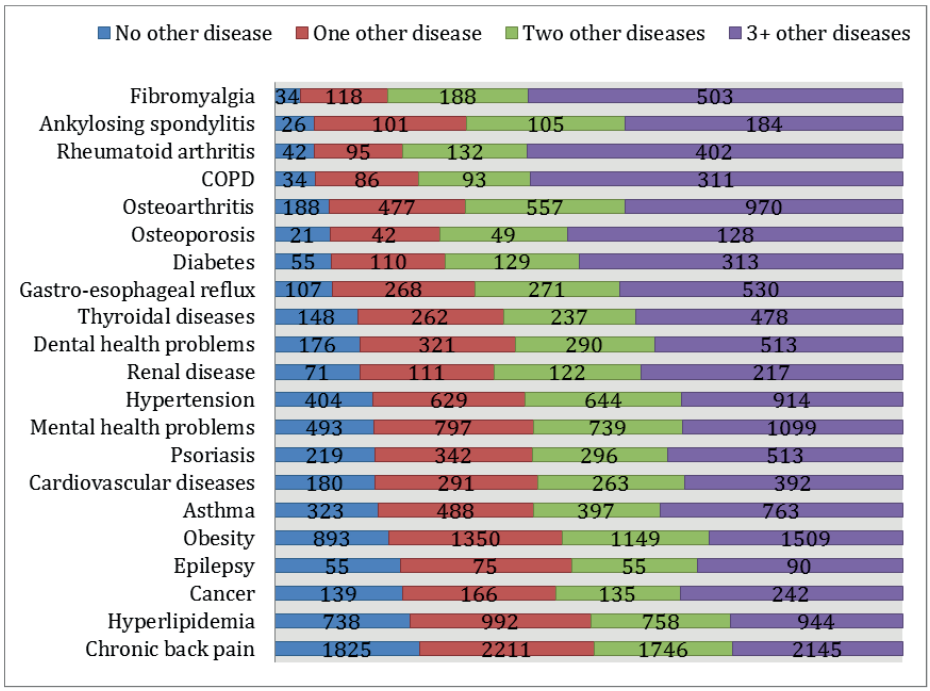


Figure 4 Five Venn-diagrams of associations between diseases in age-group 40-59 years. a) Association between cardiovascular group (cardiovascular diseases, hypertension or hyperlipidemia), mental health problems and metabolic diseases (diabetes or obesity). b) Association between mental health problems, fibromyalgia and thyroidal diseases. c) Association between mental health problems, rheumatoid arthritis (RA) and lung diseases (COPD or asthma). d) Association between musculoskeletal problems (chronic back pain, fibromyalgia, rheumatoid arthritis, osteoarthritis or ankylosing spondylitis), gastro-esophageal reflux and mental health problems and e) Association between musculoskeletal problems, dental problems and cardiovascular group

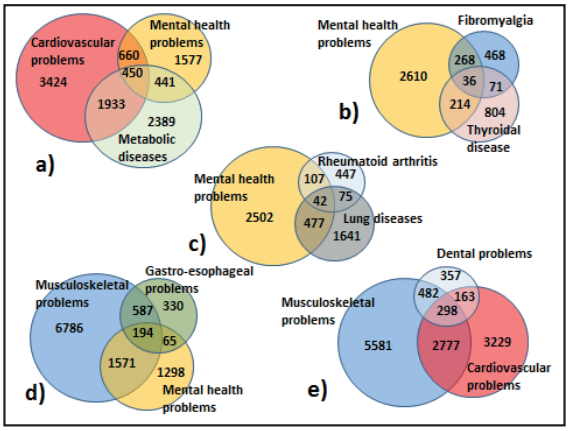


Table 3 Odds ratio of having a second defined disease if index disease is already present, age-group 40-59 years. Further definition from the Venn-diagrams (Figure 4)

Diseases/Conditions	Odds ratio	P-value	95% CI
Mental health problems & CVD group[a]	1.32	<0.001	1.22-1.43
Mental health problems & Metabolic diseases[b]	1.28	<0.001	1.18-1.40
Mental health problems & Fibromyalgia	3.54	<0.001	3.06-4.09
Mental health problems & Thyroidal diseases	1.73	<0.001	1.49-2.00
Mental health problems & Rheumatoid arthritis	1.70	<0.001	1.41-2.05
Mental health problems & Lung diseases	1.92	<0.001	1.72-2.13
Mental health problems & Musculoskeletal problems[c]	1.91	<0.001	1.77-2.06
Mental health problems & Gastro-esophagal reflux	1.71	<0.001	1.48-1.97
Musculoskeletal problems & Gastro-esophagal reflux	2.80	<0.001	2.48-3.17
Musculoskeletal problems & Dental health problems	2.10	<0.001	1.88-2.36
Musculoskeletal problems & CVD group	1.32	<0.001	1.25-1.40
CVD group & Dental health problems	1.29	<0.001	1.15-1.45
CVD group & Metabolic diseases	2.49	<0.001	2.33-2.66
Fibromyalgia & Thyroidal diseases	2.79	<0.001	2.85-3.45
Lung diseases[d] & Rheumatoid arthritis	1.85	<0.001	1.51-2.27

[a]CVD group: Cardiovascular disease group (cardiovascular disease, hypertension or hyperlipidemia), [b]metabolic diseases: Diabetes or obesity, [c]musculoskeletal problems: Chronic back pain, fibromyalgia, rheumatoid arthritis, osteoarthritis or ankylosing spondylitis, [d]lung diseases: COPD or asthma

From the perspectives of adaptation and resilience, evidence of restorative (salutogenic) factors and their relation to allostatic processes [82] can be encompassed in an ethnically and culturally sensitive manner, ranging from a clean environment, healthy nutrition and physical activity to societal justice, organizational fairness [30] and respectful, supportive relationships [74,83]. In our mind, even the most fundamental human issues can be evoked: as a biomedical model for an imbalance between that which *gains* and that which *drains* a given individual [84] or biological system, the concept of allostasis might be illuminated by philosophical and artistic representations of human nature. Linked to the concept of allostasis [73] and as only one of several current research trajectories, telomere research already offers some striking illustrations of how 'hi-tech' science can shed new light on old humanistic insight - and *vice versa* [42,85-88].

As this is the third survey in the HUNT Study, its main strength lies in the experience of the staff organizing and carrying out these comprehensive data collections. All sampling methods have been re-evaluated and well standardized. Around 78% of our present study population also participated in the HUNT 2 Survey in 1995-97, which opens the possibility for time trend analyses in the wake of this study. The fact that the HUNT population is ethnically homogenous, with high and socially equitable access to primary healthcare [15], might be considered a strength, as it confirms that the phenomenon of multimorbidity should not only be viewed mainly as a reflection of social deprivation but also an artifact rooted in the current biomedical paradigm.

A weakness of our study is the limited participation rate, which must nevertheless be seen as acceptable in a contemporary international context. Nevertheless, the participation rates in the important age groups were good. Participation rates were lowest in the youngest and oldest age groups, especially for young males. A comparison between participants and non-participants showed that the latter were of lower socioeconomic status and had higher prevalence of index diseases and higher mortality [46,47]. This might contribute to an underestimation of multimorbidity in our study.

As the HUNT Study was conceived in accordance with the traditional biomedical focus on single disease conditions according to the "disease silo" model [2], both the researchers who designed the survey and the participants, were "blinded" to the research questions, so expectation bias can be ruled out. Most diagnoses/diagnostic labels in our study are self-reported, in contrast to studies based on medical records. This can be considered both a weakness and a strength. Self-reported health information might better reflect the individual's quality of life [89] and can be seen as providing a more person-centered overview of the medical history and experienced burden of disease than medical records do.

Conclusions, implications and recommendations

Contributing evidence from an unselected, general population in an affluent Nordic society, our study confirms that disease clustering and patterns of multimorbidity seem to support that they are more the rule than the exception, at least in Western societies. So what practical implications do we see? On the level of primary practice, we advocate person-focused care as outlined by the late Barbara Starfield [4,90], including attention to the patient's lived experience as appropriate [91] and wise

support of each individual's adaptability and experience of health [92]. Consultation time should be allocated according to needs [29]. Disease-oriented guidelines should be adapted to clinical realities [93-95]. On a societal and political level, it is urgent to define and, as far as possible, eliminate the major contributions of social inequality and detrimental life circumstances to the burden of morbidity [29,91]. But our professional response to the challenge of multimorbidity must definitely extend even beyond practical, organizational and political action. A thorough analysis of the essence of the multimorbidity phenomenon is needed. The observation that so many diseases tend to cluster is likely to represent an artifact of the reigning medical classification systems, as opposed to an appraisal of the true nature of disordered and painful being, referring to explanations anchored in pathophysiological substrates, on the one hand and an understanding of disease burdens springing from existential and experiential hardship, on the other [25,61,78]. A deeper understanding of the ultimate sources of pathogenesis and recovery is needed to aid researchers, clinicians and policymakers to move forward in a sensible and sustainable manner. As explained above, we think further, interdisciplinary work linked to the concept *allostatic load* might be fruitful.

Acknowledgements and Conflicts of Interest

The authors thank Henrik Vogt, MD and Research Fellow at the General Practice Research Unit in Trondheim, for contributing substantial knowledge to the discussion in general and in particular regarding current development in systems medicine. This has relevance for further work with the concept of allostasis and multimorbidity in the clinical setting.

The HUNT3 Survey was mainly funded by the Norwegian Ministry of Health, the Norwegian University of Science and Technology, the Norwegian Research Council (the FUGE program), Central Norway Regional Health Authority, the Nord-Trøndelag County Council and the Norwegian Institute of Public Health. Funding was also contributed by some commercial enterprises and other contributors [46]. The present analysis received support from the Research Fund of the Icelandic College of Family Physicians. The authors declare no conflicts of interest.

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Paper II

PLOS | ONE

RESEARCH ARTICLE

Self Reported Childhood Difficulties, Adult Multimorbidity and Allostatic Load. A Cross-Sectional Analysis of the Norwegian HUNT Study

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OPEN ACCESS

Citation: Tomasdottir MO, Sigurdsson JA, Petursson H, Kirkengen AL, Krokstad S, McEwen B, et al. (2015) Self Reported Childhood Difficulties, Adult Multimorbidity and Allostatic Load. A Cross-Sectional Analysis of the Norwegian HUNT Study. PLoS ONE 10(6): e0130591. doi:10.1371/journal.pone.0130591

Academic Editor: Chang-Qing Gao, Central South University, CHINA

Received: August 28, 2014

Accepted: May 22, 2015

Published: June 18, 2015

Data Availability Statement: Due to restrictions related to patient consent and Norweign privacy laws, data are available upon request. More information is available at the following URL (http://www.ntnu.edu/hunt/data) and interested parties may contact Dr. Steinar Kronstad (steinar.krokstad@ntnu.no) with further questions.

Funding: The HUNT3 Survey was mainly funded by the Norwegian Ministry of Health, the Norwegian University of Science and Technology, the Norwegian Research Council (the FUGE program), Central Norway Regional Health Authority, the Nord-

Abstract

Background

Multimorbidity receives increasing scientific attention. So does the detrimental health impact of adverse childhood experiences (ACE). Aetiological pathways from ACE to complex disease burdens are under investigation. In this context, the concept of *allostatic overload* is relevant, denoting the link between chronic detrimental stress, widespread biological perturbations and disease development. This study aimed to explore associations between self-reported childhood quality, biological perturbations and multimorbidity in adulthood.

Materials and Methods

We included 37 612 participants, 30–69 years, from the Nord-Trøndelag Health Study, HUNT3 (2006–8). Twenty one chronic diseases, twelve biological parameters associated with allostatic load and four behavioural factors were analysed. Participants were categorised according to the self-reported quality of their childhood, as reflected in one question, alternatives ranging from 'very good' to 'very difficult'. The association between childhood quality, behavioural patterns, allostatic load and multimorbidity was compared between groups.

Results

Overall, 85.4% of participants reported a 'good' or 'very good' childhood; 10.6% average, 3.3% 'difficult' and 0.8% 'very difficult'. Childhood difficulties were reported more often among women, smokers, individuals with sleep problems, less physical activity and lower

Trøndelag County Council and the Norwegian Institute of Public Health. The present analysis received support from the Research Fund of the Icelandic College of Family Physicians. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

education. In total, 44.8% of participants with a very good childhood had multimorbidity compared to 77.1% of those with a very difficult childhood (Odds ratio: 5.08; 95% CI: 3.63–7.11). Prevalences of individual diseases also differed significantly according to childhood quality; all but two (cancer and hypertension) showed a significantly higher prevalence ($p<0.05$) as childhood was categorised as more difficult. Eight of the 12 allostatic parameters differed significantly between childhood groups.

Conclusions

We found a general, graded association between self-reported childhood difficulties on the one hand and multimorbidity, individual disease burden and biological perturbations on the other. The finding is in accordance with previous research which conceptualises allostatic overload as an important route by which childhood adversities become biologically embodied.

Introduction

Most consultations with adults in primary care involve more than one health problem or disease [1,2]. Multimorbidity, defined by WHO as being affected with two or more chronic health conditions [3], has received increased recognition over the past years [4,5] and has even been termed one of the major medical challenges of the 21st century [3,6]. Recent research sheds light on various aspects of multimorbidity, mostly focusing on prevalence data [5,7–10] and specific patterns of clustering [11–13]. Multimorbidity increases with age [7,8,14] and is more common in lower socioeconomic groups [8,15,16]. Beyond this, scientific knowledge pertaining to multimorbidity is still incomplete [10,17].

Multimorbid disease clusters tend to defy diagnostic categories within the 'somatic' and 'mental health' domains respectively, and typically also transgress this dichotomy [10,11]. This evokes the question whether multimorbidity ought to be seen as an artefact of the reigning biomedical classification systems, sometimes referred to as medical 'silo' thinking [10,18–20].

Recognizing multimorbidity as a fundamental challenge to both medical theory and practice, authoritative voices have called for a shift from fragmented, disease-oriented medical care to an integrative 'person-focused' or 'person-centered' care [21,22]. Irrespective of on-going controversies relating to the practical delivery of clinical care, the link between low socio-economic status and multimorbidity has actualized a scientific interest in potential underlying causes of ill health in general [15,17,20]. Using terms such as 'the causes behind the causes' and 'the biology of disadvantage' researchers draw scientific attention to the general impact of relational and socio-political factors which undermine human health [10,23].

The technological capacity to explore bio-molecular mechanisms which might link lifetime experiences to human health and disease has evolved rapidly during recent years. Researchers focus on various pathways or markers, such as immune mechanisms [24–27], autonomic imbalance [27–31], endocrine stress responses [32–34], epigenetic mechanisms [35,36], and telomere maintenance [37,38]. This reflects how stress exerts its effects on various biological subsystems and indicates the relevance of exploring the human physiological adaptive systems as a complex whole. The concept of allostasis (gr: stability through change) [39] is based on such an integrative perspective, as previously described [10,23]. Essentially, *allostasis* refers to a living organism's physiological ability to guard its integrity (including cellular homeostasis)

when encountering challenges and stressors. *Allostatic load* denotes the cumulative impact of strain on the organism over time, while allostatic *overload* denotes a 'red flag' physiological risk scenario, where the organism's adaptive and restorative capacity is overtaxed to such an extent that adaptability and flexibility decline prematurely [39–41]. Allostatic overload results in a gradual loss of physiological flexibility, initially reflected by subtle but wide-spread physiological perturbations and an increased risk of complex disease development, informed by congenital and acquired susceptibilities [10].

The trajectory from adverse childhood experiences to health problems in adult life has received increasing scientific attention since the late 1990s. The US Adverse Childhood Experiences Study represented a milestone as it documented a linear relationship between the number of adversity categories in childhood and morbidity-burden in adult life, both in the somatic and mental domains [42,43]. Associations between adverse childhood experiences and health problems in adult life (somatic and psychiatric conditions, including addictive behaviours and sleep problems) have later been confirmed in various contexts [44–54]. These studies have typically focused on predefined adverse experiences, including different forms of abuse, neglect and dysfunctional households [50,54–59]. Increasing evidence links adverse childhood experiences to future health problems with reference to allostatic overload [60–63]. To our knowledge, the association between a *subjective*, *global* evaluation of the childhood and adult health has not been examined.

Research hypothesis

In light of the documented association between adverse childhood experiences and health problems, as well as conceptual and empirical links between childhood difficulties and allostatic overload, we outline a framework for our hypothesis, based on our understanding of the topic and the research literature (Fig 1). The aim of the present study was to explore the connections indicated in the model by studying the association between experience of childhood and multimorbidity in adult life, taking into account the possible effect of behavioural factors as well as markers of allostatic overload.

Study Population and Methods

The Nord-Trøndelag Health Study (HUNT) is a renowned, population based study whose third wave, HUNT3, was carried out in 2006–2008. Every adult living in Nord-Trøndelag County, Norway, was invited to participate and 54% accepted participation [64]. The HUNT3 population has been considered fairly representative of the Norwegian population. It is ethnically homogenous, and since Nord-Trøndelag lacks large cities, the social inequalities in the HUNT population might be smaller than for Norway in general [64,65].

The HUNT3 data were collected through questionnaires, physical examinations and blood samples. For the present analysis people aged 30–69 years who answered the question regarding childhood experience were included, in total 37 612 participants with participation rate of 58% (missing 373 individuals or 1% that did not answer regarding childhood experience) [64]. The youngest age groups were somewhat underrepresented, with only 31% participation rate for people aged 20–29 years [66]. They were therefore excluded from the present analyses along with people aged 70 years or more in whom multimorbidity is highly prevalent due to age [7].

Assessment of childhood difficulties in HUNT3

The overall quality of the respondents' childhood was addressed in HUNT3 by one single question with five fixed response alternatives, referring to the respondent's subjective, global

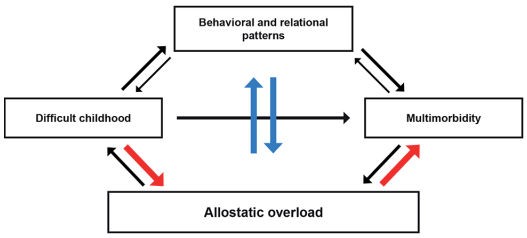

Fig 1. Model illustrating the hypothesized links between childhood difficulties and multimorbidity. All arrows indicate potential pathways connecting adverse childhood experiences to multimorbidity. The solidity of the arrows reflect the proposed relative impact of the illustrated factors. Our main hypothesis is indicated by the red arrows leading from a difficult childhood to multimorbidity through allostatic overload. The blue arrows indicate a presumed impact of behavioural and relational patterns in this development. The black arrows reflect additional pathways that might play a significant but generally more limited role.

doi:10.1371/journal.pone.0130591.g001

perception of his/her childhood. Our *childhood experience question* was phrased (here translated to English): 'When you think about your childhood, would you describe it as': 'Very good–good–average–difficult–very difficult'. The question appeared among relatively neutral questions related to everyday topics such as intake of dairy products and living with pets in childhood (questionnaire accessible at www.hunt.no). We worded the question with respect to the local linguistic and cultural context, supported by a linguist.

Assessment of multimorbidity, behavioural patterns and allostatic parameters

We defined multimorbidity as two or more coinciding chronic diseases or conditions in accordance with international consensus [3,18]. For a fair evaluation of multimorbidity, data on at least twelve relevant chronic diseases are needed [9]. Our analysis includes 21 chronic diseases or conditions, as has previously been described in more detail [10]. Any case of missing data was defined as absence of the disease in question.

Regarding behavioural patterns, we included daily smoking and mean number of cigarettes, sleep problems and physical activity. Daily smoking was defined as use of cigarettes, cigars, pipes and/or snuff daily. Physical activity was measured as a combination of light and hard exercise during the last year, measured in hours as no activity, less than three hours of light activity, more than three hours of light but less than one hour of hard activity and finally more than one hour of hard activity per week.

The HUNT3 database lacks direct data on socioeconomic status (SES). Information regarding educational level was however accessible for 76% of our respondents who had also completed the HUNT2 survey 10 years earlier [64]. This was used as a marker of adult SES.

Sleep problems were defined as difficulty falling asleep, waking up repeatedly during the night or waking too early and not being able to fall asleep again, several times per week for the last month.

To address the possibility of recall bias associated with depression, multimorbidity analyses were also performed after adjusting for indications of current depression, defined as eight or more points on the Hospital Anxiety and Depression Scale (HADS). Multimorbidity and experience of childhood were also compared between depressed and non-depressed groups, respectively.

Allostatic load parameters have been classified as *primary* (being mostly chemical messengers in response of short term stress), *secondary* (reflecting cumulative actions of primary

parameters in a tissue/organ-specific manner) and *tertiary* (emerging as clinical diseases or disorders) [67,68]. Somewhat different parameters have been applied and combined to estimate allostatic load in different studies [69]. Our analysis includes twelve secondary allostatic parameters.

For the estimation of systolic and diastolic blood pressure, heart rate and pulse pressure, HUNT3 participants using antihypertensive medication or diagnosed with cardiovascular disease were excluded to avoid medication bias. Likewise, participants reporting diabetes were excluded from estimation of serum glucose. Similar precautions were not possible for cholesterol, as information on cholesterol-lowering medication was unavailable.

Statistical analyses

Descriptive analyses were stratified according to childhood experience. The categorical variables were expressed as frequencies with percentages and continuous variables as means with standard deviations. Differences between childhood groups with p-trends were estimated with Mantel-Haenszel test for linear association and ANOVA test for linearity as appropriate.

Prevalences were estimated for the number of diseases in each group of childhood experience with 95% confidence intervals (CI). The same was performed for individual diseases. Mantel-Haenszel test for linear association was used to test if disease prevalence followed a gradient from very good to very difficult childhood.

Binomial logistic regression was used to assess the odds ratios (OR) of multimorbidity according to childhood experience. All logistic calculations were adjusted for age and gender. Behavioural and biological factors were then introduced to the model, both individually and in different combinations. Participants with missing data regarding allostatic parameters were excluded in all logistic regression models, but missing data on behavioural factors were coded as an additional group for precise comparison between models.

Parameters pertaining to allostatic load were analysed according to childhood experience for each gender. Means were estimated with participants reporting a very good childhood as the reference group. Deviances from the mean according to each group of childhood experience, as well as p-trend, were subsequently estimated with linear regression after adjusting for age.

SPSS statistical program (version 20) was used for all analyses.

Ethics Statement

Each participant in the HUNT Study signed a written consent regarding the screening and the use of data for research purposes. The study was approved by the Norwegian Data Inspectorate and the Regional Committee for Ethics in Medical Research (2010/2627-3).

Results

Data from 20 338 women and 17 274 men aged 30–69 years were analysed in accordance with their self-reported, global perception of their childhood. In total, 85.4% of the respondents characterised their childhood as very good or good, 3.3% as difficult and 0.8% as very difficult (Table 1).

In general, individuals reporting a difficult or a very difficult childhood were younger (p-trend significant when stratified by gender) and more often female. Smoking was more prevalent in this group and they reported higher cigarette consumption than smokers in other groups. They also reported more sleep problems, less physical activity and a lower educational level. A significant trend was observed from very good to very difficult childhood in all baseline characteristics except for age.

Table 1. Baseline characteristics of participants aged 30–69 years according to childhood experience in the HUNT Study (2006–8).

	Childhood experience:					
	Very good	Good	Average	Difficult	Very difficult	p trend*
Number of participants	17 759 (47.2)	14 351 (38.2)	3 993 (10.6)	1 225 (3.3)	284 (0.8)	Na
Mean age	50.9 (±10.6)	52.1 (±10.6)	51.3 (±10.5)	49.5 (±10.3)	47.6 (±10.3)	0.72
Gender						
Female	9 574 (53.9)	7 463 (52.0)	2 328 (58.3)	784 (64.0)	189 (66.5)	<0.001
Male	8 185 (46.1)	6 888 (48.0)	1 665 (41.7)	441 (36.0)	95 (33.5)	
Daily smoking	4 644 (26.2)	3 881 (26.6)	1 116 (27.9)	438 (35.8)	123 (43.7)	<0.001
Mean nr of cigarettes	11.7 (± 7.2)	12.1 (± 6.9)	12.7 (±7.5)	13.6 (±7.1)	15.7 (±10.3)	<0.001
Insomnia	3 159 (17.8)	3 168 (22.1)	1 131 (28.3)	442 (36.1)	113 (39.8)	<0.001
Physical activity						
None	332 (2.4)	263 (2.3)	91 (2.9)	50 (5.2)	17 (7.6)	<0.001
Low	3 191 (22.7)	2 765 (24.0)	789 (24.9)	237 (24.8)	66 (29.6)	
Medium	4 580 (32.6)	3 943 (34.3)	1 055 (33.3)	308 (32.3)	65 (29.2)	
High	5 949 (42.3)	4 528 (39.4)	1 229 (38.8)	360 (37.7)	75 (33.6)	
Education						
Primary	2 933 (21.3)	2 834 (25.5)	753 (25.7)	219 (27.4)	49 (34.8)	<0.001
Secondary	7 077 (51.4)	5 645 (50.8)	1 479 (50.6)	421 (52.6)	72 (51.1)	
University	3 754 (27.3)	2 632 (23.7)	693 (23.7)	160 (20.0)	20 (14.2)	

Standard deviation (SD) and percentages within brackets as appropriate.

*p trend calculated with ANOVA or Mantel-Haenszel test for linear association as appropriate.

doi:10.1371/journal.pone.0130591.t001

Multimorbidity and childhood experience

Fig 2 (and S1 Table) shows the *prevalence of number of diseases* for each given group. Respondents characterising their childhood as very good had a lower number of diseases, with 26.3% reporting no disease, compared to 9.5% and 4.2% for those reporting a difficult and a very difficult childhood, respectively. The total prevalence of multimorbidity increased from 44.8% among respondents reporting a very good childhood to 77.1% among those with a very difficult childhood. For individuals reporting a very difficult childhood, the age adjusted prevalence ratios gradually rose to 1.90, compared to those reporting a very good childhood.

A similar trend was found for the prevalence of *individual diseases* (Fig 3). The prevalence increased significantly with increasing degrees of childhood difficulty for all diseases, except hypertension and cancer. The increase was sevenfold for mental health problems, fourfold for chronic obstructive pulmonary disease (COPD) and dental health problems, and more than double for fibromyalgia, gastro-oesophageal reflux disease (GERD), rheumatic arthritis and asthma. The prevalence increased almost parallel in both genders, although the absolute prevalence of some diseases differed.

Logistic regression analyses

In the first crude model which did not include any intervening factors, the OR of multimorbidity increased from 1.20 for those with a good childhood to 5.08 (95% CI 3.63–7.11) for individuals reporting a very difficult childhood, compared to very good childhood as reference (Table 2).

The behavioural factors were then introduced one by one to evaluate their association with multimorbidity (S2 Table). Smoking, physical activity and educational level all lowered the OR

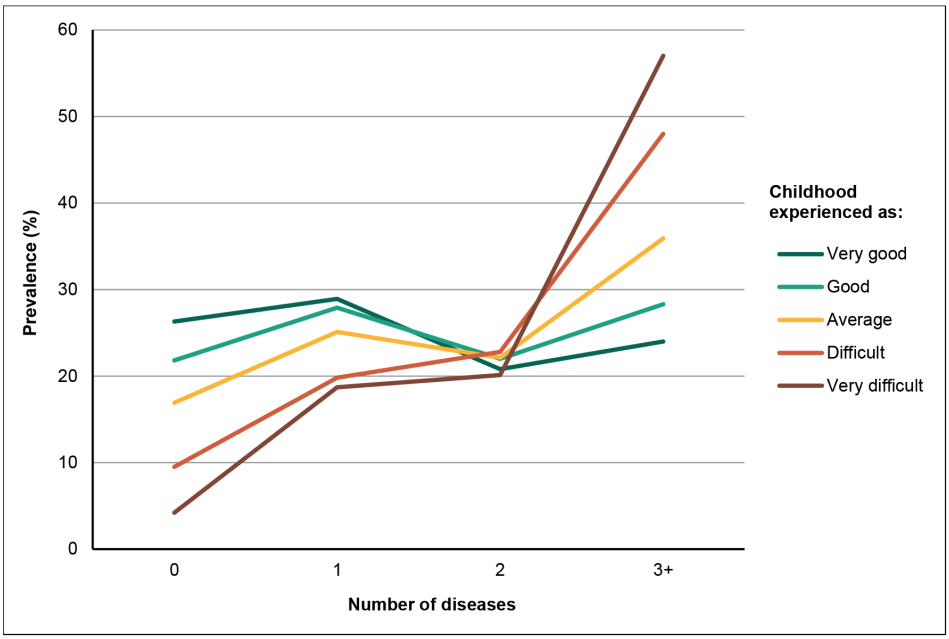

Fig 2. Number of diseases in adulthood (30–69y) according to childhood experience in the HUNT3 Study.

doi:10.1371/journal.pone.0130591.g002

marginally. The strongest single factor impact was found for sleep problems with OR declining from 5.08 to 4.32 (95% CI 3.07–6.07) for participants with a very difficult childhood.

Analysed individually, the allostatic parameters showed marginal or no impact on OR (S2 Table). When introduced to the model in combination (Table 2- Model 3) the OR associated with a very difficult childhood declined from 5.08 to 4.73 (95% CI 3.30–7.68) with no effect on OR for the other groups of childhood experience. Combined, the behavioural factors had a stronger impact on OR in very difficult childhood (OR 3.98, Model 3). When all behavioural and allostatic factors were combined, the OR declined to 3.78 (95% CI 2.61–5.47) (Model 4).

Adjusting for current depression in the crude model reduced the OR for very difficult childhood from 5.08 to 4.52 (95% CI 3.20–6.36). In the group with current depression, 11.1% reported a difficult or a very difficult childhood, compared to 4.1% in the group in general. The prevalences of different childhood qualities and multimorbidty did not differ significantly after excluding participants reporting current depression.

Childhood experience and allostatic load

The mean values of eight of the 12 analysed allostatic parameters (Tables 3 and 4) differed according to the participants' description of their childhood ($p<0.05$). Those reporting a difficult or very difficult childhood had, on average, shorter stature, larger waist circumference, higher waist hip ratio and BMI, higher resting heart rate, lower systolic blood pressure, and lower pulse pressure, compared to the other groups. Females but not males reporting a difficult childhood had significantly higher non-fasting blood glucose. Correspondingly, males but not females had a statistically significant trend towards lower diastolic blood pressure (Tables 3 and 4).

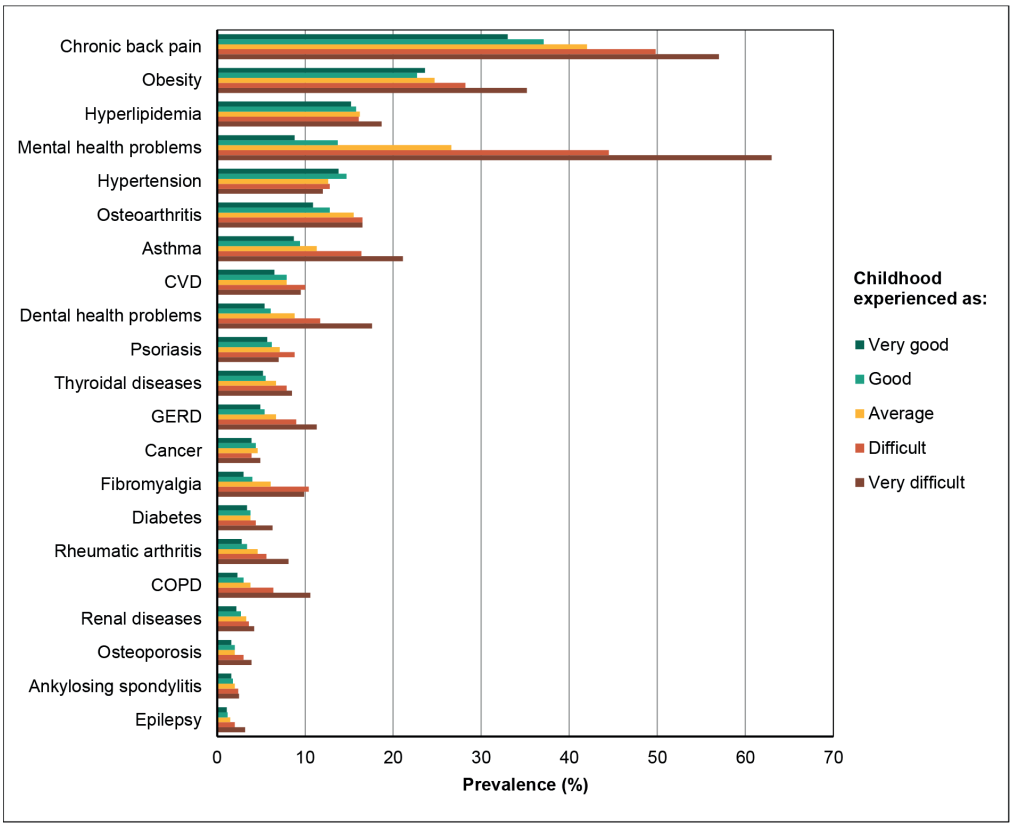

Fig 3. Prevalence of diseases/conditions according to childhood experience for adults (30–69y) in the HUNT3 Study.

doi:10.1371/journal.pone.0130591.g003

Table 2. Logistic models for multimorbidity according to childhood experience for participants aged 30–69 years in the HUNT Study (2006–8).

	Childhood experience:									
	Very good		Good		Average		Difficult		Very difficult	
Logistic models	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Model 1	1.0	Ref.	1.20	1.13–1.26	1.77	1.63–1.93	3.52	3.00–4.13	5.08	3.63–7.11
Model 2	1.0	Ref.	1.15	1.09–1.22	1.64	1.50–1.79	3.00	2.55–3.53	3.98	2.82–5.62
Model 3	1.0	Ref.	1.23	1.16–1.30	1.82	1.67–2.00	3.55	3.00–4.21	4.71	3.29–6.75
Model 4	1.0	Ref.	1.19	1.12–1.26	1.70	1.55–1.87	3.03	2.54–3.61	3.77	2.61–5.45

Odds ratios (OR) and 95% confidence intervals (95% CI) with very good childhood as a reference (Ref.).
Model 1: Adjusted for age and gender; Model 2: Adjusted for age, gender, smoking, insomnia, physical activity and education; Model 3: Adjusted for age, gender and allostatic factors; Model 4: Adjusted for all factors mentioned before.

doi:10.1371/journal.pone.0130591.t002

Table 3. Age adjusted difference from reference values of secondary allostatic parameters with 95% confidence intervals (95% CI) according to childhood experience among women aged 30–69 years, in the HUNT Study (2006–8) (N = 20 338).

	Childhood experience:					
	Very good	Good	Average	Difficult	Very difficult	
Women	Reference	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	p trend
Height (cm)	165.54	-0.02 (-0.20 to 0.15)	-0.65 (-0.91 to -0.38)	-0.69 (-1.12 to -0.27)	-1.71 (-2.54 to -0.87)	<0.001
Waist (cm)	90.36	-0.25 (-0.63 to 0.13)	0.20 (-0.37 to 0.76)	1.80 (0.89 to 2.70)	3.93 (2.15 to 5.72)	<0.001
WHR	0.87	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.01 (0.01 to 0.02)	0.02 (0.01 to 0.03)	<0.001
BMI (kg/m^2)	27.01	-0.16 (-0.30 to -0.01)	0.21 (-0.01 to 0.42)	0.72 (0.37 to 1.07)	1.54 (0.85 to 2.23)	<0.001
SBP (mmHg)	124.87	-0.76 (-1.31 to -0.21)	-1.01 (-1.81 to -0.20)	-1.65 (-2.98 to -0.33)	0.63 (-1.99 to 3.26)	0.002
DBP (mmHg)	71.05	-0.50 (-0.85 to -0.15)	-0.11 (-0.63 to 0.41)	-0.49 (-1.34 to 0.36)	0.83 (-0.85 to 2.51)	0.26
Heart rate	71.04	0.13 (-0.25 to 0.50)	0.27 (-0.28 to 0.82)	0.44 (-0.46 to 1.35)	2.36 (0.59 to 4.14)	0.03
PP (mmHg)	91.82	-0.63 (-1.05 to -0.21)	-0.43 (-1.05 to 0.19)	-1.19 (-2.22 to -0.17)	1.08 (-0.94 to 3.09)	0.03
CRP (mg/L)	2.65	-0.01 (-0.20 to 0.19)	0.01 (-0.28 to 0.31)	0.47 (-0.01 to 0.95)	0.89 (-0.04 to 1.83)	0.08
Chol (mmol/L)	5.58	-0.01 (-0.04 to 0.02)	0.03 (-0.02 to 0.07)	0.03 (-0.04 to 0.11)	0.19 (0.04 to 0.34)	0.07
Glu (mmol/L)	5.31	-0.01 (-0.05 to 0.02)	0.00 (-0.05 to 0.05)	0.11 (0.03 to 0.18)	0.19 (0.04 to 0.34)	0.04
Crea (μmol/L)	75.81	0.08 (-0.36 to 0.51)	0.00 (-0.65 to 0.65)	0.38 (-0.68 to 1.43)	-0.31 (-2.39 to 1.76)	0.73

WHR = Waist hip ratio; BMI = Body mass index; SBP = Systolic blood pressure; DBP: Diastolic blood pressure; PP = Pulse pressure; CRP = C-reactive protein; Chol = S-Cholesterol; Glu = Non-fasting S-glucose; Crea = S-Creatinine.

doi:10.1371/journal.pone.0130591.t003

Discussion

Based on data from a large, stable and relatively affluent Norwegian population, we have documented a clear association between self-reported childhood difficulties and adult disease burden. With increasing childhood difficulties, the prevalence of multimorbidity, as well as most

Table 4. Age adjusted difference from reference values of secondary allostatic parameters with 95% confidence intervals (95% CI) according to childhood experience among men aged 30–69 years, in the HUNT Study (2006–8) (N = 17 274).

	Childhood experience:					
	Very good	Good	Average	Difficult	Very difficult	
Men	Reference	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	p trend
Height (cm)	178.56	0.01 (-0.20 to 0.21)	-0.27 (-0.60 to 0.07)	-0.50 (-1.10 to 0.11)	-1.87 (-3.15 to -0.59)	0.001
Waist (cm)	97.58	0.09 (-0.24 to 0.41)	0.66 (0.12 to 1.19)	2.66 (1.69 to 3.63)	2.06 (0.01 to 4.11)	<0.001
WHR	0.94	0.00 (0.00 to 0.00)	0.01 (0.00 to 0.01)	0.02 (0.01 to 0.02)	0.02 (0.01 to 0.04)	<0.001
BMI (kg/m^2)	27.72	-0.04 (-0.16 to 0.08)	0.07 (-0.13 to 0.27)	0.70 (0.34 to 1.06)	0.55 (-0.21 to 1.30)	0.01
SBP (mmHg)	131.76	-0.30 (-0.87 to 0.26)	-0.81 (-1.74 to 0.13)	-1.30 (-3.01 to 0.40)	-3.82 (-7.40 to -0.23)	0.007
DBP (mmHg)	77.19	-0.23 (-0.61 to 0.14)	-0.65 (-1.27 to -0.03)	-0.24 (-1.37 to 0.89)	-2.52 (-4.89 to -0.14)	0.01
Heart rate	67.80	0.35 (-0.06 to 0.77)	0.07 (-0.62 to 0.75)	3.07 (1.82 to 4.32)	0.84 (-1.80 to 3.47)	<0.001
PP (mmHg)	97.16	-0.17 (-0.62 to 0.29)	-0.70 (-1.45 to 0.06)	-0.21 (-1.58 to 1.16)	-3.10 (-5.98 to -0.22)	0.04
CRP (mg/L)	2.37	0.00 (-0.19 to 0.19)	0.05 (-0.26 to 0.37)	0.64 (0.06 to 1.21)	0.15 (-1.05 to 1.36)	0.19
Chol (mmol/L)	5.53	0.01 (-0.02 to 0.05)	0.00 (-0.05 to 0.06)	0.02 (-0.08 to 0.12)	0.22 (0.01 to 0.43)	0.24
Glu (mmol/L)	5.56	-0.01 (-0.05 to 0.04)	0.00 (-0.07 to 0.06)	0.20 (0.08 to 0.33)	0.12 (-0.15 to 0.39)	0.11
Crea (μmol/L)	90.10	-0.07 (-0.61 to 047)	0.48 (-1.37 to 0.41)	0.53 (-1.10 to 2.17)	-1.80 (-5.23 to 1.64)	0.48

WHR = Waist hip ratio; BMI = Body mass index; SBP = Systolic blood pressure; DBP: Diastolic blood pressure; PP = Pulse pressure; CRP = C-reactive protein; Chol = S-Cholesterol; Glu = Non-fasting S-glucose; Crea = S-Creatinine.

doi:10.1371/journal.pone.0130591.t004

of the eligible diseases and disorders, increased in a dose-response manner. Sleep problems, physical activity and smoking habits followed a similar trend. The cross-sectional study design does not permit direct, causal inferences. Our findings are however concordant with an increasing body of evidence which links childhood adversities to ill health in a life-course perspective [70–72].

The fact that one question about subjective childhood experience gave such could yield such results, is a new finding. The approach needs further validation in other contexts, but might ultimately prove to have certain qualities in common with the single item questions about self-rated health [73].

Since this is a cross-sectional study, recall bias connected to the respondents' childhood cannot be ruled out. A heavy disease burden might theoretically be blamed on childhood adversities. Previous studies which have compared retrospective and prospective data on childhood adversity have however not found evidence of recall bias [49,74,75]. The possibility is further diminished as we adjusted for current depression.

Approximately four percent of the HUNT3 study participants reported a difficult or very difficult childhood. This number is low, if compared to those that have focused on specified types of adverse events in childhood [52,53,76,77]. Our global experience question is obviously different, as it addresses the respondent's personal appraisal of what might be described as the overall balance between adverse ("drain") and supporting and resilience ("gain") factors [78] in childhood. The low figure might also reflect the relatively favourable socioeconomic conditions in North-Trøndelag population. A direct link between severe poverty in childhood, biological perturbations and disease in adult life has been found in several populations, including the Norwegian county Finnmark in the years 1890–1967 [79]. It is highly unlikely that reported childhood difficulties in HUNT3 refer to food shortage or poor housing on a comparable scale.

One important factor that can´t be evaluated in our study is the impact of parental health. Common genetic disease susceptibilities remain a potential bias that would most likely be of variable importance across the spectrum of diseases.

Concerning the measured allostatic load parameters, eight of the 12 showed an association with childhood experience. This is not surprising, as allostatic parameters are likely to change during the life-course, and we applied measurements performed in adulthood. Furthermore, not all parameters could be optimally evaluated (see methods section). Exclusion of respondents who reported a clinician-diagnosed (and thus presumably treated) diabetes and/or medicated hypertension should lead to underestimation of serum glucose and blood pressure levels. The same applies to cholesterol, as some respondents might have been taking cholesterol-lowering drugs.

The rise in individual disease prevalence with increasing childhood difficulties varied considerably in our study, but the general trend was a dose-response association. The slope was steepest for pain conditions and mental health problems, in accord with previous studies on the health impact of childhood adversity [45,48,80–82] and compatible with a recent study on the relationship between self-rated health and allostatic load in the HUNT population [83]. The trend was also present regarding a number of conditions where physiological dysregulation and life-style are known to interact and even enhance each other, such as obesity, diabetes, dental problems, asthma, COPD, and GERD [42,54,76,84,85]. We did not find any dose-response relationship for hypertension in our study. Some studies indicate an association between childhood adversities and hypertension [85], but this association may be complex, as blunting of the HPA-axis can occur over time, resulting in flattening of the diurnal cortisol rhythm [40,86–88].

As the HUNT Study was conceived in accordance with the traditional biomedical focus on single disease conditions according to the 'silo' model [19], both the researchers who designed

the survey and the questionnaire respondents were 'blinded' to the research question of the present study. Consequently, expectation bias can be ruled out. The fact that diagnoses are self-reported, in contrast to studies based on medical records, can be considered both a weakness and strength, depending on the chosen perspective.

The fact that the HUNT population is ethnically homogenous, with high and socially equitable access to primary healthcare [65], might be considered a strength, as it documents that multimorbidity is a ubiquitous phenomenon in contemporary Western societies, not only related to social deprivation.

Socioeconomic status has a well documented link to multimorbidity, as previously mentioned [8, 16]. The lack of comprehensive SES data represents a clear weekness of our study. However, the County of North-Trøndelag has been a stable community with a less steep social gradient than many other populations [65].

A general weakness of the HUNT3 study is the limited participation rate, which must nevertheless be seen as acceptable in a contemporary international context, especially for the age groups included in the current analysis. Participation rates were lowest in the youngest and oldest age groups, especially for young males. It is, however, relevant to notice that younger participants generally reported a higher prevalence of a very difficult childhood than older participants. This might lead to underestimation of the total multimorbidity count in the population. Furthermore, a comparison between participants and non-participants in the HUNT3 study showed that non-participants tended to have a higher prevalence of index diseases as well as a higher mortality [64,66]. In total, our study probably underestimates the disease burden in the overall population.

Conclusions and implications

Based on data from a general and relatively affluent Norwegian population, we have documented a general, graded association between self-reported childhood difficulties on the one hand and multimorbidity, individual disease burden and biological perturbations on the other. The finding is in accordance with an increasing body of research which conceptualises allostatic overload as an important route by which childhood adversities become biologically embodied [89]. Consequently, we argue that future research on the aetiology and demanding clinical management of multimorbidity [90] should direct more attention to the biological impact of the patients' life experiences [23].

From the perspective of childhood adversity research, our study applied an original one-item "childhood experience question". The finding of a strong relation between self-reported childhood difficulties and adult disease burden indicates that this approach can have considerable epidemiological and clinical relevance, worthy of further investigation.

Supporting Information

S1 Table. Gender specific prevalence of multimorbidity and age adjusted prevalence ratios (PR) with 95% confidence intervals (95% CI), associated with childhood experience in the HUNT Study (2006–8) (N = 37 612).
(DOCX)

S2 Table. Odds ratios (OR) with 95% confidence intervals (CI) of developing multimorbidity according to childhood experience for participants aged 30–69 years in the HUNT Study (2006–8) with very good childhood as a reference (Ref). All anlyses adjusted for age and gender and then according to different possible behavioural and allostatic factors.
(DOCX)

Acknowledgments

The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between the HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health.

We thank the HUNT Research Centre for contributing data, Tom Ivar Lund Nilsen for statistical advice and Henrik Vogt for theoretical contributions.

Author Contributions

Conceived and designed the experiments: LG ALK IH JAS MOT. Performed the experiments: SK. Analyzed the data: JAS HP MOT. Wrote the paper: MOT JAS HP LG ALK SK BM IH.

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S1 Table. Gender specific prevalence of multimorbidity and age adjusted prevalence ratios (PR) with 95% confidence intervals (95% CI), associated with childhood experience in the HUNT Study (2006–8) (N = 37 612).

		Childhood experience:				
		Very good	Good	Average	Difficult	Very difficult
Women						
0-1 diseases		4990 (52.1)	3444 (46.2)	940 (40.4)	222 (28.3)	43 (22.7)
Multimorbidity		4584 (47.9)	4019 (53.8)	1388 (59.6)	562 (71.7)	146 (77.3)
	PR (95% CI)	1.00 (Reference)	1.09 (1.06-1.13)	1.25 (1.21-1.30)	1.59 (1.51-1.66)	1.82 (1.69-1.97)
Men						
0-1 diseases		4821 (58.9)	3688 (53.5)	738 (44.3)	136 (30.9)	22 (23.2)
Multimorbidity		3364 (41.1)	3200 (46.5)	927 (55.7)	305 (69.2)	73 (76.8)
	PR (95% CI)	1.00 (Reference)	1.08 (1.04-1.12)	1.30 (1.24-1.37)	1.70 (1.59-1.81)	2.01 (1.82-2.22)
Total						
0-1 diseases		9811 (55.2)	7132 (49.7)	1678 (42.0)	358 (29.2)	65 (22.9)
Multimorbidity		7948 (44.8)	7219 (50.3)	2315 (58.0)	867 (70.8)	219 (77.1)
	PR (95% CI)	1.00 (Reference)	1.08 (1.06-1.11)	1.28 (1.24-1.32)	1.64 (1.58-1.71)	1.90 (1.79-2.02)

S2 Table. Odds ratios (OR) with 95% confidence intervals (CI) of developing multimorbidity according to childhood experience for participants aged 30–69 years in the HUNT Study (2006–8) with very good childhood as a reference (Ref).

	Childhood experience:									
	Very good		Good		Average		Difficult		Very difficult	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Basic model	1.0	Ref.	1.20	1.13-1.26	1.77	1.63-1.93	3.52	3.00-4.13	5.08	3.63-7.11
Models adjusted for:										
Smoking	1.0	Ref.	1.20	1.13-1.26	1.77	1.62-1.93	3.45	2.94-4.04	4.86	3.47-6.81
Insomnia	1.0	Ref.	1.16	1.10-1.23	1.64	1.50-1.79	3.07	2.61-3.61	4.32	3.07-6.07
Physical activity	1.0	Ref.	1.191.13-1.26		1.78	1.63-1.94	3.53	3.01-4.15	5.03	3.58-7.07
Education	1.0	Ref.	1.18	1.13-1.25	1.74	1.60-1.90	3.41	2.91-4.00	4.78	3.42-6.69
Allostatic factors:										
Height	1.0	Ref.	1.20	1.13-1.26	1.76	1.61-1.92	3.50	2.99-4.11	4.90	3.50-6.85
Waist	1.0	Ref.	1.22	1.15-1.30	1.84	1.68-2.01	3.60	3.04-4.26	5.14	3.60-7.34
BMI	1.0	Ref.	1.20	1.13-1.26	1.77	1.63-1.93	3.52	3.01-4.13	5.09	3.64-7.12
SBP	1.0	Ref.	1.20	1.14-1.27	1.80	1.65-1.96	3.63	3.10-4.26	5.13	3.66-7.18
DBP	1.0	Ref.	1.20	1.14-1.27	1.79	1.65-1.95	3.60	3.07-4.22	5.15	3.68-7.22
Pulse	1.0	Ref.	1.20	1.14-1.27	1.78	1.63-1.94	3.49	2.98-4.09	5.00	3.57-7.00
Cholesterol	1.0	Ref.	1.19	1.13-1.26	1.77	1.62-1.93	3.51	3.00-4.12	5.08	3.63-7.10
Glucose	1.0	Ref.	1.20	1.14-1.27	1.79	1.64-1.95	3.50	2.98-4.11	4.98	3.55-6.98
CRP	1.0	Ref.	1.20	1.13-1.26	1.78	1.63-1.94	3.49	2.98-4.09	4.98	3.56-6.97
Creatinine	1.0	Ref.	1.20	1.13-1.26	1.78	1.63-1.94	3.51	3.00-4.12	5.14	3.68-7.19

Paper III

BMJ Open

Does 'existential unease' predict adult multimorbidity? Analytical cohort study on embodiment based on the Norwegian HUNT population

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To cite: Tomasdottir MO, Sigurdsson JA, Petursson H, *et al*. Does 'existential unease' predict adult multimorbidity? Analytical cohort study on embodiment based on the Norwegian HUNT population. *BMJ Open* 2016;**6**:e012602. doi:10.1136/bmjopen-2016-012602

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-012602).

Received 11 May 2016
Revised 16 September 2016
Accepted 5 October 2016

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ABSTRACT

Objectives: Multimorbidity is prevalent, and knowledge regarding its aetiology is limited. The general pathogenic impact of adverse life experiences, comprising a wide-ranging typology, is well documented and coherent with the concept *allostatic overload* (the long-term impact of stress on human physiology) and the notion *embodiment* (the conversion of sociocultural and environmental influences into physiological characteristics). Less is known about the medical relevance of subtle distress or unease. The study aim was to prospectively explore the associations between *existential unease* (coined as a meta-term for the included items) and multimorbidity.

Setting: Our data are derived from an unselected Norwegian population, the Nord-Trøndelag Health Study, phases 2 (1995–1997) and 3 (2006–2008), with a mean of 11 years follow-up.

Participants: The analysis includes 20 365 individuals aged 20–59 years who participated in both phases and was classified without multimorbidity (with 0–1 disease) at baseline.

Methods: From HUNT2, we selected 11 items indicating 'unease' in the realms of self-esteem, well-being, sense of coherence and social relationships. Poisson regressions were used to generate relative risk (RR) of developing multimorbidity, according to the respondents' ease/unease profile.

Results: A total of 6277 (30.8%) participants developed multimorbidity. They were older, more likely to be women, smokers and with lower education. 10 of the 11 'unease' items were significantly related to the development of multimorbidity. The items 'poor self-rated health' and 'feeling dissatisfied with life' exhibited the highest RR, 1.55 and 1.44, respectively (95% CI 1.44 to 1.66 and 1.21 to 1.71). The prevalence of multimorbidity increased with the number of 'unease' factors, from 26.7% for no factor to 49.2% for 6 or more.

Conclusions: In this prospective study, 'existential unease' was associated with the development of multimorbidity in a dose–response manner. The finding indicates that existential unease increases people's vulnerability to disease, concordant with current literature regarding increased allostatic load.

Strength and limitations of this study

- This large, prospective study explores subtle aetiological factors of multimorbidity, a fairly new area of investigation.
- The study shows that relatively subtle, existentially demanding life circumstances are associated with the development of multimorbidity.
- The data come from a large, homogenous and relatively affluent population. Finding effect of subtle unease on future health even in this population highlights its importance.
- The basic science concept allostatic load is key to our hypothesis. We described the participants' allostatic load at the level of tertiary outcomes (established diseases/conditions) in accordance with the literature. Our findings suggest that a subjective experience of existential unease is associated with allostatic load in a long-term perspective.
- The findings have relevance for general practice/primary healthcare and raise the question whether attentive, person-centred dialogues can contribute to treatment and prevention of complex disease within the frame of an established doctor–patient relationship.

INTRODUCTION

In recent years, there has been increasing interest in the phenomenon multimorbidity, that is, the co-occurrence of two or more chronic diseases in the same individual.[1 2] Initially, multimorbidity research tended to focus on older patients and prevalence figures. However, the scope has gradually widened, documenting significant prevalence of multimorbidity also among younger

age-groups and, overall, an uneven distribution along social gradients.[3–5]

The origins of multimorbidity are evidently multifactorial and complex,[6] and knowledge as to the true sources is quite limited. We regard the concept *allostatic load*[7] as a central key to understanding why some individuals develop a host of complex, common diseases, while others do not.[5 8 9] The model conceptualises how demanding life circumstances (physical and mental) affect the organism over time, and how long-standing unbuffered stress might eventually overtax the body's capacity for adaptation. The result is a tendency to physiological disruption with increased susceptibility to disease.[10 11] Allostasis thus depicts the physiology of a process termed embodiment. The notion of embodiment, derived from a phenomenology of the body,[12 13] allows to account for how sociocultural experiences and other environmental influences translate into physiological and anthropometric characteristics of the body, whereby clearly relevant for epidemiological research.[8 14 15] There is currently no consensus regarding measurement of allostatic load. However, an authoritative researcher in the field characterises three types of allostatic load parameters.[11] Well-known risk factors, such as hypertension or hyperlipidaemia, are classified as secondary mediators, while diagnosed diseases are classified as tertiary allostatic outcomes. Consequently, disease development in general and multimorbidity in particular have relevance as indicators of allostatic overload.[11]

From an epidemiological perspective, the pathogenic impact of traumatic experiences involving neglect and integrity violations is well documented in the somatic and mental domains. There is also clear evidence of a social gradient in health, reflecting how environmental and existential stressors and demands tend to accumulate with increasing social deprivation.[16–21] Furthermore, it is becoming increasingly clear how subtle yet long-standing challenges impact on the human physiology and predispose to disease.[22–25] Likewise, it is acknowledged that it is *subjective experience*, not objectively quantifiable events, that becomes biologically inscribed.[9 26] This implies that every person perceives and interprets himself or herself, and relations with other people within a socioculturally framed system of values. As practitioners and researchers, we see this as relevant in the clinical setting, but recognise that it is challenging to explore the topic in a scientifically valid manner. Our main hypothesis is that over time, existential *Un-ease* in the above-mentioned realms might contribute substantially to allostatic load and thereby to the development of complex, medical *dis-ease*. The present study was designed to further test the plausibility of this argument.

For this purpose, we analysed data from the Norwegian HUNT study. From their comprehensive questionnaire, we identified questions which we suppose to shed light on the respondents' evaluation of self, experienced purpose in life, well-being, and significant, social relations. As noted by the US Centres of Disease Control and Prevention,[27] the scientific literature contains a wide range of concepts related to the notion of health-related quality of life, such as well-being, flourishing, life satisfaction and happiness. We have so far not found an established term that accommodates our clinically rooted research question and the applied data set.

We therefore decided to introduce a new term, *existential unease*, to describe lack of self-esteem, well-being, meaning and/or social interrelatedness. The word 'existential' points to existential philosopher Maurice Merleau-Ponty who most explicitly linked experiences to subjectivity and the body by emphasising that human beings by necessity experience the world by means of their bodies,[12] thus providing a framework of relevance also for medical research in general[19] and epidemiology in particular.[14] It is not our primary intention to develop a new tool for research or clinical practice. Our main interest is to contribute some new perspectives on the phenomenon embodiment, particularly with regard to the aetiology of complex disease and multimorbidity.

To sum up, the aim of this study was to prospectively explore associations between existential unease, on the one hand, and indications of general biological disruption, expressed through an increased risk of developing multimorbidity, on the other.

STUDY POPULATION AND METHODS

Our data are derived from the HUNT study, a renowned population-based study carried out in Nord-Trøndelag County in Norway. It has, to date, had three phases. The second phase, HUNT2, was carried out in 1995–1997, whereas HUNT3 took place in 2006–2008. All adults aged over 20 years and receding in the county were invited to participate. In total, 65 237 persons (69.5% of the population) took part in HUNT2 and 50 807 (54.1%) took part in HUNT3. In total, 37 071 persons (73% of the HUNT3 population) took part in both phases.[28] Participants in the HUNT study have been considered fairly representative of the Norwegian population.[29] However, being a rural area, educational levels and mean income are somewhat lower, and the population is more homogenous than in urban areas, in terms of ethnicity and social gradients.[30]

The HUNT data were collected by means of questionnaires, physical examinations and blood samples. For this prospective study, we included participants who took part in HUNT2 and HUNT3. We identified individuals who were 20–59 years at baseline and reported 0–1 chronic disease (no multimorbidity), in total 20 365 participants. We subsequently compared individuals reporting multimorbidity in HUNT3 with those who did not (see online supplementary figure S1) to explore possible differences between the groups. Participants aged 60 years or older at baseline were excluded from analysis as the prevalence of multimorbidity increases steeply in older age.[5]

Selection of items reflecting existential unease

The questionnaires integrated in the HUNT2 survey were informed by contemporary theoretical frameworks from various domains, especially sociologist Pierre Bourdieu's theories concerning social and cultural capital,[31–33] sociologist Aron Antonovsky's concept Sense of Coherence[34 35] and the psychological notions of self-esteem and well-being.[36–38] As previously explained, we purposefully selected questions which we considered particularly indicative of an existentially, and thereby also a biologically, demanding lifeworld.[12 14]

In total, 11 items were included in our analysis. Together they cover thematically related, but nevertheless, distinct perspectives. Two of the items, 'being satisfied with life' and 'having a positive opinion of oneself', stem from the Rosenberg Self-esteem questionnaire, validated and predominantly applied in sociological studies.[36 38] The remaining nine were single-item questions.

The list of questions is presented in online supplementary appendix 1 as they appeared in the HUNT2 questionnaire. The response options were then rearranged to have the reference group of the least stressful or most positive outcome to be presented at the top. For further analyses, response options were collapsed and binary variables were constructed when relevant. Three of the 11 items were originally binary with yes/no answers, but for the others, the two most unfavourable response options were combined to indicate existential unease. Finally, a summation of the binary variables was used as to indicate more distress or unease, and thus, hypothetically, a higher allostatic load.

Assessment of multimorbidity

Multimorbidity was defined according to international consensus as two or more coinciding chronic diseases within the same individual.[2] Seventeen chronic conditions were accessible by the same definitions through the questionnaires from HUNT2 and HUNT3. Eleven of these were self-reported in response to the question "have you had or do you have the following medical condition" or "has a doctor said that you have the following condition?" The definition of the remaining six conditions has previously been described in more detail.[5] Online supplementary appendix 2 shows a list of the included conditions.

As supplementary analyses, we evaluated adult existential unease with regard to difficult childhood, to link the present study to our previous work on difficult childhood, allostatic load and adult multimorbidity (see online supplementary appendix 3 and figure S2).[9]

Missing data

For estimations of multimorbidity, as well as for the summation of binary unease factors, missing data were defined as the absence of the disease or unease item in question. In statistical analyses of relative risk (RR), respondents with missing data on each confounder were defined as a specific group.

Statistical analyses

Descriptive analyses were stratified according to the development of multimorbidity between the two phases of the study. The categorical variables were expressed as frequencies with percentages and continuous variables as means with SDs.

Poisson logistic regression for prospective data was used to estimate the RR with 95% CI of multimorbidity associated with each of the different variables expressing unease. The variables were analysed independently. All associations were adjusted for age (continuous) and gender (woman and man) in model 1. In model 2, we also included smoking (no or yes to 'daily use of cigarettes, cigars and/or pipes'), education (primary, secondary or university) and physical activity (no activity, <3 hours of light activity and no hard activity, >3 hours of light and/or <1 hour of hard activity and 1 hour or more of hard activity per week). To address possible confounding by current undiagnosed depression at baseline, we conducted additional analyses adjusting for indication of current depressive symptoms, defined as eight or more points for depression on the Hospital Anxiety and Depression Scale (HADS) and presented as model 3. Assessment was made for possible multicollinearity between the unease variables, which appeared not to occur.

The same method for Poisson regression was used in the assessment of RR for binary variables, as well as for the variable summing all the binary factors, adjusting for possible confounding by age, gender, smoking, physical activity and education.

The sum of binary variables for existential unease was then grouped as 0, 1–2, 3–4 and 5+ and assessed with regard to developing increasing number of diseases 11 years later as well as with self-reported experience of childhood.

SPSS statistical program (V.22) was used for all analyses.

The article was adjusted to STROBE recommendations for cohort studies in epidemiology.

RESULTS

Prospective data on 20 365 individuals who participated in HUNT2 and HUNT3 were analysed with respect to the development of multimorbidity between the surveys (table 1). In total, 6 277 persons (30.8%) acquired multimorbidity during the 11 years. They were on average older, more likely to be women and smokers, less physically active and had lower education.

Table 2 summarises the RR of developing multimorbidity associated with each of the 11 items indicating existential unease. The factors with the strongest association are 'being dissatisfied with life', 'having a negative opinion of self', 'having financial worries', 'not feeling

Table 1 Baseline characteristics of participants aged 20–59 years in HUNT2 according to the development of multimorbidity over a period of 11 years*

	Total	Multimorbidity	
		No	Yes
	n=20 365	n=14 088	n=6 277
Mean age	40.62 (±10.0)	39.45 (±9.94)	43.24 (±9.62)
Gender			
Women	10 938 (53.7)	7 201 (51.1)	3 737 (59.5)
Men	9 427 (46.3)	6 887 (48.9)	2 540 (40.5)
Smoking			
No	13 272 (65.2)	9 450 (67.1)	3 822 (60.9)
Yes	3 326 (16.3)	2 142 (15.2)	1 184 (18.9)
Physical activity			
None	1 018 (5.0)	705 (5.0)	313 (5.0)
Low	5 388 (26.5)	3 494 (24.8)	1 894 (30.2)
Medium	6 669 (32.7)	4 588 (32.6)	2 081 (33.2)
High	6 747 (33.1)	4 979 (35.3)	1 768 (28.2)
Education			
Primary	3 900 (19.2)	2 340 (16.6)	1 560 (24.9)
Secondary	10 543 (51.8)	7 390 (52.5)	3 153 (50.2)
University	5 735 (28.2)	4 235 (30.1)	1 499 (23.9)

*Percentages and SDs within brackets as appropriate.

calm and good' and 'poor self-rated health', all having RRs above 1.4 for the subgroups indicating most distress in model 2. Adjusting for current depressive symptoms according to the HAD scale attenuated the RR slightly, especially for the subgroups indicating most distress as shown in model 3.

The RRs changed slightly after constructing binary factors from the unease items (see figure 1). For the binary model, 'being dissatisfied with life', 'poor self-rated health', 'having sleeping problems affecting work', 'not feeling calm and good' and 'having financial worries', all had a RR above 1.3. When assessing according to gender, the results were quite similar, except for 'not having enough friends' which was a stronger predictor for women and 'boiling with anger but not showing it' which was a stronger predictor for men.

We then evaluated the effect of increasing numbers of unease factors in relation to multimorbidity (figure 2). There we found a dose–response association in RR from having one factor, RR being 1.18 (95% CI 1.11 to 1.25) up to RR 1.81 (95% CI 1.50 to 2.18) for six or more, the prevalence of multimorbidity being 26.7% for those with zero factors at baseline and linearly increasing up to 49.2% for those with six or more. Figure 3 shows that those with no unease factors are more likely to remain free from multimorbidity after 11 years of follow-up, compared to those reporting unease. With an increasing number of unease factors, the prevalence of 2, 3 or 4+ diseases at follow-up becomes higher, with 2.8% among those with no unease factor having 4+ diseases, compared to 8.8% among those with five or more unease factors.

Finally, we looked at the number of unease factors in light of self-reported childhood experiences (see online supplementary figure S2 with comments).

DISCUSSION

In this comprehensive population-based study, baseline indications of what we conceptualised as 'existential unease' were associated with the risk of developing multimorbidity 11 years later. The increase in RR with an increasing number of unease indicators suggests something similar of a dose–response effect as more existential domains become involved. The findings support our initial hypothesis that existential unease might contribute to allostatic load and thereby increase the susceptibility to disease in a life-course perspective.

The questions used in our study were originally based on the sociological and psychological theories (ie, sense of coherence, social capital, self-esteem and well-being, as previously mentioned), which were from the beginning theoretically associated with the concept of health. We will not open a discussion pertaining to the medical relevance of each particular theory or concept as it was originally formulated, but highlight that recent research from a variety of sources sheds light on their biological relevance. Our findings are, for instance, in concordance with studies of the pathogenic impact of perseverative cognition, ruminations and worries.[39] Correspondingly, low self-esteem,[40] unfairness,[41] lack of well-being,[25 42] work dissatisfaction,[43] loneliness,[44] lack of social relationships,[45] subjective social–evaluative threat[46] and anger[47] have been related to impaired health. A perceived lack of purpose in life has recently been connected to allostatic load,[48 49] as has compromised sleep quality.[50–52]

The strong association shown between poor self-rated health and multimorbidity in our study is concordant with extensive literature on self-rated health in connection to disease development and mortality, where it has been shown to be a powerful independent risk factor.[53] However, the strong association shown for many of the other items, such as 'dissatisfaction with life', 'negative self-opinion', 'financial worries' and 'lack of inner calm', gives a wider view of how different aspects of our existence or life world can significantly affect future health.

With regard to the included survey questions, it is not evident to what extent they all represent precursors of chronically impaired biological function, as some of them might tap into an early pathogenic process not yet manifested as clinical disease. Recent evidence has suggested a relationship between self-rated health and allostatic load.[53 54] In other words, a subjective perception of poor health might develop concomitantly with, and not prior to, high allostatic load. The same might, to a certain extent, pertain to impaired sleep, but according to our clinical experience and in line with existing evidence[55] we also see sleep to be a relevant indicator of primary unease. Although the exact, causal contribution of each individual 'unease' factor cannot be fully determined, the clinical relevance of considering such factors is likely to persist.

Our finding of a dose–response increase in RR of multimorbidity, as well as increasing prevalence of higher

Table 2 RR of developing multimorbidity within 11 years with regard to different items indicating existential unease in HUNT2, adjusted for common confounders

	Multimorbidity		Model 1*	Model 2†		Model 3‡	
Variable	**No**	**Yes**	**RR**	**RR**	**95% CI**	**RR**	**95% CI**
Life satisfaction							
Satisfied	7 489	2 781	1.0	1.0	Ref.	1.0	Ref.
Somewhat satisfied	5 060	2 473	1.18	1.16	1.10 to 1.23	1.16	1.10 to 1.23
Neither nor	1 236	836	1.47	1.44	1.33 to 1.56	1.40	1.29 to 1.52
Somewhat dissatisfied	112	90	1.66	1.65	1.33 to 2.03	1.56	1.26 to 1.90
Dissatisfied	49	39	1.60	1.51	1.10 to 2.08	1.39	1.00 to 0.192
Positive self-opinion							
Strongly agree	2 253	753	1.0	1.0	Ref.	1.0	Ref.
Agree	9 012	4134	1.13	1.12	1.03 to 1.21	1.11	1.02 to 1.20
Disagree	658	444	1.43	1.38	1.23 to 1.56	1.30	1.15 to 1.47
Strongly disagree	30	22	1.56	1.49	0.97 to 2.27	1.37	0.89 to 2.09
Living a meaningful life							
Yes	10 444	4 518	1.0	1.0	Ref.	1.0	Ref.
No	1 391	781	1.23	1.21	1.12 to 1.30	1.15	1.06 to 1.25
Enjoying work							
A great deal	3 857	1 626	1.0	1.0	Ref.	1.0	Ref.
A fair amount	6 726	3 066	1.03	1.03	0.97 to 1.09	1.02	0.95 to 1.08
Not much	432	240	1.23	1.21	1.05 to 1.38	1.16	1.01 to 1.33
Not at all	39	20	1.25	1.23	0.79 to 1.91	1.15	0.73 to 1.79
Financial worries							
No, never	8 786	3 723	1.0	1.0	Ref.	1.0	Ref.
Yes, though seldom	1 966	908	1.21	1.18	1.10 to 1.27	1.18	1.10 to 1.27
Yes, sometimes	1 016	580	1.36	1.30	1.19 to 1.42	1.30	1.19 to 1.42
Yes, often	254	184	1.58	1.50	1.29 to 1.74	1.46	1.25 to 1.70
Having enough friends							
Yes	10 002	4 424	1.0	1.0	Ref.	1.0	Ref.
No	1 973	958	1.12	1.13	1.06 to 1.22	1.10	1.03 to 1.18
Distrusting neighbours							
Strongly disagree	4 795	1 941	1.0	1.0	Ref.	1.0	Ref.
Somewhat disagree	3 511	1 491	1.09	1.08	1.01 to 1.15	1.07	1.00 to 1.15
Not sure	2 047	1 057	1.22	1.19	1.10 to 1.28	1.17	1.09 to 1.27
Somewhat agree	1 245	650	1.19	1.14	1.04 to 1.25	1.13	1.03 to 1.23
Strongly agree	322	202	1.21	1.15	0.99 to 1.33	1.13	0.98 to 1.32
Boiling with anger							
Almost never	5 237	2 239	1.0	1.0	Ref.	1.0	Ref.
Sometimes	5 571	2 580	1.05	1.03	0.97 to 1.09	1.02	0.96 to 1.08
Quite often	713	345	1.14	1.13	1.01 to 1.27	1.11	0.99 to 1.24
Almost always	267	139	1.14	1.10	0.93 to 1.31	1.09	0.92 to 1.30
Feel calm and good							
Almost all the time	5 877	2 325	1.0	1.0	Ref.	1.0	Ref.
Often	4 793	2 184	1.10	1.09	1.03 to 1.16	1.09	1.03 to 1.15
Sometimes	1 352	881	1.39	1.36	1.26 to 1.47	1.3	1.20 to 1.41
Never	47	38	1.71	1.67	1.21 to 2.30	1.47	1.06 to 2.05
Sleeping problems affecting work							
No	11 223	4 831	1.0	1.0	Ref.	1.0	Ref.
Yes	770	556	1.39	1.39	1.27 to 1.51	1.34	1.22 to 1.46
Self-rated health							
Very good	4309	1037	1.0	1.0	Ref.	1.0	Ref.
Good	8782	4279	1.56	1.51	1.41 to 1.62	1.51	1.41 to 1.62
Not so good	881	886	2.26	2.16	1.97 to 2.37	2.12	1.93 to 2.33
Poor	25	26	2.34	2.24	1.52 to 3.31	2.23	1.50 to 3.23

*Adjusted for age and gender.
†Adjusted for age, gender, smoking, physical activity and education.
‡Adjusted for same as model 2 and current depressive symptoms.
RR, relative risk.

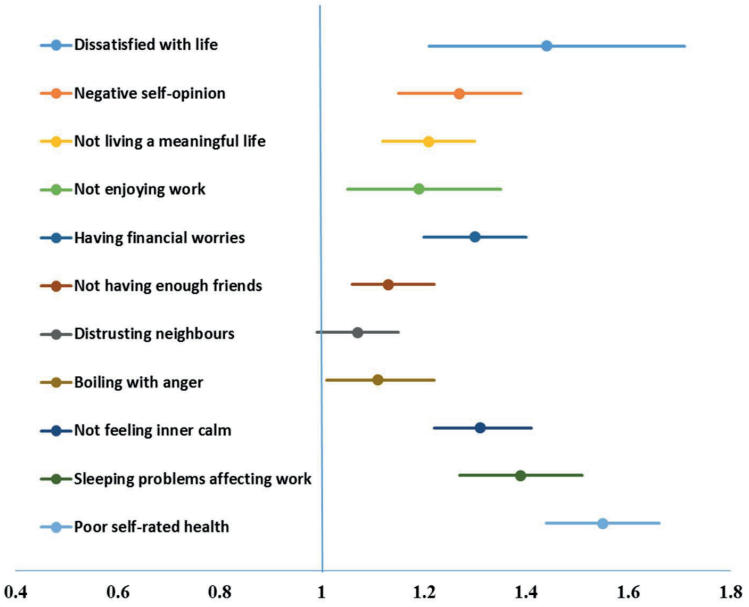

Figure 1 RR of developing multimorbidity within 11 years with regard to different binary factors indicating existential unease in HUNT2, adjusted for possible confounders. RR, relative risk.

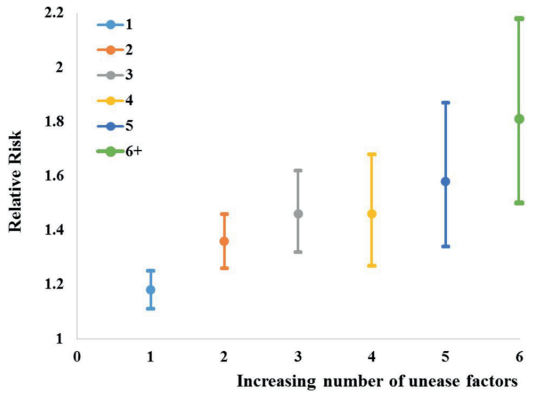

Figure 2 RR of developing multimorbidity within 11 years according to an increasing number of factors indicating existential unease in HUNT2, adjusted for possible confounders and with zero factors as reference. RR, relative risk.

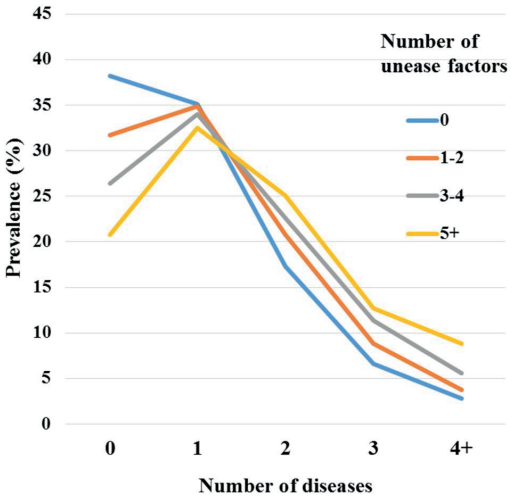

Figure 3 Prevalence of different numbers of diseases in HUNT3 with regard to an increasing number of factors indicating existential unease in HUNT2. RR, relative risk.

number of diseases, as the number of existential unease factors accumulates, is interesting in light of the results of the ACE study,[17] which found a linear increase in disease prevalence with an increasing number of adverse experience categories. In both cases, the notion of dose refers to an increasing number of adversity (or unease) types, not the intensity or frequency of any one exposure. Our supplementary analysis adds to the picture of causal relations, as we found that childhood difficulties are related to existential unease (see online supplementary figure S2 with comments). In both instances, it is likely that allostatic load, and eventually the susceptibility to complex disease, increases with the number or types of adversity or unease involved.

The demographic difference between the groups developing multimorbidity and remaining healthy in our study is in line with current literature.[1 3] Multimorbidity is generally more prevalent in older populations and lower socioeconomic groups, and shows a gendered pattern with higher prevalence in women.[1 3]

However, in our study, the impact of unease items on disease development did not differ between genders. The almost equal effect suggests that although the impact of specific types of adversities or distress might be gendered, experiencing unease as such might undermine health in men and women.

Another interesting finding in our study was the small changes in RRs for multimorbidity development after adjusting for confounders. Adjusting for physical activity, smoking and educational level attenuated the findings only slightly. The same was the case when adjusting for current depressive symptoms. This concords with literature showing that current depressed mood might not be a confounder but a mediator when evaluating subjective experience.[56] In our study, however, the effect of these factors appears to be weak.

Strength and limitations of the empirical analysis

The main strength of our analysis lies in the generally high quality of the HUNT database.[30] The fact that the HUNT population is ethnically quite homogenous and relatively affluent, with good and equitable access to primary healthcare,[29] is also a strength, as it lowers the potential for confounding by socioeconomic factors not fully accounted for in the analysis. However, as the HUNT study was not designed with the present study in mind, some limitations apply. The 17 diagnoses available for assessing self-reported multimorbidity were fewer than would have been ideal for a comprehensive assessment. However, a count of 12 or more chronic conditions should lead to a fair evaluation of multimorbidity.[1] A similar problem arose regarding the definition of the phenomenon we termed 'existential unease'. This category is not based on a validated battery of questions, but on a purposeful collection of items which we deemed particularly relevant on the basis of clinical experience and existing evidence, allowing for reflection on empirical data in light of theoretical or experiential preknowledge. This might represent a methodological weakness, but from the perspective of innovation, it can be seen as a strength. Our approach sheds new light on the biological relevance of various established psychosocial concepts and theories and thereby might contribute to increased appreciation of the broad relevance of the epidemiological concept embodiment. Another potential methodological weakness is selection bias occurring between the two survey phases. A comparison between participants and non-participants in HUNT3 showed that the latter were older, weaker and with more morbidity.[28 57] It is possible that some of the individuals who experienced substantial worsening of their health between the two phases were lost to follow-up. This might imply underestimation of the multimorbidity prevalence in HUNT3.

Conclusions and implications

Based on data from an unselected, general Norwegian population, the present prospective study demonstrates an intriguing connection between subtle indicators of existential unease and the development of multimorbidity later in adult life. The RR of multimorbidity rose as the number of statements reflecting unease increased. The findings are concordant with an increasing body of literature describing how distressing challenges tend to affect the human physiology by rising allostatic load, whereby undermining health through embodiment of the 'wear and tear'[7] of a burdening everyday life.

From the perspective of primary care, our findings highlight the importance of an encompassing, person-centred approach, not the least in the face of complex disease and multimorbidity.[58 59] Subjective experiences pertaining to the self, one's life project and relationships with other people apparently matter, in a literal sense. As we conclude so, it is, however, not our intention to medicalise every aspect of the human lifeworld and suggest that human happiness should be subjected to systematic, medical surveillance.[60] What we hope to contribute to is a more comprehensive medical understanding that does justice to the human nature.[61] This is ultimately a fundamental prerequisite for good healthcare.

Acknowledgements The Nord-Trøndelag Health Study (the HUNT study) is a collaboration between the HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council, Central Norway Health Authority and the Norwegian Institute of Public Health. The authors thank the HUNT Research Centre for contributing data and Steinar Krokstad for assistance regarding background information on the HUNT study.

Contributors The theoretical background and research question was developed by MOT, LG, JAS and ALK. Statistical analyses were performed by MOT, JAS, HP and TILN. All authors contributed to writing of the article.

Funding The HUNT3 Survey was mainly funded by the Norwegian Ministry of Health, the Norwegian University of Science and Technology, the Norwegian Research Council (the FUGE program), Central Norway Regional Health Authority, the Nord-Trøndelag County Council and the Norwegian Institute of Public Health. The present analysis received support from the Research Fund of the Icelandic College of Family Physicians. The funders had no role in study design, data collection or analysis, decision to publish or preparation of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Each participant in the HUNT study signed a written consent regarding the screening and the use of data for research purposes. The study was approved by the Norwegian Data Inspectorate and the Regional Committee for Ethics in Medical Research.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Owing to restrictions related to patient consent and Norwegian privacy laws, data are available on request. More information is available at the following URL (http://www.ntnu.edu/hunt/data) and interested parties may contact Dr Steinar Krokstad (steinar.krokstad@ntnu.no) with further questions.

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BMJ Open

Does 'existential unease' predict adult multimorbidity? Analytical cohort study on embodiment based on the Norwegian HUNT population

Margret Olafia Tomasdottir, Johann Agust Sigurdsson, Halfdan Petursson, Anna Luise Kirkengen, Tom Ivar Lund Nilsen, Irene Hetlevik and Linn Getz

BMJ Open 2016 6:
doi: 10.1136/bmjopen-2016-012602

Supplementary file

Does 'existential unease' predict adult multimorbidity? Analytical cohort study on embodiment based on the Norwegian HUNT population

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Table of contents:

APPENDIX 1

Questions used for evaluation of ´existential´ unease as they appear in the HUNT2 questionnaire:

Thinking about your life at the moment, would you say that you by and large are satisfied with life, or are you mostly dissatisfied?

Very satisfied, Satisfied, Somewhat satisfied, Neither satisfied nor dissatisfied, Somewhat dissatisfied, Dissatisfied, Very dissatisfied

I have a positive opinion of myself

Strongly agree, Agree, Disagree, Strongly Disagree

Do you feel that you have a meaningful life?

Yes, No

All things considered, how much do you enjoy your work?

A great deal, A fair amount, Not much, Not at all

During the last year, has it at any time been difficult to meet the costs of food, transportation, housing and such?

Yes, often; Yes, now and again; Yes, though seldom; No, never

Do you feel that you have enough good friends?

Yes, No

Answer with regard to your environment, i.e. neighbourhood/group of farms:

One cannot trust each other here

Strongly agree, Somewhat agree, Not sure, Somewhat disagree, Strongly disagree

I boil with anger, but I don´t show it to others

Almost never, Sometimes, Quite often, Almost always

During the last week: Do you by and large feel calm and good?

Almost all the time, Often, Sometimes, Never

During the last year, have you been troubled by insomnia to such a degree that it affected your work?

Yes, No

How is your health at the moment?

Poor, Not so good, Good, Very good

APPENDIX 2

List of the 17 conditions used for estimation of multimorbidity:

- Cardiovascular disease
- Hypertension (excluding those with cardiovascular disease)
- Hyperlipidaemia
- Obesity
- Diabetes
- Chronic back or neck pain
- Thyroid disease
- Asthma
- Cancer
- Mental health problems
- Epilepsy
- Gastro-oesophageal reflux
- Ankylosing spondylitis
- Osteoarthrosis
- Rheumatic arthritis
- Fibromyalgia
- Osteoporosis

APPENDIX 3

Assessment of the relationship between childhood difficulties and existential unease

In response to one reviewer's suggestion, we also evaluated adult existential unease with regard to difficult childhood, in line with our earlier published work on difficult childhood and adult multimorbidity.

In HUNT 3, the overall quality of the respondents´ childhood was addressed by one single question: *´When you think about your childhood, would you describe it as´: 'Very good-good-average-difficult-very difficult'.* This question has been described in further detail in our earlier publication.[9]

Figure S2 below is presented to link our present study with this previous work, but it is important to note that the inclusion criteria at baseline in the present study (having only 0-1 established diseases at the age 20-59 years) lead to exclusion of more than half of all respondents who reported a difficult or very difficult childhood, as they were already multimorbid.

Those reporting a very good childhood in HUNT3 reported less unease factors in adult life while the prevalence for higher numbers of unease factors in adulthood increased with the presence of reported childhood difficulties.

A total of 57.9% of those reporting a very good childhood reported no unease factor in adult life compared to 28.1% of those with a very difficult childhood and 1.3% with a very good childhood having 5 or more unease factors compared to 17.2% of those with a very difficult one.

Figures

Figure S1. Flow chart of included participants

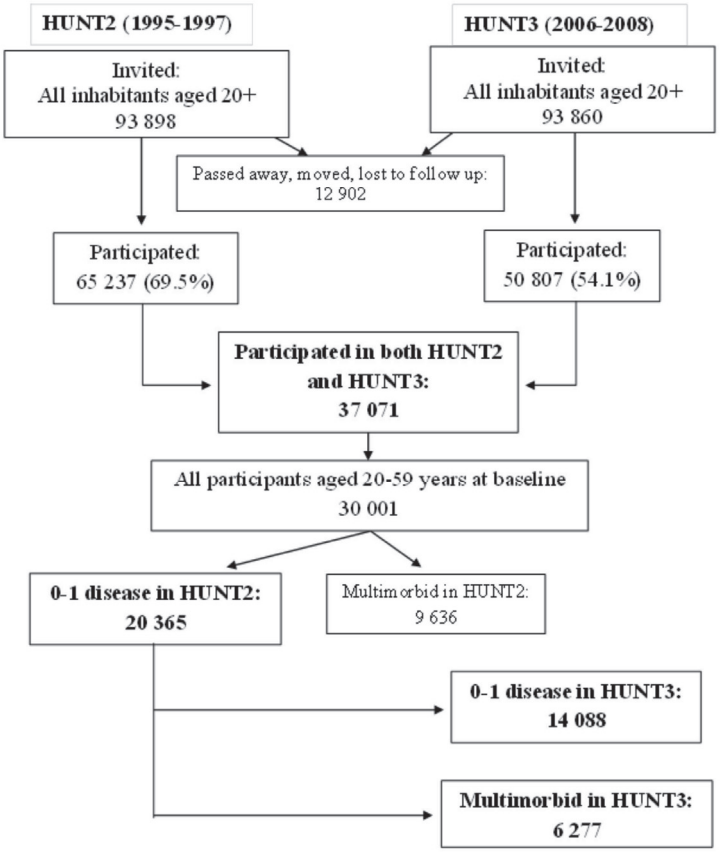
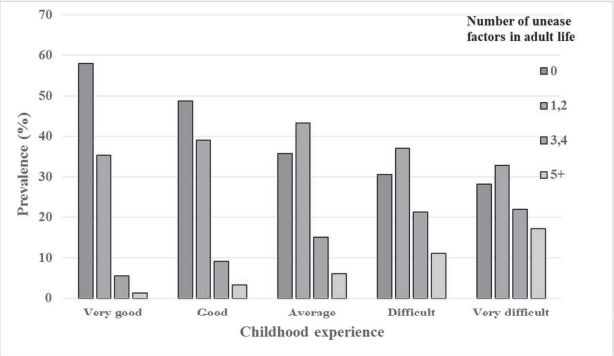


Figure S2. Prevalence of each group of unease factors in HUNT2 with regard to self-reported experience of childhood in HUNT3



Appendix 1

List of diseases/conditions and questions from the HUNT questionnaires pertaining to the definition of multimorbidity

Questions from HUNT3 pertaining to the definition of multimorbidity as they appear in the questionnaire (translated to english):

Cardiovascular disease (yes to any of the following)

- Have you had or do you have any of the following:
  - Myocardial infarction (heart attack)
  - Angina pectoris (chest pain)
  - Heart failure
  - Other heart disease
  - Stroke/brain haemorrhage

Kidney disease

- Have you had or do you have any of the following:
  - Kidney disease

Asthma

- Have you had or do you have any of the following:
  - Asthma

COPD

- Have you had or do you have any of the following:
  - Chronic bronchitis, emphysema or COPD

Diabetes

- Have you had or do you have any of the following:
  - Diabetes

Psoriasis

- Have you had or do you have any of the following:
  - Psoriasis

Cancer

- Have you had or do you have any of the following:
  - Cancer

Epilepsy

- Have you had or do you have any of the following:
  - Epilepsy

Rheumatoid arthritis

- Have you had or do you have any of the following:
  - Arthritis (rheumatoid arthritis)

Ankylosing spondylitis

- Have you had or do you have any of the following:
    - Bechterew´s disease

Osteoporosis

- Have you had or do you have any of the following:
    - Osteoporosis

Fibromylagia

- Have you had or do you have any of the following:
    - Fibromylagia

Osteoarthritis

- Have you had or do you have any of the following:
    - Degenerative joint disease (Osteoarthritis)

Mental health problems

- Have you had or do you have any of the following:
    - Mental health problems you sought help for

Chronic back/neck pain

- In the last year, have you had pain or stiffness in muscles or joints that has lasted at least 3 consecutive months? (if yes – where)
    - Neck
    - Upper back
    - Lower back

Thyroid disease

- Has it ever been verified that you have/had:
    - Hypothyroidism
    - Hyperthyroidism

Gastro-oesophageal reflux disease

- To what degree have you had the following in the last 12 months
    - Heartburn/acid regurgitation
- Positive if answered “much”

Dental health problems

- How would you say your dental health is?
- Described as a problem if “bad” or “very bad”

Hypertension

- Do you take or have you taken medication for high blood pressure
- Hypertension defined if yes to the above question and/or if mean blood pressure measurement above 180mmHg for systole and/or 110mmHg for diastole

Hyperlipidaemia

- Defined if measurement from random blood sample showed total cholesterol above 7,0 mmol/L and/or triglycerides above 3.0 mmol/L

Obesity

- Defined if BMI measurement above 30

Appendix 2

Questions from the HUNT2 questionnaire pertaining to the concept of existential unease

Questions used for evaluation of ´existential´ unease as they appear in the HUNT2 questionnaire:

Thinking about your life at the moment, would you say that you by and large are satisfied with life, or are you mostly dissatisfied?

Very satisfied, Satisfied, Somewhat satisfied, Neither satisfied nor dissatisfied, Somewhat dissatisfied, Dissatisfied, Very dissatisfied

I have a positive opinion of myself

Strongly agree, Agree, Disagree, Strongly Disagree

Do you feel that you have a meaningful life?

Yes, No

All things considered, how much do you enjoy your work?

A great deal, A fair amount, Not much, Not at all

During the last year, has it at any time been difficult to meet the costs of food, transportation, housing and such?

Yes, often; Yes, now and again; Yes, though seldom; No, never

Do you feel that you have enough good friends?

Yes, No

Answer with regard to your environment, i.e. neighbourhood/group of farms:

One cannot trust each other here

Strongly agree, Somewhat agree, Not sure, Somewhat disagree, Strongly disagree

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During the last year, have you been troubled by insomnia to such a degree that it affected your work?

Yes, No

How is your health at the moment?

Poor, Not so good, Good, Very good

Appendix 3

Poster presented at Preventing Overdiagnosis, Oxford 2014

Too many diagnoses - multimorbidity as a medical artefact?

Margret Olafia Tomasdottir, Linn Getz, Johann A. Sigurdsson, Halfdan Petursson

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Contemplations:

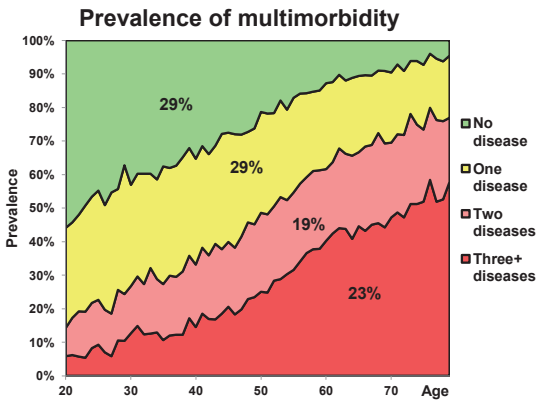
Is multimorbidity a true epidemic on the rise, or another aspect of too much medicine?

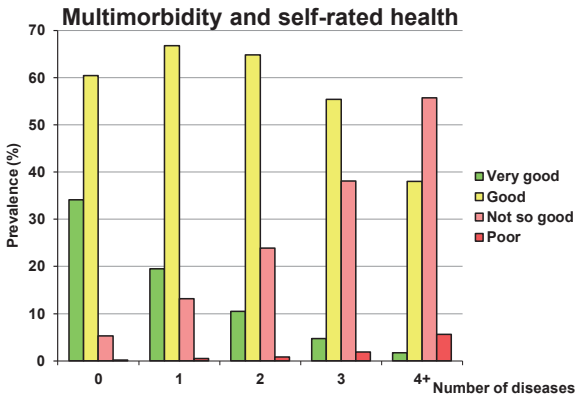
Does the prevalence stem from real health problems, or flawed in the biomedical thinking?

Aims:

To look at the overwhelming prevalence of multimorbidity in the light of self-perceived health

To look at possible explanatory patterns of multimorbidity





Background:

Multimorbidity is by convention defined as two or more co-existing chronic diseases or conditions. It seems to be increasing in prevalence and has been termed one of the biggest medical challenges of the 21st century, has even been described as a "normal state" for people seeking help in GP´s office. A logical consequence of multimorbidity is polypharmacy. Medicine has no good grip on the notion of common "root causes" beneath the more disease-specific causes.

Results:

The age-standardized prevalence of multimorbidity was 42% (39% for men and 46% for women). Most of the diseases were strongly associated with multimorbidity clusters and patterns were not easily identified. Most people with two or three diseases still identified their health as good and only those with four or more chronic diseases felt predominantly in ill health.

Methods:

We used data from the Nord-Trøndelag Health Study, HUNT 3 (2006-8) , a renowned population based study with 47.959 participants aged 20-79 years. 21 chronic disease conditions were used in estimation of multimorbidity and association between diseases evaluated. The connection between self-rated health and multimorbidity was estimated with chi-square.

Conclusions:

Most multimorbid people still identify their health as good

Multimorbid disease clusters typically defy not only diagnostic categories within the somatic and mental health domains, but also the dichotomy between these

Multimorbidity, as currently conceptualized might, to a certain extent, represent an artefact of the reigning biomedical classification system

The current definition of multimorbidity might lack clinical meaning as it does not correlate well with changes in self-rated health

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Appendix 4

Commentary article

COMMENT AND DEBATE

Origins of heath inequalities: the case for Allostatic Load

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http://dx.doi.org/10.14301/llcs.v7i1.325

Abstract

In an opening paper Delpierre et al. explore the concept of allostatic load. The impact of the environment on our biological systems is summarised by the concept of embodiment. The biological embedding of social conditions could therefore be a relevant mechanism to partly explain the social gradient in health. A key issue is how to measure the 'physiological reality' – the biological expression of embodiment at individual and population levels. Allostatic load (AL) has been proposed as a measure of the overall cost of adapting to the environment and may be a relevant tool or concept for measuring the way we have embodied our environment. Social inequalities in health may be partly explained by the embodiment of social environments, and AL may allow us to measure and compare embodiment between socioeconomic groups. However, before operationalising AL, a number of issues deserve further exploration. Among these, the choice of biological systems, and variables within each system, that should be included to remain 'loyal' to the theory of biological multisystem wastage underlying AL and the most appropriate methodological approach to be used to build an AL score, are particularly important. Moreover, studies analysing the link between adverse environments (physical, chemical, nutritional, psychosocial) across the life course and AL remain rare. Such studies require cohorts with data on socioeconomic and psychosocial environments over the life course, with multiple biological measures, made at various stages across the life span. The development and maintenance of these cohorts is essential to continue exploring the promising results that could enhance our understanding of the genesis of the social gradient in health by measuring embodiment. These points are then debated in commentaries by Linn Getz and Margret Olafia Tomasdottir, Tony Robertson and Per Gustafson. The commentaries are followed by a response from the authors of the opening paper.

Keywords

Allostatic load, embodiment, social epidemiology

Allostatic load as a measure of social embodiment: conceptual and empirical considerations

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(Received October 2014 Revised July 2015)

Introduction

The impact of the environment on our biological systems is summarised by the concept of embodiment. Krieger (2005) described embodiment as "how we, like any living organism, literally incorporate, biologically, the world in which we live, including our societal and ecological circumstances". The notion of embodiment refers to the fact that every human being is both a social and a biological organism that incorporates the world in which (s)he lives.

In consequence, an adverse socioeconomic environment may be implicated in the development of future diseases by modifying certain biological processes especially when exposures occur early in life. In the 1990s Barker (1990) showed that intrauterine growth retardation was associated with an increased risk of cardiovascular and metabolic diseases in adulthood, introducing the foetal origin of disease hypothesis. This postulates that environmental conditions during specific windows of development can have long-term effects on organogenesis, and metabolic and physiological processes. However, embodiment is a continuous process that occurs throughout life, with some periods of life being more sensitive than others to changes induced by the environment. As a phenomenon occurring over the life course, embodiment may partly explain the social gradient observed for the vast majority of chronic diseases. Hertzman (1999) wrote "the process whereby differential human experiences systematically affect the healthfulness of life across the life cycle has been termed *biological embedding*". If embodiment, or biological embedding, refers to the concept of environmental adaptation shared by living beings, a key question is how to measure the physiological reality, the biological expression of embodiment at individual and population levels?

Recently, we showed that psychosocial adversity during childhood (child spent time in care, physical neglect, parental contact with the prison service, parental separation including by death or divorce, family experience of mental illness, family experience of substance abuse) increased twofold the risk of cancer diagnosis and all-cause mortality before 50 years of age, after adjusting for several confounding factors like socioeconomic characteristics at birth, birth weight and breastfeeding. Including mediating factors in the model, like health behaviours or adult socioeconomic position, only slightly decreased the effect of childhood psychosocial adversity (Kelly-Irving et al., 2013a; Kelly-Irving et al., 2013b). Of course, there are a number of possible explanations for these results, such as methodological flaws in design and analysis, or not including an *a priori* confounding or mediating factor. However, one possible explanation is that the childhood psychosocial environment might have resulted in changes to biological systems during development that may alter health over time.

Due to immaturity at birth, humans, as with other altricial mammals, mature in constant interaction with the environment. Our environment

is highly variable requiring the permanent adaptation of physiological systems. This adaption through changes is crucial for survival and refers to allostasis (Sterling & Eyer, 1988). Three main systems, nervous, endocrine and immune, are involved in the allostasis processes, all of which mature during the postnatal period and into adulthood (Adkins, Laclerc and Marshall-Clarke, 2004; Gogtay et al., 2004). Chronic exposures to psychosocial stressors and inter-individual differences in the susceptibility to stress are both associated with a prolonged activation of these allostatic systems. This may lead to an allostatic overload with potentially detrimental health consequences. Allostatic load (AL) is therefore the price paid by the body over time for adapting to challenges. It refers to the concept of biological multisystem wastage, whereby "the strain on the body produced by repeated ups and downs of physiologic response, as well as by the elevated activity of physiologic systems under challenge, and the changes in metabolism and the impact of wear and tear on a number of organs and tissues, can predispose the organism to disease" (McEwen & Stellar, 1993).

An AL score should, by definition, be a composite measure including various physiological systems in order to capture overall physiological wear-and-tear. The MacArthur Study of Successful Aging was the first to propose an AL score (Seeman, Singer, Rowe, Horwitz & McEwen, 1997). Parameters included systolic and diastolic blood pressure (indexes of cardiovascular activity); waist-hip ratio (an index of more long-term levels of metabolism and adipose tissue deposition), thought to be influenced by increased glucocorticoid activity; serum high-density lipoprotein (HDL) and total cholesterol levels (indexes of long-term atherosclerotic risk); blood plasma levels of total glycosylated haemoglobin (an integrated measure of glucose metabolism during a period of several days); serum dehydroepiandrosterone sulphate (DHEA-S) (a functional HPA axis antagonist); 12-hour urinary cortisol excretion (an integrated measure of 12-hour HPA axis activity); 12-hour urinary norepinephrine and epinephrine excretion levels (integrated indexes of 12-hour sympathetic nervous system activity). Some variants of the original items can be found in the literature but the markers most commonly used are associated with cardiovascular and metabolic diseases (blood pressure, heart rate, blood glucose, insulin, blood lipids, body mass index or waist circumference), HPA axis (cortisol, DHEA-S), sympathetic nervous system (epinephrine, norepinephrine, dopamine) and inflammation (C-reactive protein, IL-6) (Seeman, Epel, Gruenewald, Karlamangla & McEwen, 2010). These various scores of AL have been shown to be better predictors of mortality and functional limitations than the metabolic syndrome or any of the individual components used to measure AL when analysed separately (Seeman, McEwen, Rowe & Singer, 2001). AL score is also associated with an increased incidence of cardiovascular disease, and poorer cognitive function (Seeman et al. 1997). Recent research also suggests a link between early environment and AL (Danese & McEwen, 2012; Danese et al., 2009; Shonkoff & Garner, 2012).

As a measure of the global cost of adapting to (and coping with) the environment, AL may be a relevant tool or concept for measuring the way we have embodied our environment. As the way in which human populations embody their environment may partly explain social inequalities in health, we guess that AL may be a relevant and useful tool for measuring and comparing embodiment between population and socioeconomic groups. However, some important issues regarding AL deserve consideration:

Representing multiple biological systems

There is increasing evidence that many chronic diseases are related: this disease interrelatedness, or human disease network, is well established for metabolic diseases like obesity, diabetes and vascular diseases, and more recently for Alzheimer's disease/dementia, and cancer (Barabasi, Gulbahce & Loscalzo, 2011). There is biological plausibility behind the observed associations between these diseases that exemplify health decline and aging processes over the life course. Endocrine physiology and inflammatory processes are shared and many of the same risk factors, such as hyperglycaemia, inflammatory responses or health behaviours, are common to these pathologies. Further progress in understanding therefore requires the development of a measure representing the physiological systems relevant to these diseases. However the AL scores most commonly used are strongly focused on the cardiovascular or metabolic systems. The conceptualisation of AL as a dysregulation across

multiple physiological systems requires that the measure includes a balance of relevant systems, as well as the cardiovascular or metabolic ones. For instance, the inflammatory and immune systems that are involved in various chronic diseases ought to be represented. A main question is therefore how to decide which systems to represent. One of the solutions is to adopt an *a priori* definition of the systems that should be included in the measure of AL by choosing major regulatory systems known to be involved in chronic stress responses. An alternative may be to select major biological systems affecting health (Seeman et al., 2010) with the risk to be limited for studying the link between AL and subsequent health, if health is included in AL score. It may be possible that one single combination of markers do not equally predict different chronic diseases like cardiovascular or metabolic diseases, cancer or Alzheimer's disease, so that our measure of embodiment may need to be adapted according to the health condition under investigation.

Choosing relevant biological markers in each system

After identifying the physiological systems relevant for inclusion in an AL score, it is necessary to define the biological markers within each system that are the most appropriate proxies to summarise the state of that system. Moreover, AL markers could be drawn from several very different physiological 'levels' from epigenetic regulations (DNA methylation, telomere length) to 'health outcomes' (illness, BMI, waist-hip ratio). The cascade of events linked to stress responses, physiological burden and disease thus needs careful consideration. Currently, some markers are presented as primary mediators (cortisol, DHEA-S, catecholamines), some others as secondary mediators (HDL, glucose level and more generally 'biological risk factors') and some others as tertiary mediators (diseases) (McEwen & Seeman, 1999). Furthermore, some mediators are more variable than others. In particular primary mediators, like cortisol, vary according to circadian rhythm and acute environmental challenges whereas secondary mediators, like HDL, are more stable. For primary indicators, multiple measures are required whereas for secondary or tertiary mediators, one measure may suffice. Furthermore, the total hormone level is not necessarily a good index of the active part of the hormone. In this case, transport proteins (such as CBG for cortisol) and salivary or urine assessment (free cortisol) should be measured. This issue raises general methodological considerations regarding AL score construction from various measures. Moreover this issue also raises questions on the feasibility of collecting such biomarkers in accessible samples like blood, saliva or urine.

Building a score

Considering the two previous points, the question of how to go about summarising, in one single score, information contained from a number of biomarkers is fundamental. In practice an AL score is usually built pragmatically from available data. The most widely used method to build an AL score uses a summary measure representing the number of biomarkers within a high risk percentile defined from the biomarkers' distribution in the studied population (Juster, McEwen & Lupien, 2010). Maybe more critical than questions on how to define 'subclinical' thresholds representative in various populations, this approach is empirical and is in large part not based on a theoretical concept of AL. Consequently, some scores are composed of variables that lead to one physiological system being over-represented versus the others. This is often the case with the cardiovascular or metabolic systems that can be measured through several easily-collected variables (HDL, LDL cholesterol total, blood pressure, glucose and insulin level, waist hip ratio, BMI) whereas HPA axis, sympathetic nervous system, inflammatory and immune systems tend to be represented using one or two variables. By simply summing these variables to build a score, it is likely that the score will be well correlated with cardiovascular diseases and less so with other diseases. It may be possible to weight the score according to the outcome measure of interest. The score would then be composed of the same variables weighted differently according to the disease studied. However, using such an approach raises issues about the capability of such a score to 'truly' measure global physiological wear and tear. Additionally, such a method also raises questions related to the fact that these variables are not independent, some of them being linked by physiological pathways. In consequence how best to take the nature of these different relationships into account in the overall score is an important issue. In response to these questions, more sophisticated methods like recursive partitioning or canonical correlation analyses have been used to

manage weighting and interrelation between biomarkers (Juster et al., 2010). More recently new approaches based on confirmatory factor analysis and structural equation modelling have been proposed which could be particularly relevant to 'capture' the concept of AL (Seeman et al. 2010; Booth, Starr & Deary, 2013; McCaffery, Marsland, Strohacker, Muldoon & Manuck, 2012). These methods, based on the covariation of biomarkers, present several advantages including: the possibility of testing an *a priori* hypothesised model or structure linking biomarkers and physiological systems which is relevant to analyse AL; the construction of AL as a latent variable (metafactor) by modelling shared variance among biological systems which is in accordance with the general idea of wear and tear included in the AL concept; testing factorial invariance which could be useful to test the stability of the AL score in various groups of the population (age, gender); the use of continuous variables; the fact that no assumption on weight is required as the weight of each parameter is defined empirically.

Allostatic load across the life course

Taking a life course approach to studying health raises questions regarding how best to measure wear and tear over the life span. AL is by definition the consequence of a cumulative adaptive response to challenges. Thus this is a dynamic process and therefore its measure should be dynamic as well. Moreover, the question of timing is key. The physiological systems identified to measure AL, and how to measure them, are indeed likely to vary considerably according to age. The physiological responses to stress vary by developmental stage in early life, with sensitive periods of brain development and consequent physiological responses occurring well into late adolescence. Sensitive periods of brain change also occur in older age, and are likely to have an impact on physiological stress reactivity (Lupien, McEwen, Gunnar & Heim, 2009). How to measure early stages of physiological wear and tear at different periods of life as well as differences in sex/ gender stress response each deserve further investigation (Bale, 2011).

The mediating role of AL between socioeconomic position and mortality deserves in-depth examination. Though the link between AL and subsequent health is relatively well studied, not many studies analyse the link between adverse environments (physical, chemical, nutritional, psychosocial) and AL, taking a life course approach. Very recent studies using a life course approach have shown very promising results on the link between socioeconomic position over the life course and AL score (Gruenewald et al., 2012; Gustafsson, Janlert, Theorell, Westerlund & Hammarstrom, 2011; Gustafsson, et al. 2012; Merkin, Karlamangla, Roux, Shrager & Seeman, 2014; Robertson, Popham & Benzeval, 2014). These studies justify that in order to identify mechanisms or causal chains linking environmental challenges, AL and subsequent health, a life course approach is required, particularly if interventions are to be implemented. To study such complex mechanisms, implicating direct and indirect effects of adverse exposures over time necessitates rich longitudinal datasets with long follow-ups. Socioeconomic position being a proxy for various exposures, datasets with large panels of variables on socioeconomic and psychosocial environment are particularly precious to disentangle which aspects contained in socioeconomic position influence both health and AL. Another essential ingredient in these datasets is the inclusion of biological samples, repeatedly collected to represent the dynamic nature of AL.

Conclusion

Here, we consider AL as a useful conceptual tool in measuring the biological effect of embodiment that can play a role in the production of the social gradient of many chronic diseases. Measures of the way people cope with their environment, from early life onwards, offer many possibilities regarding public health interventions both at a societal level by investing in childhood or in social environment, and at an individual level by preventing diseases through behavioural or treatment interventions. Before operationalising AL as a measure of embodiment, a number of issues deserve further exploration. To remain loyal to the theory behind AL we highlight that measures used should be constructed, where possible, to represent multiple biological systems. In order to achieve this, good quality stable biological markers of the different physiological systems are needed, as well as data on the psychosocial and socioeconomic environment. All these questions are therefore conditioned by the availability of such markers in human cohorts. The development and maintenance of these cohorts is

essential, including information on socioeconomic and psychosocial environments over the life course, with multiple biological measures, made at various stages across the life span.

Acknowledgements

All authors contributed to the conceptualisation and design of this paper via dedicated meetings and workshops. Cyrille Delpierre and Michelle Kelly-Irving drafted the manuscript. All authors contributed to the writing of subsequent drafts.

This project received funding from INCa-Cancéropôle GSO N°2012-E18 and is part of the IBISS project supported by funds from The French National Research Agency (ANR-12-DSSA-0004). Funding was used for meetings and workshops but there was no role of the study sponsors in the study design or in the collection, analysis and interpretation of the data or in the writing of the report and in the decision to submit the paper for publication.

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Introduction

The paper by Delpierre and colleagues on 'Allostatic load as a measure of social embodiment' offers an interesting and timely discussion of allostatic load as a mediating mechanism of embodiment, a way to scientifically conceptualise the interrelatedness of life-time experiences and human health. From an epidemiological perspective the authors see a need to operationalise allostatic load in a consensual manner for future application across different populations.

The general practice research group to which we belong has for years taken an interest in allostatic load. The presented connection between allostatic load and the phenomenon embodiment (Krieger, 2005) is highly concordant with our thinking (Getz, Kirkengen, & Ulvestad, 2011; Kirkengen, 2001, 2010; Kirkengen et al., 2015; Kirkengen & Thornquist, 2012; Mjolstad, Kirkengen, Getz, & Hetlevik, 2013; Thornquist & Kirkengen, 2015; Tomasdottir et al., 2014; Tomasdottir et al., 2015; Vogt, Ulvestad, Eriksen, & Getz, 2014). The interrelatedness of human biology and biography has long been evident to experienced doctors in general practice (GPs) who encounter individuals over time across varying circumstances and stages of life (Kirkengen, 2005). Until recently it has been very hard to think and communicate professionally about the topic. We have simply been short of an adequate, non-dualistic terminology. The concepts *embodiment* and *allostatic load* are now gaining momentum as conceptual tools to help establish and consolidate new and relevant medical knowledge. Much work will however be needed before these concepts are likely to influence significantly the mainstream of medical thought and practice.

We support the authors who see a need to further develop 'allostatic load' as an empirical construct. In the initial, tentative phases of allostatic load research (including our own) somewhat differing variables and algorithms have indeed been applied, to a large extent reflecting practical availability of data in each case. Theoretical consensus and empirical rigor are now needed to consolidate and advance this important field.

But we see a lot more to the concept allostatic load than a quantifiable score. We see it as a potential keystone in coherent, integrative (in the sense of non-dualistic) thinking in future medicine (Tomasdottir et al., 2015; McEwen & Getz, 2013). From this perspective, we argue that the concept allostatic load needs more than algorithmic refinement. We must also tend to it as a philosophical concept, and to its associated metaphors.

Before elaborating further on these thoughts we comment on two concrete arguments found in the index paper. Firstly, we will consider the vision of a finite allostatic load score (AL score) in view of ongoing mega-projects in systems biology, captured by the keywords '–omics' and 'big data'. Secondly, we will comment on the existing level of knowledge pertaining to the social gradient in health, and the current implications of this knowledge.

Building an allostatic load score in the age of systems biology

The paper for debate asks which aspects of human physiology ought to be included in the AL score, and whether different algorithms might be useful, depending on the outcome(s) in question. Looking at these questions from a different angle, it seems likely that the search for finite AL algorithm(s) will soon be located in a whirlpool of biological data downstream of techno-scientific megaprojects such as 'the virtual physiological human' (http://www.vph-institute.org/) and 'the 100K wellness project' (www.systemsbiology.org/research/100k-wellness-project/). These prestigious projects aim to mathematically model the human body as a complex system, and are as such in full concordance with the approach of allostasis research. The systems biology projects, however, are not geared towards demarcated, finite algorithms. Their approach is based on high-throughput analysis of 'big data' involving billions of datapoints for each individual attempting to monitor even the faintest

reflections from the individual's norms (Chen et al., 2012; Hood, Lovejoy, & Price, 2015; Hood & Tian, 2012).

The term allostatic load has recently started to appear in association with '-omics' projects (Ghini, Saccenti, Tenori, Assfalg, & Luchinat, 2015) and the idea of applying *systems biology to medicine* has definitely been launched (Boissel, Auffray, Noble, Hood, & Boissel, 2015; Bousquet et al., 2011). In light of this development we wonder how long allostasis research will be based on parameters of the type currently involved in AL scores, e.g. as outlined by McEwen (2015). The new systems biology projects aim to elicit data on all conceivable '–omics levels' of the human organism, from genomics via transcriptomics and metabolomics 'upwards' in the direction of clinical and even behavioural data. From a relative distance we assume that future evaluations of allostatic load will involve '–omics' data/patterns. The optimal way of characterising 'wear and tear' in an organism might in fact evolve as new candidate markers/patterns surface from the hi-throughput analyses. The AL score thereby becomes 'a moving target'.

As we see it the 'billion datapoints' scenario of systems biology represents both an opportunity and a threat to the idea of allostasis as a keystone concept in medical thought and practice. In this state of ambivalence we think that what matters most is to safeguard the philosophical (conceptual) meaning of allostatic load in a way that makes it relatively inert in the face of techno-scientific and political trends and commercial pressure (Diamandis, 2015; James, 2014; Karlsen & Strand, 2009).

Current knowledge – an imperative for action

Our second immediate response to the index paper relates to the existing level of knowledge about the social gradient in health. From the perspective of scientific incompleteness we agree that there is a lot we still do not know and would like to find out. However, we argue that the overall picture is already quite clear, and this fact must not be understated (Forssen, Meland, Hetlevik, & Strand, 2011; Heath, 2010; Marmot, 2010). We have access to hundreds of high quality publications from epidemiology, clinical cohorts, the basic sciences, and neuroimaging, as well as the social sciences and other sources. The term 'the biology of disadvantage' has been used to sum up our existing insight in how social adversity undermines human health (McEwen & Getz, 2013). In the post-genomic era (Hayden, 2010) it has become easier to promote and stimulate knowledge about the impact of social and relational adversity on health across various disciplines. To illustrate the emergence of new and fruitful collaborations we note three publications that emerged independently of each other in 1998. The first introduced the physiological concept allostatic load to a broad medical audience (McEwen, 1998). The second presented the Adverse Childhood Experiences Study, based on clinical-epidemiological data collected by Kaiser Permanente in Southern California (Felitti et al., 1998). The third was a qualitative medical study rooted in phenomenology, later published as *Inscribed bodies - the health impact of childhood sexual abuse* (Kirkengen, 2001). Since then an immense amount of concordant evidence on the detrimental impact of early life adversity has become available (Getz et al., 2011; Kirkengen, 2010). In our research unit – the General Practice Research Unit at the Department of Public Health and General Practice, Norwegian University of Science and Technology – we apply insight from these different perspectives to deal with the conundrum of multimorbidity (Tomasdottir et al., 2014, 2015). So while agreeing that more research would strengthen existing knowledge, we acknowledge that it is possible to pave a good way for public health and primary care with the knowledge we already possess.

Allostatic load and human stories

We observe how the discourse related to allostatic load has started to dismantle walls between traditional "knowledge silos" and unify the perspectives of researchers/clinicians from various areas, including neuroscientists, endocrinologists, immunologists, psychologists, epidemiologists, public health and primary care researchers/practitioners. We believe such "breakthroughs" are facilitated by the fact that allostatic load can be addressed both in everyday metaphorical language ("wear and tear") and as a scientific-empirical construct (Heath, 2013). This seems to draw the individual experts' attention in the same direction, away from fragmented sub-systems in direction of the whole and undividable, living, striving organism . In the context of medicine,

and especially primary health care, the organism in question can best described as *a person*, with reference to physician-philosopher Eric Cassell (E. J. Cassell, 2010).

Already in 1992 Cassell (1992) pointed out that (personal) human agency must necessarily involve the whole human being, all the way down to the mitochondria . Today the basic sciences have reached a point where we can view both Cassell's argument and the mitochondria in terms of allostatic load (Picard, Juster, & McEwen, 2014). This convergence of philosophical and physiological perspectives opens new perspectives on narrative in medicine and the medical relevance of attending to human stories in the clinical encounter (Behforouz, Drain, & Rhatigan, 2014; McEwen & Getz, 2013; Scannell, 2012). It is hardly a coincidence that Nancy Krieger's (2005) erudite discussion of embodiment, the departing point of the index paper, revolves around the term "story", as does anthropologist and systems thinker Gregory Bateson's seminal work *Mind and Nature – a necessary unity* (Bateson, 1979): «But I come with stories – not just a supply of stories to deliver to the analyst but stories built into my very being».

Reflecting on human stories in the light of allostatic load we should keep in mind that such narratives evolve around the past, the present and, not the least, an imagined future. We now possess considerable knowledge about the biological processes by which past and present experiences become embodied. Schulkin (2011) reminds us that yet another essential determinant of a person's allostatic load lies in the person's own view of the future, the anticipation of that which has yet to come.

The metaphors of allostasis: from 'wear and tear' to 'gains and drains'?

Based on the metaphor "wear and tear," the concept *allostatic load* can effectively accommodate knowledge pertaining to the pathogenetic impact of socioeconomic disadvantage and adverse lifetime experiences (Tomasdottir et al., 2014). However, between the lines of the allostasis literature we also encounter considerations pertaining to salutogenetic factors which promote and uphold health. An explicit focus on resilience can be found in recent key publications about allostasis (Ghini et al., 2015; Karatsoreos & McEwen, 2013; McEwen, Gray, & Nasca, 2015). Consequently, we suggest that a metaphorical expression of the fundamental idea of *allostasis* should involve both detrimental ("draining") and health promoting ("gaining") phenomena (Kirkengen, 2010; Tomasdottir et al., 2014). Depiction of an existential balance between drains (adversity) and gains (buffering support) is in fact needed to grasp the very essence of the terms "positive," "tolerable" and "toxic stress" which have become tightly connected to the concept of allostatic load (Shonkoff, Boyce & McEwen, 2009. See also http://developingchild.harvard.edu/). In order to further refine the metaphors of allostasis it is also important to keep underlining the fundamental difference between an *exposure* (objectively categorized) and an *experience* (subjectively lived) (Kirkengen & Thornquist, 2012; Seery, 2011; Tomasdottir et al., 2015; Ulvestad, 2012; Vie, Hufthammer, Holmen, Meland, & Breidablik, 2014; Waller, 2015).

Closing remark

Clinical evaluation of allostatic load might obviously involve a quantifiable score. Although not explicitly defined as such, most risk factors currently monitored in primary health care represent allostatic variables (McEwen, 2015), including blood pressure, lipid profile, glucose metabolism and body composition. As we have discussed, it will be interesting to see what happens to the AL score in the era of systems medicine based on big data. But whatever algorithms are used, it takes more than de-contextualised measurements to appreciate the balance between gaining and draining factors in a clinically meaningful and ethically responsible way (Evans, 2003; Juster et al., 2015; Repetti, Robles, & Reynolds, 2011; Upchurch et al., 2015). From the clinical viewpoint we might speak of a capacity for integrative perception that might at some point become conceptually linked to professional empathy (Ferrari, 2014). The word *gestalt* comes to mind in relation to the perception of another person's allostatic balance, in the sense of being-in-the-world as an embodied *person* (Cassell, 2010). We are indeed speaking of "a structure, configuration, or pattern of physical, biological, or psychological phenomena so integrated as to constitute a functional unit with properties not derivable by summation of its parts" (definition of *gestalt* in Merriam-Webster dictionary, acc. June 30, 2015).

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Commentary by

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Introduction

In this edition of the journal Delpierre et al. open a discussion on the use of the allostatic load concept as means to measure the term 'embodiment' (also referred to as 'biological embedding'), essentially how our cultural, social and economic circumstances 'get under the skin' to eventually damage our physiological systems and play a role in disease development (Adler & Ostrove, 1999). As described by Delpierre and colleagues the allostatic load concept has a long history starting in the late 1980s (Sterling & Eyer, 1988), but it truly came into being as a concept and research tool a decade later with the merging of the theory and a practical score (McEwen, 1998; Seeman, McEwen, Rowe, & Singer, 2001; Seeman, Singer, Rowe, Horwitz, & McEwen, 1997). Delpierre and colleagues summarise the concept and operationalisation of allostatic load, including its strengths, weaknesses and some future considerations, eloquently enough to avoid unnecessary repetition here. However, there are three points linked to those issues raised that I would like to discuss further.

Gaining credibility

The use of concepts such as allostatic load to try and better understand how the environments we live in can affect our physiology and health falls under a holistic approach, in contrast to the more reductionist approach often sought in epidemiology. While the reductionist approach has great value, especially in trying to elucidate causal mechanisms underpinned by theory and biological plausibility, this approach can feel somewhat incongruous given the complex milieu in which we live our day-to-day lives. In addition, given the strong evidence for almost all chronic diseases being socially patterned and following a social gradient (those with lower socioeconomic position having poorer health), the concept of common biological pathways, as offered with allostatic load, in helping explain this patterning is enticing (Adams & White, 2004; Robertson, Benzeval, Whitley, & Popham, 2015). However, in the pursuit of a better understanding of the 'black box' that links our socioeconomic circumstances and our health, this embodiment/embedding/common biological pathways approach, as measured by allostatic load, introduces a type of black box itself. Are we simply combining individual biomarkers that are easy to measure and available together with no strong theory for linking them? How do we intervene at social and healthcare levels to reduce damage across multiple physiological pathways? Is measuring a patient's allostatic load any more helpful than the seemingly ill-fated NHS Health Checks (Capewell, McCartney, & Holland, 2015), or simply more of the same?

What is clear, and of greatest value in getting wider support for the concept, is the evidence that supports allostatic load as a better predictor of morbidity and mortality as compared with the individual biomarkers that comprise the score (Borrell & Crawford, 2011; Duru, Harawa, Kermah & Norris, 2012; Gruenewald, Seeman, Ryff, Karlamangla & Singer, 2006; Hwang et al., 2014; Karlamangla, Singer & Seeman, 2006; Seeman et al., 2004). Recent analyses found that allostatic load shows similar socioeconomic patterning to chronic disease outcomes, including across the life course, with childhood and adolescence/early adulthood representing particularly sensitive periods for poorer socioeconomic circumstances impacting on allostatic load (Gruenewald et al., 2012; Gustafsson, Janlert, Theorell, Westerlund & Hammarstrom, 2012; Gustafsson et al., 2014; Robertson, Popham & Benzeval, 2014). Furthermore, the association between socioeconomic position and allostatic load appears to be largely mediated by material factors (e.g. income, ownership of goods), but not behavioural and psychological factors (Robertson et al., 2015). This indicates that policies and programmes targeted at more downstream factors (such as health behaviours) may have minimal returns in reducing health and physiological inequalities, as shown for morbidity and mortality (Acheson, 1998; Adler & Stewart, 2010; Macintyre, 2007; Marmot, 2010; Marmot, Friel, Bell, Houweling & Taylor, 2008; Scott et al., 2013). As Delpierre and colleagues discuss, it is through this type of evidence, supported by more multi-disciplinary, longitudinal and life course research that also

incorporates causal inference, that the allostatic load concept will not only gain support, but will also be challenged further and naturally improved also.

Biological ageing: A competing or complementary concept?

Many of the ideas and theoretical pathways linking allostatic load and embodiment discussed by Delpierre and colleagues and earlier in this commentary can also be represented by another common biological pathway – biological ageing. This is "the incremental, universal, and intrinsic degeneration of physical and cognitive functioning and the ability of the body to meet the physiological demands that occur with increasing chronologic age" (Robertson et al., 2013). However, the rate at which this ageing occurs will differ given the (socioeconomic) circumstances in which we live. Increased exposures to physical and psychological insults, along with more unhealthy behaviours, have the potential to increase cellular and genomic damage, thereby accelerating biological ageing (Adams & White, 2004). People in more disadvantaged circumstances, where these insults are more prevalent (Adler & Stewart, 2010), would therefore be expected to be 'biologically' older than their more affluent counterparts of the same chronological age (Robertson et al., 2012). Like the allostatic load concept, identifying biomarkers of ageing that can completely encompass the theory has proved difficult and there remain several questions over how biomarkers could and should be combined (Der et al., 2012). The most promising marker of biological ageing to date has been white blood cell telomere length. Telomeres are protective structures present at the ends of chromosomes that typically erode over time to protect against irreversible chromosomal damage, so that their length is a potential predictor of biological ageing (de Lange, 2002). Therefore, this represents accumulated damage over time that goes across large parts, if not the whole, of the body and is strongly influenced by social and economic circumstances and particularly the stress response. Sound familiar?

It has been proposed that markers such as telomere length are simply alternatives to the allostatic load model currently used (multiple physiological markers linked to health conditions in middle and later-ages), especially at younger ages (Theall, Brett, Shirtcliff, Dunn & Drury, 2013). Biomarkers of ageing have been defined as biological measures that "either alone or in some multivariate composite will, in the absence of disease, better predict functional capacity at some late age than will chronological age" (Baker & Sprott, 1988). Allostatic load could claim to be such a marker, although it has not yet been tested in such a fashion as telomere length (Der et al., 2012). Alternatively, would adding measures such as telomere length to the allostatic load construct add some predictive power over the current operationalisation? Again, this is a feature which has not been explored. Finally, is biological ageing/telomere length more of an outcome of allostatic load and somewhat further down the causal chain? In my opinion, this is difficult to answer given current data (see below), but both allostatic load and biological ageing incorporate what can be considered primary (e.g. cortisol vs. oxidative stress) and secondary (e.g. blood pressure vs. telomere length) physiological markers. In addition, our biological systems are active and dynamic, potentially being responsive to changes in our environments and repairing themselves to some degree (Epel, 2012). Hence, there is not really an end-point where one could say someone has reached, for example, allostatic *overload* and that could be considered a true outcome. So, where do we go from here?

Bio-social collaborations

The emergence of this field linking the biological and the social has grown over the last twenty years, but especially over the last decade, with the increasing inclusion of biomarkers in many large, population-based health and social surveys. This growth in collecting simultaneous biological and social data, longitudinally and across the life course, is key if we are to continue to advance our knowledge of the biological impacts of our environments and society. So far, much of the evidence is based on cross-sectional data or comes from biomarkers measured once, but with longitudinal social data for the same individuals. These emerging longitudinal measures will help us to better understand how our physiologies change over time and at different stages in life, exploring the importance of relative change within individuals (i.e. is it a high allostatic load that matters or the change in allostatic load score over time?). We must also begin to embrace theories and methods from

other fields, such as 'system dynamics' (Ford, 1998) and 'complexity theory' (Byrne, 1998). The increase in data linkage to routinely collected data records (e.g. health surveys and hospital admissions) is allowing us to research the long-term health consequences of socioeconomic circumstances, even after studies and surveys have ceased. It may also be possible in the future to link into biomarker data that are collected as is now done with hospital admissions and death records. There are obviously challenges and negatives linked to these ideas, but they offer possibilities to broaden our knowledge of the social determinants of health and to help design better policies and programmes for reducing inequalities and improving health.

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Introduction

The authors give a thoughtful and incisive outlook on the theory and study of allostatic load (AL). In addition to a number of specific and concrete contributions I particularly welcome the general attention the authors pay to conceptual clarity, both with regard to the conceptual framing of the AL, and to its operationalisation. I believe that the conceptual ideas suggested by the authors have merit, and also that there are several details that invite further thought and discussion. Therefore, in this commentary I aim to highlight certain conceptual issues relevant for two links the authors explore; first, the one between the concept of AL and its operationalisation; and second, the link between the concepts of AL on one hand and embodiment on the other. I hope that my reflections will be helpful in furthering the endeavors the authors have initiated.

In the article, the authors mention the need to remain *loyal,* more precisely loyal to the theory of AL in the process of operationalising the concept. I think that describing it as a matter of (conceptual) loyalty is a very apt expression for situations where you aim to keep in concordance to an underlying theory (or belief system or ideology). I also think it may be a heuristic term to illustrate some of the complexities that may arise when dealing with concepts. My commentary can be viewed as an exploration of some conceptual loyalties, disloyalties and conflicts of loyalties in play in the operationalisation and conceptual framing of AL discussed by the authors.

Loyalty in operationalisation

I will start by commenting on loyalty in the sense the authors use it; that is, as staying true to the concept in the process of operationalisation. The authors make several constructive points here that if followed, would promote conceptual loyalty. For example, the observations that the definition of thresholds deviates from the concept of AL, the interesting possibility of constructing different AL scores for different manifest diseases, and the consequences of the heterogeneous stability of AL components. I also appreciate that they revitalise the idea of the causal ordering of the mediators and effects, which I regard as an important part of AL theory, but which unfortunately has received comparatively little empirical attention.

I would also like to comment on a specific issue where I do not seem to agree with the authors; or more specifically, where I do not see how their reasoning promotes loyalty to the concept of AL. The issue concerns the authors' discussion on selection of the multiple biological systems. Here, the authors seem to frame loyalty to the theory of AL only with respect to the degree AL operationalisations (or the set biological systems) predict manifest disease. Yet AL was developed as a concept and a measure designed to connect the social and the biological worlds or realities, with AL acting as a link between stressful experiences and the pathogenesis of manifest disease (McEwen, 1998). The theory of AL thus makes assumptions on both the predictor and outcome side of AL, and AL could be said to have the putative causal status of a mediator or intervening variable between environmental exposures on one hand, and manifest disease outcomes on the other. While the 'disease criterion' (AL as a predictor of manifest disease) is commonly considered in discussions and empirical examinations of AL operationalisations, the 'environmental criterion' (AL as an outcome of environmental exposures) has been given less consideration in operationalisations of AL, but instead is left as an empirical question to be examined subsequent to and independently from the operationalisation of AL. This emphasis is also reflected in the present article.

My question is then; should not a conceptually loyal AL measure need to reflect accurately the biological impact of the (social, physical) environment to the same degree as it accurately predicts manifest disease? If no, why not; what in the theory of AL suggests that the environmental criterion is secondary to the disease criterion?

To me, this emphasis of the disease criterion in the operationalisation of AL reflects a disloyalty to parts of AL theory. I also believe that this disloyalty may have unfortunate consequences for our understanding of the role of AL. An approach considering only, or mostly, the disease criterion in

the operationalisation of AL can be expected to result in AL measures which indeed are good predictors of manifest disease, but which do not necessarily play an important role in explaining social causes of disease. This kind of approach will therefore yield poor AL measures for the purpose the authors state; AL playing an integral role in explaining social gradients in health. Ultimately, we risk ending up with the empirical results and conclusions suggesting that AL does not play a role in explaining social health differentials. However, such inferences would be laden with the repercussions of bias we introduced in our operational approach – our initial disloyalty to the theory of AL.

To the degree that such empirical considerations should influence the operationalisation of AL, I wonder if a more loyal approach should give equal consideration to both criteria; to both sides of the causal chain in which AL is supposedly a link. This would mean choosing the physiological markers most accurately reflecting environmental conditions, in addition to those that most accurately predict disease. As a statistical representation (or simply a heuristic illustration) of this dual consideration, estimates such as the 'indirect effect' used in classic regression-based mediation analysis (Baron & Kenny, 1986) could be used, as it takes the mediator's associations to both the exposure and outcome equally into account. Selecting biological systems and also individual markers guided by such a (data-driven or theory-based) approach would result in conceptually loyal AL measures, which also are given a fair chance to empirically explain social inequalities in health.

Loyalty in conceptualisation

Conceptual loyalty becomes even more intricate under situations of dual loyalty, which is the case when we seek to integrate different concepts or frameworks. Conceptual integration can of course be straightforward. Maybe the entities to be integrated have been developed in the same scientific-historical context, maybe they share a phenomenon under study, and maybe they have similar conceptual goals and terminology. But conceptual integration of two or more concepts may also be trickier than first anticipated. We might be caught in conflicts of loyalty.

In their article, the authors propose integration of two concepts. First, the concept of *allostatic load*, which was born in the scientific context of physiology and stress research, based on the writing of Sterling and Eyer (1988) on allostasis and developed by McEwen and Stellar (McEwen, 1998; McEwen & Stellar, 1993). Second, the concept of *embodiment,* which has a more diverse history and which has been used (often implicitly) with widely different meanings in the health sciences literature (Hammarstrom, et al., 2014), e.g. by the sociologist Raewyn Connell (Connell, 2011), or within the phenomenological tradition (Bullington, 2009). In the present paper the authors use the embodiment concept of Nancy Krieger, who developed her own formulation of embodiment within a distinctly social epidemiological context during the 1990s and 2000s, as one central concept within the larger theoretical framework of *ecosocial theory* (Krieger, 1994, 2005, 2011).

At a glance, the purposes of the AL and embodiment concepts may seem readily commensurable. Both concepts are dealing with the same general phenomenon of environment and biology, and could be viewed as existing, at least partly, within the family of theories relevant to social determinants of health. Both focus on different areas of this phenomenon, but also encompass the area of the other, and both mention life course perspectives as one central tenet (but without delving into the details) (Krieger, 1994; McEwen, 1998). But what would the point be in doing such an integration? What do the two perspectives have to offer each other?

For AL theory, I would say that framing allostatic load under embodiment does have the potential to put the theory of AL into a well-developed theory of societal structure and population patterns of health and disease, in this case ecosocial theory. This I see as a substantial and much-needed conceptual gain for the theory of AL. Sure, references to society and social inequalities have always been present within AL theory, but they have generally taken the form of vague hints to frameworks without a detailed conceptual integration (Juster, McEwen, & Lupien, 2010; McEwen, 1998), or empirical examinations (Dowd, Simanek & Aiello, 2009; Seeman, Epel, Gruenewald, Karlamangla & McEwen, 2010; Szanton, Gill & Allen, 2005). Moreover, in the same way that societal structure has not been the main focus of the theory of AL, formulating specific intermediate links or health outcomes has not been a high priority within ecosocial theory. From

ecosocial theory's point of view, allostatic load could therefore contribute with a specific, concrete and operationalisable summary construct capturing a range of structural exposures that are relevant for the process of embodiment.

So, in such an integration, what do we need to pay attention to? Here, I think that we do need to clarify where our conceptual loyalties are, and also where they should be. With regard to the latter, from my point of view, conceptual loyalty should be mutual and equal towards each of the concepts or frameworks that are to be integrated. With regard to the former, in reading the article, I notice a strong conceptual loyalty towards the concept of AL, but a more tenuous one towards embodiment. This I interpret as a conflict of loyalty.

To exemplify my point, the authors title their paper, 'Allostatic load as a measure of social embodiment'. This view, where embodiment seems to be construed as something that can be captured by AL, is also expressed in parts of the paper ('AL may be a relevant and useful tool for measuring and comparing embodiment'). In other places in the article, however, the relationship between the two concepts is described as something which appears to be substantively different from in the first view; AL is described as the *biological expression* or *effect* of embodiment ('the 'physiological reality', the 'biological expression of embodiment', 'measuring the biological effect of embodiment'). My interpretation here is that AL is construed as something other than, causally subsequent to, or part of, embodiment. Thus, it seems to me that the article comprise two different conceptualisations of embodiment in relation to AL; one where the latter is an example of the former, and one where the latter is a result of the former. Here, I reminisce about the oft-cited quote referencing Hans Selye's stress theory: "Stress in addition to being itself, was also the cause of itself, and the result of itself." (Rosch, 1998).

So, which of the conceptualisations is more loyal to the concept of embodiment? With regard to the first conceptualisation I wonder whether embodiment really can be reduced to a physiological measurement. In what way are we, by summarising a number of cardiovascular risk factors and neuroendocrine markers, capturing 'how we literally incorporate, biologically, in societal and ecological context, the material and social world in which we live'? In relation to this question it is worth noting that Krieger emphasises that embodiment is not equivalent to, but encompasses more than, 'how society gets under the skin' or 'biological embedding' (Krieger, 2011, p. 222). Specifically, I interpret embodiment as not primarily reflecting how the proximal environment becomes embodied (as is the case in stress frameworks such as AL), but more how societal structure and dynamics become embodied and thereby create population patterns of disease. Here, embodiment is an alternating macro-micro-macro process, and as such by necessity a multilevel phenomenon. This does not seem to correspond well to the first conceptualisation of embodiment in the article, where embodiment is reduced to a much more limited construct, which seems to be guided more by loyalties to the theory of AL than to loyalties to the theory of embodiment. This expresses the loyalty conflict, and I would say that in this restricted sense the concept of embodiment adds little to the theory of allostatic load which was not already contained in the theory of AL. Consequently, I would advise against this conceptualisation of embodiment.

In the second conceptualisation of embodiment in the article, AL is instead construed as an effect of embodiment. Here, there are no restraints put on the concept of embodiment and what it represents; it just positions AL as one (possibly of many) biological effects of the (possibly complex and multilevel) phenomenon that is embodiment. Therefore, I regard this view of embodiment as more loyal to the concept of embodiment, and a more fruitful starting point for a conceptual integration of the two concepts.

Still, as noted above, embodiment is one concept within the larger theoretical framework of ecosocial theory, where ecosocial theory cannot be reduced to embodiment, and embodiment does not capture the entirety of ecosocial theory. To stay loyal towards the concept of embodiment I therefore think it should not be picked out as a single concept, disentangled from its theoretical context. Instead, I would rather approach the integration by framing AL within the complete ecosocial theory. This would for example mean construing AL as a phenomenon which is part of the societal arrangements of power and property; of current and changing societal patterns of disease; and for which we as researchers who study social inequalities in health, as well as those in power, are

explicitly held to account (Krieger, 2011). By using the entirety of ecosocial theory we could stay loyal to both the theories of embodiment and AL. I also believe this has a greater potential to lift the theory of AL from its individual and micro-focus, to include the grander macro-level narrative of society and its flourishing inequities. Such a perspective is offered by ecosocial theory and I believe is necessary for the theory of AL to be able to play an important role, not only in empirically explaining social gradients in health, but also in the theoretical context of equity in health.

While I hold that no theory or framework is holy or deserves our loyalty simply by its existence, I do believe that the ideas (e.g. theories, frameworks or concepts) on which we base our research are particularly important for us to articulate and scrutinise, or else our research, and the understanding we believe that we gain from it, runs the risk of simply reflecting our initial errors in thought. In this commentary I have sought to keep in line with the attention to conceptual detail of the original article, by highlighting a few problems of conceptual loyalty I perceived, as well as giving my thoughts on how to possibly solve or avoid them. Together, I hope these small reflections can contribute to further thought and discussion on the theory of AL, and I am sincerely looking forward to the authors' response.

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Response by

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We thank the authors who commented on our paper and discuss some of the most salient points they raised.

Firstly, regarding the many methodological considerations we mentioned, Getz and Tomasdottir in their comment point towards the burgeoning fields of biological systems research for potential answers. We agree that this area is promising in terms of understanding further the complexities of our biological systems and finding the most suitable way of measuring them. Indeed, the combined forces of methodological developments in the areas of bioinformatics, 'omics' research and biological systems will probably render redundant a simplified cumulative score, such as the ones typically used to measure allostatic load (AL). A more optimal method of measuring multi-system wear and tear due to stress may well emerge from these fields allowing the identification of biomarkers with a predictive or diagnostic value. A possible caveat of the increasingly accessible technologies around biological data and methodological developments within bioinformatics, is the risk of becoming overly focused on molecular-level details. Though a measure of cumulative wear-and-tear may benefit from such developments, we must not be tempted to stray too far into the attractive rabbit hole of detailed biological data and away from the original intent of the AL concept. The purpose of the measurement developed by McEwen et al (McEwen & Stellar, 1993; Seeman et al., 1997) was to capture, in one summary score, the physiological consequences of adaptations to the environment via the stress response pathways. Our aim should be to describe and capture these adequately enough to demonstrate the modifiable factors within the environment – in its broadest sense – that may be used to alter processes affecting socially structured groups of the population and leading to health inequalities. There is a risk of forgetting these important facets when faced with new and attractive methodologies.

Secondly, as mentioned by Robertson, it is relevant to question whether by attempting to understand mechanisms producing health inequalities and opening a black box, have we not formulated a new one with the concept of AL. We would argue that unlike many 'black boxes' AL has a well formulated conceptual foundation linking the environment to physiological processes via the stress response systems. Telomere length may be an interesting component of these processes, possibly to be included within an AL measure with its multi-system specificity. The links between AL and biological ageing are indeed clear. We would maintain that physiological wear-and-tear captures one set of processes potentially implicated in a wider notion of biological ageing wherein the link with stress is fundamental. Both the concepts of AL and biological ageing may deserve to be explored together, where AL is one among other potential mechanisms of biological ageing. Both concepts also deserve to be disentangled relative to the wider notions of embodiment and the framework of ecosocial theory, as pointed out by Gustafsson.

Indeed Gustafsson highlights that we were ambiguous regarding the position of the concept of AL relative to that of embodiment within the theoretical framework of 'ecosocial theory' (Krieger, 2001). We define embodiment as a dynamic concept, consisting of: i) responses to past environments and ii) an ongoing response to the present environment. The elements and mechanisms leading to the responses may vary in their nature, intensity and cadence over the life course. We suggest that AL captures one process of embodiment linking the environment, stress responses, and possible chronic damage to physiological systems, and as such this fits wholly

into the framework of ecosocial theory. Of course many other mechanisms of embodiment deserve further exploration in terms of environmental conditions across the life course, such as behavioural and psychological factors, socioemotional changes or cognitive function.

We agree with Gustasfsson that our desire to maintain an AL measure that is 'loyal' to a balance of physiological systems should be applied equally to the environmental factors that the measure attempts to capture. Now that a number of openly accessible longitudinal datasets collecting a large array of environmental and biological variables are available, it has become possible to specify plausible hypotheses to test and unpick many of the concepts raised here (Kelly-Irving, Tophoven & Blane, 2015). With this in mind, the ecosocial determinants of AL deserve to be deliberately defined and explored across contexts. Specific hypotheses that may link ecosocial factors at different environmental strata to AL need to be defined and tested using comparable data within different populations and at different stages of the life course.

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Referencing

The debate should be referenced as:

Delpierre, C., Barbosa-Solis, C., Torrisani, J., Darnaudery, M., Bartley, M., Blane, D., Kelly-Irving, M., Getz, L. & Tomasdottir, M.O., Roberston, T. & Gustafsson, P. (2016). Origins of heath inequalities: the case for Allostatic Load. *Longitudinal and Life Course Studies, 7, 79 – 103.* http://dx.doi.org/10.14301/llcs.v7i1.325