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Sammendrag på norsk

Fysisk aktivitet, mental helse og dødelighet hos personer med synsnedsettelse: Resultater fra HUNT-studien

Å fremme fysisk aktivitet i befolkningen er ansett som en av de beste strategiene for folkehelsen grunnet dens gunstige effekter på mental helse, samt i forebygging av ikke-smittsomme sykdommer og tidlig død. Allikevel, fordelene av regelmessig fysisk aktivitet kan variere mellom ulike grupper i befolkningen. Personer som lever med synstap opplever oftere problemer med å delta i fysisk aktivitet sammenlignet med personer uten synstap, samt at de har større utfordringer med helse, sosialisering og det å fungere i dagliglivet. Det er per i dag uklart hvilken betydning fysisk aktivitet har på helsen hos personer som lever med synstap.

Hensikten med denne doktorgradsavhandlingen var å undersøke betydningen av fysisk aktivitet på fritiden hos personer med og uten selv-rapportert synstap i dens sammenheng med psykiske plager og dødelighet. I alle de tre studiene som er inkludert i denne avhandlingen er det blitt benyttet data fra ungdom og voksendelen av Helseundersøkelsen i Nord Trøndelag (HUNT-studien). I tillegg ble data fra Dødsårsaksregisteret benyttet i en av studiene.

Resultatene fra de tre studiene viste at ukentlig fysisk aktivitet, helst i moderat til høy intensitet, reduserte risikoen for depresjonssymptomer og tidlig død hos personer med selv-rapportert synstap, og styrken på sammenhengen var tilnærmet lik eller sterkere hos denne gruppen sammenlignet med personer uten selv-rapportert synsnedsettelse. Sammenhengene varierte mellom alder, kjønn og personlighet hos personer med selv-rapportert synsnedsettelse, noe som tyder på at responsen av fysisk aktivitet kan virke ulikt innad i denne populasjonen. Fysisk aktivitet hadde ingen sammenheng med angstsymptomer.

Studiene bidrar til kunnskap om fysisk aktivitet og dens sammenheng med mental helse og dødelighet hos ungdom og voksne som rapporterer å ha nedsatt syn. Funnene tyder på at fysisk aktivitet kan vurderes som et sykdomsforebyggende og helsefremmende tiltak hos denne populasjonen. Allikevel, sammenhengen ser ut til å være kompleks og videre forskning er nødvendig.

Navn: Audun Brunes
Forskningsgruppe for Geriatri, bevegelse og slag
Institutt for nevromedisin og bevegelsesvitenskap,
Fakultet for medisin og helsevitenskap, NTNU
Hovedveileder: Liv Berit Augestad
Biveileder: W. Dana Flanders
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TABLE OF CONTENTS

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LIST OF PAPERS

Paper I Brunes A, Flanders WD, Augestad LB. The effect of physical activity on mental health among adolescents with and without self-reported visual impairment: The Young-HUNT Study, Norway. British Journal of Visual Impairment, 2015;33(3):183–199

Paper II Brunes A, Flanders WD, Augestad LB. Physical activity and symptoms of anxiety and depression in adults with and without visual impairments: The HUNT Study. Submitted to *Mental Health and Physical Activity*

Paper III Brunes A, Flanders WD, Augestad LB. Self-reported visual impairment, physical activity and all-cause mortality: The HUNT Study. Scandinavian Journal of Public Health, 2017;45(1):33–41

ABBREVIATIONS

BMI	body mass index
CI	confidence interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMM	effect-measure modification
EPQ	Eysenck Personality Questionnaire
GLM	generalized linear model
HADS-A	Hospital Anxiety and Depression Scale anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale depression subscale
HBSC	Health Behavior in School Aged Children
HR	hazard ratio
HUNT	The Nord-Trøndelag Health Study
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability, and Health
IPAQ-L	International Physical Activity Questionnaire – Long
LPA	low-intensity physical activity
MAR	missing at random
MICE	multiple imputation chained equations
MHPA	moderate to high-intensity physical activity
PA	physical activity
RCT	randomized controlled trial
RERI	relative excess risk due to interaction

RR	relative risk
SCL-5	Hopkins Symptom Checklist-5
SRNI	self-reported no visual impairment
SRVI	self-reported visual impairment
SWB	subjective well-being
$VO_{2\text{-max}}$	maximal oxygen consumption
WHO	World Health Organization

ABSTRACT IN ENGLISH

Introduction: Visual impairment has been described as a reduction in the functioning of the visual system. Studies have shown that visual impairment is associated with an increased risk of co-morbid conditions, functional limitations, social isolation, unemployment, and premature mortality. It is therefore essential to gain knowledge about factors that may improve the health of individuals with visual impairment. To date, regular physical activity (PA) is considered a 'best buy' in public health. However, few studies have explored whether there is a relationship between PA and the health of individuals with visual impairments.

Aim: The aim of the research for the thesis was to use epidemiological methods to acquire knowledge of the associations between PA and mental health among individuals with self-reported visual impairment (SRVI), and to compare those associations with those of individuals with self-reported no visual impairment (SRNI). A further aim was to investigate the role of PA in the association between visual impairment and all-cause mortality.

Methods: This thesis includes three papers that report three substudies, all of which were based on the main study. All studies had prospective observational designs and included data from the adolescent and adult part of the Nord-Trøndelag Health Study (The HUNT Study). The two first papers assess the association between baseline PA and symptoms of anxiety or depression at follow-up among individuals with SRVI and SRNI (Papers I and II). Paper III links the HUNT data to Norway's Cause of Death Registry (Dødsårsaksregisteret) in order to examine the role of baseline PA in the association between visual impairment and all-cause mortality. The study exposures were based on self-reported information (visual impairment and leisure-time PA). The outcome variables were either self-reported (anxiety and depression symptoms) or based on

register data (all-cause mortality). Statistical associations were examined using descriptive statistics and various regression models (generalized linear regression and Cox regression).

Results: The results of the included studies showed that individuals with SRVI had lower PA, more symptoms of anxiety or depression, and increased mortality risk compared with individuals with SRNI. The findings presented in Papers I and II show that baseline PA was significantly associated with fewer depression symptoms at follow-up among adolescents and adults with SRVI. However, the observed associations were present only among those who were more emotionally unstable or introvert (Paper I) and among women (Paper II). No significant associations were found between PA and anxiety symptoms (Paper II). The results of the third study show that the increased mortality risk associated with SRVI was stronger among individuals who reported no PA than among individuals who reported weekly hours of PA, especially among those aged < 60 years (Paper III). Moreover, adjusting for PA in the regression models resulted in similar or stronger associations between visual impairment and all-cause mortality.

Conclusions: The results from the studies contribute to the knowledge of PA and its association with mental health and mortality among adolescents and adults with SRVI. Our findings support mostly the results reported in earlier publications regarding the benefits of PA in disease prevention and health promotion, including the benefits for individuals with SRVI. However, the associations tend to be complex and more research is needed.

Candidate: Audun Brunes

Department: Department of Neuromedicine and Movement Science

Supervisor: Professor Liv Berit Augestad

Co-supervisor: Professor W. Dana Flanders

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1.0 INTRODUCTION

1.1 Background

Visual impairment has been described as a reduction in the functioning of the visual system (1), and is a quite heterogeneous condition in terms of the type of visual function affected, as well as the severity, cause, onset-age, and progression rate of the vision loss (2). The Norwegian society is known for its high level of social equalities and high standard of living. Despite this, people with visual impairments constitute one of the groups in Norway that experiences considerably lower health and welfare than the general population, including a higher risk of poor self-rated health, co-morbid conditions, functional limitations, unemployment, social isolation, and stigmatization (3, 4). Paragraph 1 of Norway's Public health Act (Lov om folkehelsearbeid (Folkehelseloven)) states that the main goal of the Act is to even out social inequalities in health by lowering mortality through disease prevention and by promoting well-being (5). However, the social disparities in health are multifactorial and complex, and attributable factors may vary across the lifespan.

Regular physical activity (PA) is viewed as one of the most powerful determinants of human development and for maintaining functioning, good health, quality of life, and longevity (6). Further, adapted PA is an integral part of the rehabilitation of people with chronic diseases and impairments (7). The White Paper *Den norske idrettsmodellen* (Meld St. 26 (2011–2012)) states that people should have the opportunity to participate in organized and unorganized PA according to their wishes and needs (8). Despite the increasing amount of attention paid to regular PA, 50% of Norwegian adolescents and 67% of Norwegian adults do not meet the minimum PA levels recommended to maintain functioning and health (9, 10). The proportion fulfilling the PA recommendations may be even lower among those living with visual

impairments (11-13). However, in the scientific community, little attention has been given to whether the health of individuals with visual impairment is related to their lower PA levels (14).

Therefore, the overall aim of this thesis was to use epidemiological methods to examine the association between leisure-time PA and mental health in individuals with and without visual impairments, in samples of adolescents and adults. A further research aim was to investigate the role of leisure-time PA in the association between visual impairment and mortality. All three studies presented in the respective papers had prospective designs, which proved valuable for discovering the directionality of the relationship. The findings presented in this thesis may have implications for the use of leisure-time PA in disease prevention and health promotion for individuals living with visual impairments.

1.2 Epidemiology of visual impairment

Epidemiology is the study of the distribution and magnitude of health-related states and events in populations (15). Its main application is to guide policy and practice in the prevention of health-related states and its consequences for populations. In this section, a description of the assessment of visual functions will be provided, followed by a description of the classification, prevalence, and causes of visual impairment.

1.2.1 Assessment of visual functions

Visual functions concern how the visual system functions. The most favoured assessments of visual functions involve the use of objective psychophysical measurements carried out in a simplified, artificial environment (1). Visual acuity and visual field are the two visual functions being assessed when classifying visual impairment. However, in clinical practice, these assessments are usually supplemented with tests for other types of visual function (e.g. contrast

sensitivity) (2). Visual acuity is the ability to resolve fine details of maximum contrast in foveal vision or in the best available parafoveal area (16), and the acuity can be expressed as a fraction, in which the numerator is the test distance in metres and the denominator indicates the smallest letter seen. Visual acuity is commonly measured using eye charts with optotypes (letters) or grating bars (Figure 1) (2). Visual field is the entire range of field when the eyes are fixated, and includes both central and peripheral vision. Visual field is frequently measured using various types of perimetry tests (Figure 1), and can be described in terms of degrees from the centre of the fixation point (16).

Direct measures of visual functions provide valid and reliable data in a rapid fashion (17), and are considered suitable for judging the efficacy of medical treatments, guiding the choice of rehabilitative strategies, and determining the etiology and prognosis of vision loss (1). However, the use of direct measures of visual functions has a number of limitations, including: (1) the need for equipment and trained personnel; (2) the fact that the results will be influenced by the measurement tools, testing personnel, and the individual's motivation; (3) testing in controlled environments hampers the external validity; and (4) and focusing on specific visual functions leads to underestimates of the total vision loss (2, 17, 18).

Self-reported measures cannot be used in the classification of visual impairment, but is a complementary assessment tool for use in health care settings and for research and survey purposes (4). Self-reports are subjective and are therefore suitable for assessing the individual's overall judgement about their visual functions (18). Furthermore, in addition to being relatively inexpensive and feasible for large-scale studies, it has been claimed that self-reports are more externally valid than direct measurements (19). However, numerous non-standardized visual functioning questionnaires have been used in research (20). A major drawback of self-reports is the significant differences in how questionnaires are constructed and administered, as well as the

low interrater-reliability of the measurements (4). This may have an impact on the proportion of people identified as having visual impairments, which would make cross-study comparison difficult.

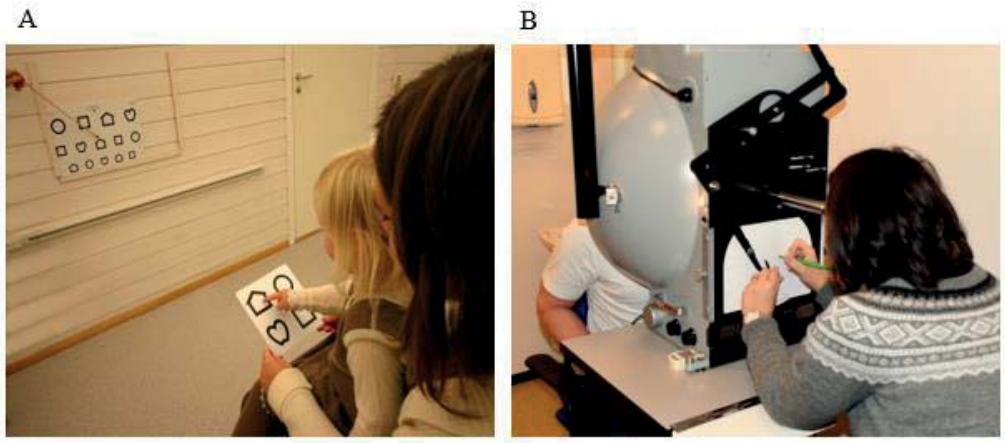


Figure 1. Two common assessment tools of measuring visual functions: A – Eye chart with symbols, for assessing visual acuity; B – Goldmann perimeter, one of many methods used for assessing visual field

1.2.2 Classification of visual impairment

The classification of visual impairment was for the first time included in the International Classification of Diseases (ICD) in 1972, and a modified version was included in the 10th revision of the ICD in 2010 (ICD-10) (21, 22). As shown in Table 1, the ICD-10 definition of visual impairment comprises seven levels of visual impairment: no visual impairment or mild visual impairment (Level 0), moderate visual impairment (Level 1), severe visual impairment (Level 2), blindness (Levels 3–5), and unspecified or undetermined visual impairment (Level 9) (22). Some researchers use the term 'socially significant visual impairment' to classify those with

a visual impairment that may affect their ability to perform certain activities (e.g. loss of their driving licence), but not severe enough to be formally classified as visual impairment (23). As mentioned in Section 1.2.1, classification of visual impairment is based on visual acuity and visual field. When classifying binocular visual impairment, visual acuity should be assessed with presenting corrections and with both eyes open, while better-seeing eye should be included in the evaluation of visual field loss. When classifying monocular visual impairment, visual acuity and/or visual field loss should apply to the affected eye (22).

Table 1. Categorization of visual impairment (VI) based on the ICD-10 classification.

	Levels of VI (ICD-10 classification)	
Levels	**Visual acuity**	**Visual field**
Mild or no VI (Level 0)	Equal to/better than 6/18	
Moderate VI (Level 1)	6/18 or equal to/better than 6/60	
Severe VI (Level 2)	6/60 or equal to/better than 3/60	
Blindness (Level 3)	3/60 or equal to/better than 1/60	≤ 10 degrees
Blindness (Level 4)	1/60 and light perception	
Blindness (Level 5)	No light perception	
Level 9	Undetermined or unspecified	

Notes: ICD-10 = International Classification of Diseases, 10th revision

Visual functions may not always represent the individual's abilities in vision-related tasks (also termed functional vision) (1). Functional vision is more complex than visual functions because it captures the dynamic interaction between the health condition, the person, and the environment in the performance of certain tasks (24). For example, in a hypothetical case in which two people

have a similar degree of visual impairment but one of them can read newspaper print more clearly than the other, the increased ability to read newspaper print might be related to other important personal or environmental factors, such as the wearing of corrective devices, cognitive abilities, or lighting conditions. The International Classification of Functioning, Disability, and Health (ICF) is a supplementary classification tool to the ICD-10 that takes this complex relationship into consideration (24). A more detailed description of the ICF is given in the 'Introduction' section under the heading '1.4.2 Functioning'.

1.2.3 Prevalence of visual impairment

The first global prevalence estimates of visual impairment were published in 1990 and the results showed that of 148 million (2.8%) with visual impairments, 38 million were blind and 110 million had moderate to severe visual impairment (25). By 2010, the corresponding estimates had increased to 285 million (4.3%), of which 39 million were blind and 246 million had moderate to severe visual impairment (26). Although the absolute numbers of persons with visual impairment increased between 1990 and 2010, the percentage had decreased when aging population, population growth, and the inclusion of refractive errors in the estimates were taken into account. The decrease may have been due to better data quality and improvements in the prevention and management of visual impairment (27). The prevalence of visual impairment increases dramatically with age, and the majority of cases are living in low-income countries (26, 28).

Norway has no national registries for visual impairment.[1] However, a cross-sectional study including registry data from Statped (Norway's support service for special needs education) identified that in 2004, 628 individuals (0.53 cases per 1000 individuals) aged < 20 years who received Statped's services had ICD-defined visual impairment (29). Augestad et al. observed in

[1] The former national registry for visual impairment was closed in 1996.

their retrospective population-based study that 287 Norwegian school-aged children received Braille education in the period 1967–2007 (30), but this number is likely to be an underestimation, since only a small proportion of the children with visual impairments received Braille education. In adult populations, three consecutive national surveys (2008, 2012, and 2015) that included representative samples of Norwegians aged ≥ 16 years respectively showed that 4%, 6%, and 8% of the participants reported difficulties in seeing newspaper text, even when wearing eyeglasses (31). In the Tromsø Eye Study, Bertelsen et al. observed that 1.2% of the 6459 participants had visual impairments (binocular corrected visual acuity: < 20/60) (32). According to data provided by the Norwegian Labour and Welfare Organization, in the period between 1995 and 2015, a total of 1259 adults in the age group 18–69 years, who lived in Nord-Trøndelag County, received assistive vision aids.[2] Since 81,381 individuals in that age group lived in Nord-Trøndelag in 2005 (33), that makes a very approximate ratio of 1.6%.

1.2.4 Causes of visual impairment

The causes of visual impairment depends on age, gender, and geographical location, as well as varies across severities of visual impairment (26, 28, 34). Whether visual impairment is treatable and/or preventable depends on its underlying cause. Globally, 80% of all visual impairments may be prevented and/or treated (26), whereas less than 50% of cases of childhood visual impairments can be prevented and/or treated (35). However, these percentages are complicated by the fact that an eye might have been affected by more than one cause and each eye might have been assigned to different causes (28). In addition, the causes of visual impairment may be both related to the function of the eyes and to the brains ability of processing visual information (2).

[2] Vision aids were handed out to those with a vision diagnosis and/or ICD-defined visual impairment

The causes of visual impairment are usually classified in terms of anatomical sites of the lesion and/or the etiological factors (36). In Norwegian children, the three principle causes of visual impairments are neuro-ophthalmological conditions (37.3%), retinal diseases (19.1%), and global eye diseases (13.9%). More than half of the cases are related to congenital conditions (29). In Norwegian adults, the causes of visual impairment are less known. However, data from the Danish Copenhagen City Eye Study showed that cataract (33%), age-related macular degeneration (32%), and diabetic retinopathy (10%) were the most common causes of moderate to severe visual impairment, whereas the leading causes of blindness were macular degeneration (43%), glaucoma (14%), and myopia-related retinal disorders (14%) (37). The study did not assess the possible impact of uncorrected refractive error.

1.4 Visual impairment and health

Health is a complex phenomenon and several health definitions exist (37). One renowned health definition in biomedical research is the World Health Organization's (WHO) Declaration of Alma-Acta adopted in 1978, in which health is defined as 'a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity' (38). A health definition published by Huber et al. states that health is 'the ability to adapt and to self-manage' (39). Although there are challenges related to defining health, the various definitions are not discussed further in this thesis.

Health measurements have been used for more than a century to identify health problems in society, policy formation, and tests on the effectiveness of medical treatment and health care (40). Health-related aspects can be assessed using various measures, ranging from global assessments of health to measures that are more specific. The primary outcome measures discussed in this thesis are anxiety symptoms, depression symptoms, and mortality. Before

presenting the current state of knowledge about the mental health and the mortality of individuals with visual impairments, two important health-related characteristics of individuals with visual impairments, namely functional limitations and co-morbidity, will be described.

1.4.1 Functioning

Functioning is a natural, required, or expected action performed by the individual (41). According to the WHO's ICF (24), a person's functioning is influenced by a number of factors that work in dynamic and multidimensional ways, and constitutes of the following factors: bodily structures, bodily functions, personal factors, and environmental factors. Reduction in an individual's functional performance may have a considerable impact on their ability to self-manage, socialize, and live a meaningful life (24).

Individual's functional capacity and the environmental demands varies across the lifespan. The transition from childhood to adulthood (age group 10–19 years) is experienced as a turbulent time for all individuals, including those living with visual impairments (42). As children become adolescents, they are expected to become more functionally independent and to participate in activities within their home and community (41). In this stage of life, individuals are maturing physically and sexually, creating their own personal identity, some are completing their education, and some are trying new pursuits, such as finding a job, forming romantic relationships, and driving a car (43). The functional demands increase in adulthood (≥ 20 years) as individuals receive more responsibilities at home, at work, and in their community (41).

Vision is a key sensory modality for many human functions because it rapidly provides relevant and detailed information about the environment (exteroception) and the human body (visual perception) (44). Visual impairment is among the most disabling of medical conditions (45), and may impact some aspects of an individual's growth and development (46, 47). Several

studies have shown that most individuals with visual impairment experience difficulties when watching, writing, driving, and reading, as well as problems with object recognition, mobility, fundamental motor skills, and domestic life chores (47-49). Vision loss may also influence psychosocial abilities such as communication, affect regulation, conceptual thinking, and social interaction behaviours (42, 46, 50, 51).

1.4.2 Co-morbidity

Co-morbid conditions are the coexistence of one or more diseases or impairments in addition to the primary disease or impairment (52). Studies of children and adolescents have shown that 53–77% of those with visual impairments have at least one co-morbid condition (29, 53, 54), and the risk of visual impairment is particularly high for individuals born prematurely, as well as those with cerebral palsy, acquired brain injury, learning impairments, hearing loss, or Down's syndrome (29, 49). In adults with visual impairments, the numbers with one or more co-morbid conditions is similarly high (55, 56). For example, in a cross-sectional study using registry data relating to Scottish elderly adults, Court et al. (55) showed that 95% of the adults with visual impairment had one chronic somatic or mental disease, whereas 53% had at least four chronic diseases. Frequent somatic conditions in adults with visual impairment are hearing loss, multiple sclerosis, diabetes, cardiovascular diseases, and joint problems (55, 57, 58).

Overweight is a global health challenge and places considerable burden on society in general (59), including people with visual impairments. In Westernized populations with visual impairments, studies have shown that the prevalence of overweight (body mass index ≥ 25 kg/m^2) is 30–40% in children and adolescents (60, 61) and 60–70% in adults (62, 63). However, there is mixed evidence regarding whether individuals with visual impairments have an increased risk of overweight compared with individuals without visual impairments (11, 62, 63).

1.4.3 Anxiety and depression

This thesis focuses on two of the most prevalent mental health problems in Western societies today, namely anxiety and depression (64). In research and clinical practice, it is customary to distinguish mental health problems from mental disorders. Mental health problems are characterized by symptoms that might influence concentration, well-being, functioning, and socialization, but do not fulfil the criteria of a mental disorder. A mental disorder is present when the number, intensity, and duration of symptoms fulfil the criteria stipulated in a diagnostic manual. The most commonly used diagnostic manuals are the WHO's ICD and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) (64). The symptoms are classified as physical, psychological, or behavioural.

Anxiety disorders includes many subtypes that are linked to specific non-dangerous objects or situations (phobia), or to sudden or uncontrolled anxiety attacks (panic anxiety), or that have a more unspecific, general form with recurrent feelings of excessive anxiety or worry (generalized anxiety disorder). Core symptoms for most anxiety disorders are anxiety/worrying, withdrawal/avoidance, and abnormal activation of the sympathetic nervous system (22). The average onset-age for most types of anxiety disorders is in the age group 10–20 years (65). Depression is a part of mood disorders (22), and the most common depression disorder is depressive episodes[3] (64). Depressive episodes are a mental state characterized by depressed mood, reduced activity, and lower energy. Capacity for enjoyment, concentration, and interest is reduced. Other symptoms may be motor retardation, low self-esteem, and ideas of guilt or

[3] ICD-10 use the term 'depressive episode' to describe a diagnosis of unipolar depression, whereas DSM-V uses the term 'major depressive disorder'.

unworthiness, as well as disturbances in sleep and appetite (22). The average onset-age of mood disorders is in the age group 30–40 years (65).

Anxiety and depression symptoms may negatively impact an individual's quality of life and life expectancy (64), and could have an even greater impact on the lives of people with visual impairments (57). The prevalence of anxiety and depression symptoms are high among people with visual impairments, but published studies have shown very different estimates. The prevalence of mental health problems has been estimated to be 29–39% in adolescents with visual impairment (51, 66, 67), and these estimates include symptoms of anxiety and depression. In adults with visual impairments, the prevalence estimates are 9.3–15.6% for subthreshold anxiety and 11.3–32.2% for subthreshold depression (68-70). The variations in the estimates are probably due to methodological differences in study designs, the identification of populations with visual impairments, and the assessment tools for anxiety and depression symptoms.

Less is known about the underlying causes of anxiety and depression. However, risk factors for anxiety and depression symptoms are based on variables that determine biological susceptibility to anxiety and depression (e.g. gender, age), mediators of stress (e.g. negative life events, somatic disorders), and characteristics associated with stress coping (e.g. personality, education) (71). In the scientific literature, it has been debated whether visual impairment is a risk factor for the development of anxiety and depression symptoms (68, 70, 72-74), but no definitive conclusion has been reached yet.

1.4.4 Mortality

Humans have never lived longer than they do today. In the period between 1964 and 2014, the life expectancy at birth in Europe increased by an astonishing 10 years, from 71 to 81 years (75). Furthermore, there has been a shift in the leading causes of death over the past 100 years, from

infectious diseases to non-communicable diseases (also called chronic diseases). Data from Norway's Cause of Death Registry (Dødsårsaksregisteret) show that 89.4% of all deaths in 2014 were caused by non-communicable diseases, and the three leading causes were cardiovascular diseases (29.0%), cancer (27.5%), and respiratory diseases (9.3%) (76).

There is evidence of an association between visual impairment and all-cause mortality. In a recent meta-analysis that included 29 prospective observational studies, adults with visual impairments were found to have a 36% greater all-cause mortality risk compared with adults without visual impairments (77). However, the authors also found large heterogeneities in the risk estimates, which they mainly attributed to differences in sampling method, assessment of visual impairment, length of the follow-up period, and adjustments for possible confounders. Possible modifying factors of the association between visual impairment and mortality may be related to age (77-79) and severity of visual impairment (77, 80), whereas findings with greater divergence have been related to gender (77, 78, 80).

A combination of mediating factors related to functioning, mental health, chronic somatic diseases, and accidents and falls may be responsible for the association between visual impairment and all-cause mortality (81). Little is known about the possible mediating role of lifestyle behaviours. Moreover, it is unclear whether visual impairment itself causes increased mortality risk, or whether the association is related to the eye condition or confounding factors such as aging and ongoing chronic diseases (82).

1.5 Physical activity and health individuals with visual impairments

The public health significance of regular PA will be described in this section, as well as the PA levels of individuals with visual impairments. The scientific literature on PA and its association

with the health of adolescents and adults with visual impairments is reviewed, with the focus only on studies that have included anxiety, depression, or mortality as outcome variables.

1.5.1 Physical activity and public health

Caspersen et al. (83) define PA as 'any bodily movement produced by the contraction of skeletal muscles that results in energy expenditure'. The energy expenditure associated with habitual PA is determined by the frequency, duration, intensity, and type of activity. This is often referred to as the 'dose' of PA (84). PA may also be categorized in different domains, such as occupational, leisure, housework, or commuting. Physical exercise is 'a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness' (83). By contrast, physical fitness is 'a set of attributes that are either health or skill related' (83). Physical fitness is determined by PA, but also by fixed components such as gender, age, and genetic traits (84).

For centuries, regular participation in PA has been recognized as an important component of the health and wellness of humans. In the mid-20th century, the hypothesis of a causal link between PA and health began to gain momentum as this hypothesis was empirically proven by some well-arranged research studies. For example, in the well-known study conducted by Jeremiah Morris et al., it was found that physically active bus conductors had a 30% lower incidence rate of coronary heart disease compared with the bus drivers who remained sedentary throughout their work day (85). To date, PA has been recognized as a powerful modifiable factor for reducing mortality (86, 87), as well as for preventing the development of chronic diseases such as cardiovascular diseases, chronic pulmonary diseases, anxiety, osteoporosis, depression, type 2 diabetes, and some cancer types (88-90). Regular PA is also recognized as a cornerstone of

human development and growth, and has the potential to promote functioning, independence, and well-being (84).

On the basis of the scientific evidence, a number of national and international PA guidelines have been created to address the optimal dose and type of PA needed to improve people's health and functioning, as well as to recommend activities that are considered safe, pleasant, and enjoyable (91). In this thesis, I use the global PA guidelines published by the WHO (6), and these are described in Table 2. The WHO's PA guidelines also targets those who live with visual impairments (6, 92).

Table 2. The WHO's global recommendations for physical activity (PA) according to age group.

Age group	Recommendations
Children (5–17 years)	• 60 minutes of moderate to high intensity PA daily • Physical activity amounting to more than 60 minutes daily will provide additional health benefits • Most daily physical activity should be aerobic • High-intensity activities should be incorporated, including those that strengthen muscles and bones, at least 3 times per week
Adults (18–64 years)	• 150 minutes of moderate-intensity aerobic physical activity per week, or 75 minutes of high-intensity aerobic physical activity per week, or a combination of the two intensities • Performed in bouts of 10 minutes or more • Increased PA levels provide additional health benefits • Muscle strengthening activities of major muscle groups at least 2 times per week
Elderly (≥ 65 years)	• Similar to the guidelines for adults • In addition, elderly persons with poor mobility should perform physical activity on 3 or more days per week to enhance balance and prevent falls • When adults in this age group cannot do the recommended amounts of physical activity due to health conditions, they should be as physically

active as their abilities and conditions allow

Source: World Health Organization (6)

1.5.2 Physical activity in people with visual impairments

Vision loss may restrict individuals' activities related to daily life and recreation (48), including leisure-time PA and sports (93-95). The results from studies that have included Westernized populations have shown that adolescents and adults with visual impairments have significantly lower weekly levels of PA than their sighted counterparts (11-13), and 73–82% of adults with visual impairments do less than 30 minutes of moderate to high intensity PA per day (96, 97).

In Norway, little is known about the PA behaviours of individuals with visual impairments. In a sample of Norwegian children and adolescents (age group 7–17 years), Bjørgen & Augestad (98) observed that 18% of those with visual impairments and 74% of those without visual impairments participated in organized leisure-time PA. The Norwegian Association of the Blind (Norges Blindeforbund) claimed that there has been a decrease in the number of individuals with visual impairments participating in sports events, as well as a decrease in the number of Paralympic athletes with visual impairments (99). However, in a representative sample of 4500 community-dwelling Norwegian adults aged ≥ 16 years, Ramm (3) found that 48% of those with self-perceived visual impairments reported that they exercised ≥ 3 times/week, and 46% of the general adult population reported the same amount of exercise.

For individuals with visual impairments, the greatest obstacles to maintaining PA are the barriers they face to becoming physically active, and commonly reported barriers are lack of motivation or interest in becoming physically active, bullying, low social support, co-morbid conditions, being dependent on others, lack of transportation, fear of falling, poor information about exercise programmes, lack of a universal design of gym and sports arenas, and lack of

qualified instructors or visual interpreters (93-95, 100-102). The barriers to PA may be a part of a vicious circle, in which case they could result in participants having negative experiences when they engage in PA, thus making the prospect of future PA less attractive. Further, a physically inactive lifestyle may result in the development of co-morbid conditions that could function as additional barriers when attempting exercise (103).

Another obstacle for maintaining PA among those with visual impairments are related to their values and priorities, as well as to values and priorities of their parents and significant others. For example, in rehabilitation settings, improving PA participation for individuals with visual impairments is of less importance than improving their abilities in activities such as education, mobility, communication, and the application of knowledge (104, 105).

1.5.3 Physical activity and symptoms of anxiety or depression

Two studies have examined the association between PA and anxiety or depression symptoms in populations with visual impairment. In a prospective observational study in the USA that included an age-matched sample of 2688 elderly adults, Capella-McDonnall (106) found that lower depression scores were significantly associated with the maintenance of ≥ 2–3 days of high-intensity PA during the 13-year follow-up among those with both vision and hearing loss, compared with those with both vision and hearing loss who maintained lower PA levels. Surprisingly, PA was not significantly associated with depression symptoms among those without vision and hearing loss. Capella McDonnall's study did not include measures of anxiety symptoms. In a cross-sectional study that included a convenience sample of 30 young Italian adults with severe visual impairment and blindness, Di Cagno et al. (107) observed significantly fewer anxiety and depression symptoms among those who played Torball (a ball game for people with visual impairments) compared with those who did not play any sports. Overall, the evidence

to date suggests that PA and sports are associated with fewer symptoms of anxiety or depression in adults with visual impairment. However, none of the studies conducted to date have assessed how anxiety or depression symptoms are associated with different PA characteristics and none of the studies have included samples of adolescents.

1.5.4 Visual impairment, physical activity, and all-cause mortality

It has been increasingly recognized that the increased all-cause mortality risk of adults with visual impairments may be explained by their lower PA levels. However, most studies to date have controlled away the effects of PA by treating the variable as a possible confounding factor in the regression models (78, 108). To my knowledge, only one study has examined whether PA explains the association between visual impairment and all-cause mortality: Kulmala et al. (109) found, in a sample of 416 Finnish elderly adults aged either 75 years or 80 years at baseline, that adding PA to the regression model explained 20% of the association between visual acuity loss (visual acuity: < 0.3 in the better-seeing eye) and all-cause mortality risk among those aged 75 years, whereas the risk estimates were pulled moderately in the opposite direction for those aged 80 years. However, the researchers had few cases in some strata, and adjusted for gender and socio-economic status only. Therefore, more research is needed.

To my knowledge, no studies have examined the joint associations of visual impairment and PA with all-cause mortality. However, Loprinzi & Joyner (110) have demonstrated that during a 7-year follow-up of 5278 adults in the age group 20–85 years, every 60-minute increase in daily accelerometer-measured total PA levels was significantly associated with a 18%, 15%, and 35% lower risk of all-cause mortality among those with no visual impairment, uncorrected refractive error, and mild to severe visual impairment or blindness, respectively. The researchers

did not test whether PA modified the association between visual impairment and all-cause mortality.

2.0 AIMS

2.1 General objective

The general objective of the research for this thesis was to use epidemiological methods to examine the association between leisure-time PA and mental health among individuals with self-reported visual impairments, and to compare those associations with those of individuals with self-reported no visual impairment. A further objective was to investigate the role of leisure-time PA in the association between self-reported visual impairment and mortality.

2.1.1 Specific aims

The specific aims of the three substudies were to investigate the following:

1. The effect of leisure-time PA on symptoms of anxiety or depression and subjective well-being among adolescents with and without self-reported visual impairment (Paper I)
2. The association between leisure-time PA levels and symptoms of anxiety and depression in adults with and without self-reported visual impairments (Paper II)
3. The association between self-reported visual impairment and all-cause mortality with and without adjustment for leisure-time PA, and the joint associations of self-reported visual impairment and leisure-time PA with all-cause mortality (Paper III).

3.0 METHODS AND MATERIALS

3.1 Study design and methods

The study was based on data from prospective observational cohort studies and the participants were followed for 4 years (Paper I), 11 years (Paper II), and 17 years (Paper III). The participants' baseline data were either linked to information from the follow-up survey (Papers I–II) or linked to the Cause of Death Registry (Paper III). The exposure variables were visual impairment and leisure-time PA, while the outcome variables were symptoms of anxiety and depression and mortality.

3.1.1 The Nord-Trøndelag Health Study (HUNT)

The HUNT Study is the longest lasting population-based health study in Norway, and aimed to include all adolescents (13–19 years) and adults (≥ 20 years) living in the county of Nord-Trøndelag. Nord-Trøndelag is a large, rural county located in central Norway, and is subdivided into 24 municipalities (Figure 2). In 1995, the county had 127,000 inhabitants, an emigration rate of 0.3%, and an immigration rate of 2.0% (111). In addition to being a stable population, the HUNT population is fairly homogeneous in terms of socio-economic status, health, ethnicity, and living conditions (112).

The HUNT Study includes a large amount of data that have been collected from a number of surveys. The adolescent surveys were conducted in the periods 1995–1997 (Young-HUNT1), 2000–2001 (Young-HUNT2), and 2006–2008 (Young-HUNT3), while the adult surveys took place in 1984–1986 (HUNT1), 1995–1997 (HUNT2), 2006–2008 (HUNT3). The data in the HUNT Study were obtained through interviews, questionnaires, clinical measurements, and biological samples.

This thesis includes data relating to those who participated in the first two waves of the adolescent part of the study (Young-HUNT1 and Young-HUNT2), those who participated in the second wave of the adult part of the study (HUNT2), and those who participated in both the second and third waves of the adult part of the study (HUNT2 and HUNT3).

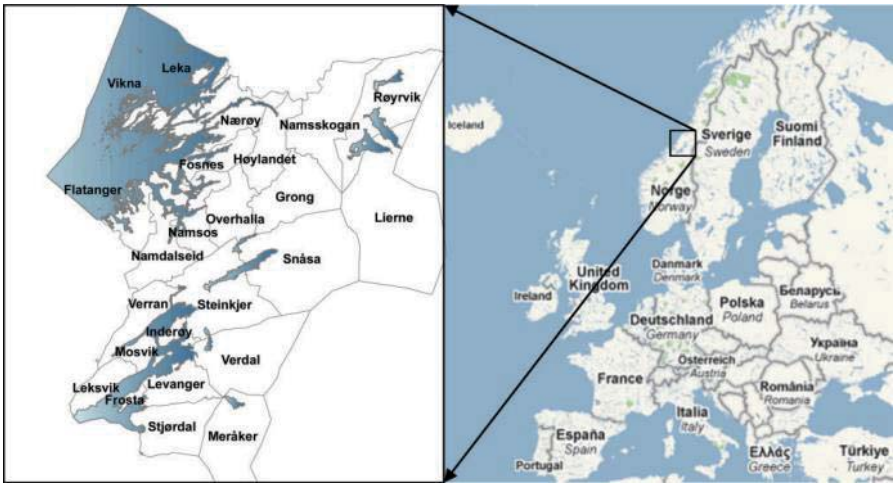


Figure 2. Location of Nord-Trøndelag County, Norway.

3.1.2 The Young-HUNT1 and Young-HUNT2 Surveys (Paper I)

The entire adolescent population living in Nord-Trøndelag in the age group 13–19 years was invited to participate in the first wave of the Young-HUNT Study (Young-HUNT1, 1995–1997), including those with impairments. School was the main study site for most of the participants. However, adolescents who did not attend a state school completed the study at home. The data were collected through a questionnaire and a clinical examination (113). The questionnaire was completed during one school hour in an exam-like setting, and teachers were present to help

those who struggled with completing the questionnaire.[4] Within one month after completing the questionnaires, the participants underwent a clinical examination by a trained nurse. Adolescents who participated in Young-HUNT1 and who were in the age group 13–16 years were invited to participate in the follow-up survey (Young-HUNT2 Survey, 2000–2001). The study design of Young-HUNT2 was similar to that of Young-HUNT1 (113).

3.1.3 The HUNT2 and HUNT3 Surveys (Papers II and III)

The baseline data used in Papers II and III were obtained from the second wave of the adult part of the HUNT Study (HUNT2, 1995–1997), which included all adults aged ≥ 20 years living in the county of Nord Trøndelag at that time point (114). HUNT2 had a three-stepped data collection procedure. The first survey questionnaire, which was mailed together with a personal invitation, was completed at the participant's home. Then, a few days after receiving the first questionnaire, the participant underwent a clinical examination at the local health centre. After the clinical examination, the participants received a second questionnaire, which they filled out at home and returned by mail. The procedure in HUNT3 was the same as for HUNT2 (114).

3.1.4 Norway's Cause of Death Registry

Norway's Cause of Death Registry holds data on deaths for the entire population registered in Norway's central population register and since 2014 the data have been maintained by the Norwegian Institute of Public Health, prior to which they were maintained by Statistics Norway (Statistisk sentralbyrå, SSB). A medical practitioner classifies the causes of death in accordance with the ICD-10 (115). This thesis focuses on all-cause mortality and on underlying causes of

[4] Personal commuication from Turid Lingaas Holmen, 20 November 2014

death. According to the ICD-10, the underlying cause of death is 'the disease or external cause of injury that started the chain of events leading directly to death' (22).

3.2. Sample and selection procedures

3.2.1 Paper I

In Young-HUNT1, 5004 adolescents were invited and 4742 (94.8%) attended by completing the questionnaire. In Young-HUNT2, 3124 were invited and 2399 (76.8%) participated (113). A total of 348 participants were excluded from the analyses due to missing data on key variables. A further 634 participants who reported either 'a little' or 'somewhat' to the question about vision impairment were excluded in order to include adolescents with the most severe visual impairment and to compare them with their counterparts who did not have any visual impairments. The final sample consisted of 1417 participants (Figure 3), of which 46 (2.2%) had severe SRVI (Table 3).

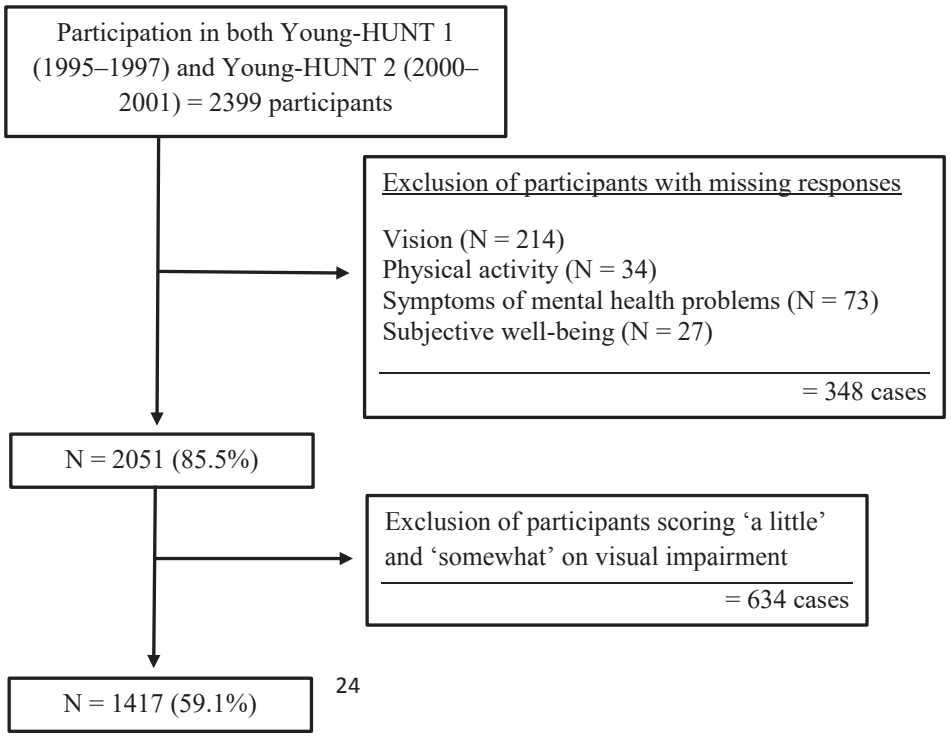


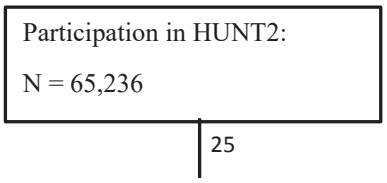
Figure 3. Flow chart showing selection procedure for Paper I.

Table 3. Numbers and percentage of visual impairment at baseline (Papers I–III).

	Visual impairment categories			
	None	A little	Some	Severe
Paper	N (%)	N (%)	N (%)	N (%)
Paper I (N = 2068)	1384 (66.9)	462 (22.3)	176 (8.5)	46 (2.2)
Paper II (N = 34,393)	30,674 (89.2)	2263 (6.6)	1134 (3.3)	322 (0.9)
Paper III (N = 65,236)	54,162 (83.0)	6263 (9.6)	3523 (5.4)	1304 (2.0)

3.2.2 Papers II and III

A total of 65,237 (69.5%) participated in HUNT2 by completing and returning the first questionnaire (Figure 4). For Paper II, those who did not complete the first questionnaire at HUNT3 were excluded from the main analyses. Moreover, those who were above the age of 67 years were excluded in order to obtain a more homogeneous sample with regard to age. For Paper III, all HUNT2 participants were linked to the Cause of Death Registry and included in the main analyses. Of the included sample at baseline, 11,074 (17.0%) had a degree of SRVI (Paper II) and 3719 (10.8%) had a degree of SRVI (Paper III). Most participants described their visual impairment as ‘a little’, followed by ‘some’ and ‘severe’ (Table 3).



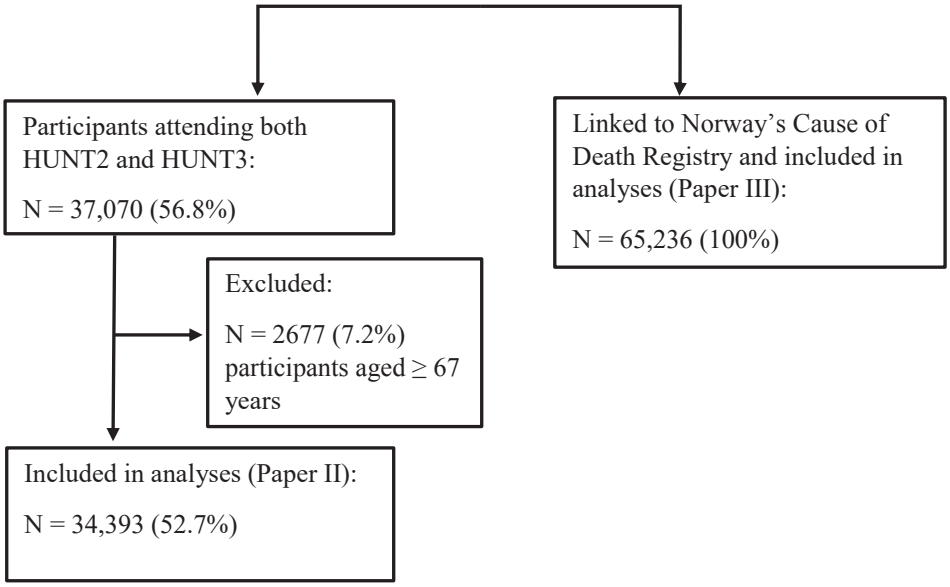


Figure 4. Flow chart showing selection procedure for the substudies reported in Papers II and III.

3.3 Study variables

Most of the data used in this thesis were sourced from The HUNT Study. The variables assessed in each HUNT Survey can be found in the Hunt Databank (116).

3.3.1 Visual impairment (Papers I–III)

Information on the participants' own judgement of their visual impairment was assessed by a two-item questionnaire. First, the participants had to answer the following question: 'Do you have a longstanding disease, injury, or condition (at least one year) of physical or mental character that impairs your functioning in daily life?' Those who answered 'yes' were asked to describe whether they had a degree of visual impairment, and the response alternatives were 'a little impairment', 'some impairment', and 'severe impairment'. For Paper I, the self-reported

visual impairment (SRVI) category included those who described their visual impairment as severe. For Papers II and III, participants were placed in the SRVI category if they reported a degree of visual impairment. Participants who reported 'no visual impairment' (Paper I) or did not report any visual impairment (Papers II and III) were included in the self-reported no visual impairment (SRNI) category.

3.3.2 Physical activity (Papers I–III)

Leisure-time PA was assessed by PA questionnaires (see Appendices I and II). For Paper I, the frequency of moderate to high intensity of weekly leisure-time PA was measured. The questions were derived from the WHO's Health Behavior in School Aged Children (HBSC) study (117). The item includes an 8-point response scale: 'never', 'less than once a month', 'not every 14th day, but more than once a month', 'not every week, but at least once every two weeks', '1 day a week', '2–3 days a week', '4–6 days a week', and 'every day'. The question about frequency of leisure-time PA has been validated for adolescents and found to have a substantial reliability (r = 0.73) and fair validity compared with peak oxygen consumption ($VO_{2\text{-peak}}$) (r = 0.39) (118). A category named 'non-weekly PA' was created by including those reporting 'not every week, but at least once every two weeks' or lower levels of PA. The category 'weekly PA' included those who responded that they were physically active at least 1 day per week.

In HUNT2, the participants reported their average weekly hours of low-intensity PA (not sweating or being out of breath) and moderate to high-intensity PA (sweating or being out of breath) during their leisure-time by selecting one of the following response alternatives for hours per week: none, < 1, 1–2, or 3 or more. The questionnaire has been validated for men (119). Moderate to high-intensity PA (MHPA) was found to correlate moderately with maximal oxygen consumption ($VO_{2\text{-max}}$) measurements (r = 0.46) and the long version of the International

Physical Activity Questionnaire (IPAQ-L) (r = 0.31). Low-intensity PA (LPA) correlated poorly with $VO_{2\text{-max}}$ (r = −0.03) and IPAQ-L (r = −0.08). For Paper II, a PA index was created in accordance with the calculations performed in other studies that had analysed data from HUNT2 (120). LPA was included as a crude score, while MHPA was weighted 2.5 for each increase in score on that particular variable. Next, the variables were summarized in a PA index score. The PA index was then categorized into low, moderate, and high scores by dividing it at the 33.3rd and 66.6th percentiles. The cut-off was 3 and 5.5 points. For Paper III, LPA and MHPA were coded into a dichotomous variable (0 hours and > 0 hours of PA per week).

3.3.3 Anxiety and depression symptoms (Papers I and II, descriptive of Paper III)

In Young-HUNT1, anxiety and depression symptoms were assessed by the 5-item version of the Hopkins Symptom Checklist (SCL) (121).[5] The scale was used to record how the participant had felt in the past 14 days and the participant reported on a 4-point Likert scale, ranging from 1 (not at all bothered) to 4 (extremely bothered). The SCL-5 scale has previously been found to correlate highly (r = 0.92) with the 25-item version of the checklist (SCL-25) (121). Sum scores from the SCL-5 were computed and divided by the number of items. The SCL-5 was treated as an untransformed continuous variable in the main analyses presented in Paper I.

In HUNT2, anxiety and depression symptoms were measured by the Hospital Anxiety and Depression Scale (HADS). HADS has been designed as a survey tool to identify anxiety and depression for medical hospital patients, but has also been shown to be a suitable tool for general population samples (122). HADS assesses the participant's feelings during the last week. The questionnaire consists of two subscales, with seven items for anxiety (HADS-A) and seven items

[5] The term 'mental health problems' is used in Paper I. However, all five items of the SCL assess anxiety symptoms (three items) and depression symptoms (two items). It is therefore more appropriate to use the term 'anxiety and depression symptoms'.

for depression (HADS-D). A 4-point Likert scale was used for each question, ranging from 0 (not present) to 3 (maximally present). Therefore, both HADS-A and HADS-D yielded a sum score ranging from 0 to 21 points (123). The HADS-A and HADS-D scales were treated as continuous variables in the main analyses (Paper II).

3.3.4. Mortality (Paper III)

Data on the cause of death were obtained from the Cause of Death Registry. Links to the register were made by an external person using the 11-digit personal identification number unique to all people resident in Norway. All-cause mortality was included as the outcome measure in the main analysis, whereas cause-specific mortality was used as a supplementary analysis (i.e. cancer, cardiovascular diseases, fatal accidents and sudden deaths, and other causes).

3.3.5 Covariates

The HUNT Databank contains more than 5000 variables, and a large number of variables were collected during each survey. This made it possible to adjust for possible confounding factors. In Papers I–III, possible confounding variables were identified using previous publications and a priori reasoning (124). All variables listed below were assessed at baseline. However, for Papers I and II, supplementary analyses included covariates that were assessed at follow-up.

3.3.5.1 Sociodemographic variables (all papers)

Baseline age was included as a continuous or categorical covariate in the main analyses. For Paper III, age was adjusted for in the statistical analysis by using chronological age as the time scale. The chronological age variable refers to the time from birth to censoring or death (125).

Occupational status was categorized as ‘in work’ and ‘not in work’. The latter included being unemployed, retired, a homemaker, in education, or in military service (Paper II). Marital status was categorized as unmarried, married/partner, divorced/separated, and widowed (Paper III). Education was divided into two or three subgroups based on the total number of years in education (Papers II and III).

3.3.5.2 Lifestyle characteristics (all papers)

In HUNT2, smoking status was defined based on the participants’ responses to the questions of whether they smoked currently, and if not, how long was it had been since they had stopped smoking. The variable was then categorized as ‘non-smokers’, previous smokers’, and ‘current smokers’. Alcohol consumption was assessed by a two-item questionnaire in HUNT2. First, the participants were asked whether they were a teetotaller. If they were not a teetotaller, the alcohol consumption variable included the average number of days during a month when alcohol was consumed, and was coded into the categories ‘teetotaller/none’, ‘1–4 times/month’, and ‘≥ 5 times/month’. For Paper I, a one-item question assessed each participant’s involvement in sports during their leisure time, and the response was coded as either ‘yes’ or ‘no’.

3.3.5.3 Clinical measures (all papers)

Body mass index (BMI) was computed as kg/m^2 from measured height and weight. For Paper I, age and gender-standardized cut-offs were calculated in accordance with the recommendations by Cole and colleagues (126, 127). For Papers II and III, the BMI variable was categorized on the basis of the WHO criteria: $< 25\ kg/m^2$, $25–29.9\ kg/m^2$, $\geq 30\ kg/m^2$ (22). However, those who were classified as underweight ($< 18.5\ kg/m^2$) were included in the ‘normal weight’ category due to too few participants in that category. For Paper III, an adverse biomarker variable was created

and coded as a no/yes response. The variable included hypertension (a blood pressure of ≥ 160/100 mm/Hg), hyperglycaemia (non-fasting levels of ≥ 11.0 mmol/L), and high total cholesterol levels (non-fasting levels of ≥ 7.0 mmol/L).

3.3.5.4 Chronic diseases and global health measures (all papers)

For all papers, a chronic disease variable was computed based on each participant's responses to questions about a history of selected chronic somatic conditions. For Paper II, the chronic disease variable included a history of mental disorders. Those who reported having a history of one or more condition were categorized as 'yes', whereas those who responded 'no' to all chronic diseases were categorized as 'no'. For Paper I, the participants' rating of their own health (poor/not so good, good, very good) was added to the fully adjusted models.

3.3.5.5 Psychosocial measures (Paper I)

The modified short-version of the Eysenck Personality Questionnaire (EPQ) was used to measure extraversion and neuroticism (128). The sum scores on the EPQ-extraversion scale and EPQ-neuroticism scale were either treated as continuous or dichotomized by the median score. Loneliness was assessed by asking the participants' whether they felt lonely and their response coded as follows: 'no/rarely, 'sometimes', and 'often/very often'. Self-esteem was assessed by the 4-item version of the Rosenberg Self-esteem Scale (129). A sum score was calculated and the variable was dichotomized by the median score (< 2.5, ≥ 2.5).

3.4 Statistical methods

3.4.1 Descriptive statistics and main analyses (Papers I–III)

The statistical analyses were performed using PASW Statistics 22 (SPSS Inc. Chicago, IL, USA) (Paper I) and Stata version 13.0 for Windows (Stata Corporation, College Station, Texas) (Papers I–III). For all three papers, the statistical procedures included descriptive statistics and different types of regression models. Statistical significance was set at $\alpha = 0.05$, and the associated uncertainty of the estimates was assessed by 95% confidence intervals (CIs).

Descriptive statistics included numbers and percentages for each baseline characteristic. For Paper I, Person's chi-squared analyses were used to examine differences between observed and expected frequencies for each baseline characteristic. For Paper III, age-standardized mortality rates were calculated for all levels of each baseline characteristic.

For Paper I, generalized linear models (GLMs) with a gamma distribution and log-link relationship were used to estimate differences in the continuous probability of the SCL-5 score at follow-up for each category of the baseline PA (non-weekly versus weekly PA). Beta-values (β) and corresponding 95% CIs were computed with the participants reporting weekly PA as the referent category. The GLMs were: (1) unadjusted; (2) gender and age-adjusted; (3) adjusted for gender, age, personality, chronic somatic diseases, and baseline scores on SCL-5; or (4) adjusted for gender, age, personality, chronic somatic diseases, baseline scores on SCL-5, body mass index, feeling lonely, self-rated health, self-esteem, and sports involvement.

For Paper II, GLMs with a gamma distribution and log-link function was used to estimate the mean HADS-A or HADS-D scores at follow-up for each category of the baseline PA index, and compared with those in the referent category (low PA). Relative risks (RRs) and its standard error were used to calculate the 95% CIs. The GLMs were either unadjusted or they were

adjusted for age, gender, smoking status, monthly alcohol consumption, occupational status, education, and a history of somatic or mental conditions.

For Paper III, the associations between visual impairment and all-cause mortality were examined by using Cox regression models. Hazard ratios (HRs) and their standard errors were used to compute the 95% CIs. In a separate analysis, we examined whether PA contributed to the association between visual impairment and all-cause mortality by adding LPA and MHPA to the model, including all indicated covariates. When estimating the joint associations, a variable with four subgroups was created and added to the Cox models. The four subgroups were: SRNI and hours of LPA or MHPA (referent category); SRNI and no LPA or MHPA; SRVI and hours of LPA or MHPA; SRVI and no LPA or MHPA. The Cox models were either age and gender-adjusted or adjusted for age, gender, smoking status, alcohol consumption, body mass index, marital status, education, a history of diabetes or any cardiovascular diseases, and having any adverse biomarkers. To check the proportional hazards assumption, the visual impairment variable was included in the Cox models as an interaction term with a linear or a logarithmic function of time. A violation of the proportional hazards for the visual impairment variable with all-cause mortality was accounted for by fitting the Cox models separately for restricted groups of chronological age (< 60, 60–84, ≥ 85 years).

3.4.2 Missing data (Papers I–III)

In all three papers, complete cases were used in the primary statistical analyses, while multiple imputation with chained equations (MICE) was used as a supplementary method to examine the possible impact of missing data. A number of variables were added to the imputation model in order to reach the missing at random (MAR) assumption. For Papers I and II, a low to moderate probability for reaching MAR was assumed, while for Paper III, a moderate to high probability of

reaching MAR was assumed. The imputation model was built in accordance with the guidelines published by White, Royston, and Wood (130). Continuous variables were imputed using linear regression, semi-parametric continuous variables were imputed using predictive mean matching, and categorical variables were imputed using either ordinal or nominal logistic regression. Augmentation was used to prevent perfect prediction when imputing categorical variables. The building of the imputation model is included in the supplementary material in each substudy reported in this thesis.

3.4.3 Effect-measure modification (Papers I–III)

We tested for effect-measure modification (EMM) on multiplicative (Papers I–III) and additive scales (Paper III). Departure from multiplicativity was examined by including the variables of interest as product terms in the regression model and using likelihood ratio tests to assess their combined statistical significance with $\alpha = 0.05$. Test of EMM on an additive scale was carried out by calculating relative excess risk due to interaction (RERI). RERI was derived from the beta coefficients and covariance matrix obtained from the Cox models (131). A RERI > 0 indicated a positive EMM on a risk difference scale.

For Papers I–II, EMM was examined between PA and each covariate, and between PA and visual impairment. For Paper III, EMM was tested between visual impairment and each covariate, and between visual impairment and PA.

3.5 Ethical considerations

The present study has been approved by the Regional Committee for Medical and Health Research Ethics for Central Norway (Regional komitee for medisinsk og helsefaglig forskningsetikk, avdeling Midt Norge (REK midt)) (reference number 2012/1365). The HUNT

Research Centre and the Norwegian Institute of Public Health gave me and the co-authors of the three papers permission to analyse their data. All participants aged 18 years or older gave their written consent to participate in the surveys, and for data related to them to be used for research purposes (Papers I–III). Persons who were younger than 16 years obtained written consent from one of their parents (Paper I). Participation in the study was voluntarily. All participants were informed that they could withdraw from the study at any time and refuse permission for future use of information collected about them.

4.0 MAIN RESULTS

The main results for each substudy are presented separately in Sections 4.1, 4.2, and 4.3.

4.1 Paper I: The effect of physical activity on mental health among adolescents with and without self-reported visual impairment: The Young-HUNT Study, Norway

The underlying aim of the first substudy was to examine the effect of leisure-time PA on anxiety and depression symptoms and subjective well-being (SWB) among adolescents with SRVI and SRNI. In total, 46 adolescents with severe SRVI and 1371 adolescents with SRNI were included in the main analyses after exclusions. At follow-up, compared with adolescents with SRNI, adolescents with severe SRVI had slightly higher mean SCL-5 scores (mean = 1.64 versus 1.49).

In the unadjusted GLM of the entire study sample, the associations between PA and symptoms of anxiety and depression were similar within levels of SRVI (χ^2 (df: 1, 1413) = 1.93, p = 0.17). In the unadjusted models among adolescents with SRNI, those who reported non-weekly PA had a significantly more symptoms of anxiety and depression (unadjusted $\beta = 0.08$, 95% CI = 0.02, 0.14) compared with those who reported weekly PA. After adjusting for possible confounders and handling the possible impact of missing data, the associations were pulled towards the null and became statistically non-significant. Furthermore, in adolescents with SRNI, no product terms between visual impairment and other covariates reached statistical significance ($p > 0.05$).

For adolescents with severe SRVI, we found that the associations between leisure-time PA and the SCL-5 variable were dependent on the adolescents' EPQ-neuroticism and EPQ-extraversion scores. For adolescents with severe SRVI who were classified as more emotionally unstable (EPQ-neuroticism score ≥ 3) or as more introverted (EPQ-extraversion score < 3), non-

weekly PA at baseline was significantly associated with more anxiety and depression symptoms at follow-up compared with weekly PA (Figure 2 in Paper I). Leisure-time PA was not associated with mean SCL-5 scores among those who were more emotionally stable (EPQ-neuroticism score < 3) or more extraverted (EPQ-extraversion score ≥ 3) (Figure 2 in Paper I). However, the estimates were unadjusted and there were too few adolescents with severe SRVI to run fully adjusted analyses.

4.2 Paper II: Physical activity and symptoms of anxiety and depression symptoms in adults with and without visual impairments: The HUNT Study

The study aim of the second paper was to examine the association between leisure-time PA and symptoms of anxiety and depression in adults with SRVI and SRNI. The main analyses included 34,393 participants in the age group 20–67 years. Of those, 3719 (10.8%, mean age: 51.7 years) adults had SRVI and 30,674 (89.2%, mean age: 44.2 years) had SRNI. At follow-up, the prevalence of HADS-defined anxiety and depression (score ≥ 8) was almost twice as high among adults with SRVI as among adults with SRNI.

As shown in Table 2 in Paper II, among both adults with SRVI and adults with SRNI, fewer depression symptoms at follow-up was significantly associated with high baseline PA index scores compared with low PA scores after adjusting for possible confounders. For men with SRVI, leisure-time PA was not related to mean HADS-D scores. Moreover, our results showed that the association between PA and depression symptoms was weaker among those with SRVI than among those with SRNI, but the EEM was non-significant ($p = 0.34$). For women, the strength of the association between PA and depressive symptoms across categories of the visual impairment variable was in the opposite direction to that found among men. However, the EMM did not reach statistical significance ($p = 0.54$). The findings from the supplementary analyses

were consistent with those found in the main analyses. However, after adjusting for baseline HADS-D scores, the association between leisure-time PA and depression symptoms turned moderately towards the null, and became statistically non-significant for women with SRVI and women with SRNI (Table S5).

For both women and men, after adjusting for possible confounders, no significant associations were shown between PA and mean HADS-A scores among adults with SRVI and SRNI (Table 3 in Paper II). Similar results were shown in the supplementary analyses as those observed in the main analyses.

4.3 Paper III: Self-reported visual impairment, physical activity, and all-cause mortality: The HUNT Study

The aim of the third study was twofold. The first main aim was to examine the association between visual impairment and mortality, with and without adjustment for PA. The second main aim was to analyse the joint associations of visual impairment and PA with mortality. In total, 65,236 participants were included in the study. Of those, 11,074 (17.0%, mean age: 62.6 years) had SRVI and 54,162 (83.0%, mean age: 47.6 years) had SRNI. A total of 44.3% of adults with SRVI and 16.0% of adults with SRNI died during the follow-up period (median follow-up: 14.5 years, person-years: 947,031).

As shown in Table 2 in Paper II, after the adjustments, adults with SRVI had a significantly higher risk of all-cause mortality than adults with SRNI for those aged < 60 years (HR: 2.17, 95% CI: 1.77, 2.66) and 60–84 years (HR: 1.37, 95% CI: 1.17, 1.32), but not for those aged ≥ 85 years (HR 1.03, 95% CI: 0.96, 1.10). Additional adjustments for LPA and MHPA resulted in an increased RR in the age group < 60 years, whereas minor changes were observed in the age groups 60–84 years and ≥ 85 years (Model III in Table 2). In the cause-specific analyses,

adults with SRVI were more likely to die from cancer, cardiovascular diseases, and other causes compared with adults with SRNI. Fatal accidents and sudden deaths were not related to visual impairment (Table S2). Minor changes in the estimates were observed after handling missing data and addressing the possibility of misclassification of the covariates and the PA variables.

In the joint associations among adults in the age group < 60 years, an increased all-cause mortality risk of SRVI was shown among those who reported no LPA or MHPA compared with the risk among those who reported weekly hours of LPA or MHPA, after adjusting for age and gender (Tables 3 and 4 in Paper II). The observed EMM by leisure-time PA was indicated by a large, positive departure from additivity for LPA (RERI: 2.02, 95% CI: −0.45, 4.48) and for MHPA (RERI: 1.80, 95% CI: 0.85, 2.75). In the age groups 60–84 years and ≥ 85 years, similar but weaker associations were observed for the joint associations between visual impairment and PA with all-cause mortality, and the RERI estimates did not show any departure from additivity (Tables 3 and 4).

5.0 DISCUSSION

5.1 Summary of main findings

The three papers presented in this thesis include studies with prospective population-based designs, which were conducted to obtain knowledge about the association between PA and mental health among individuals with SRVI and SRNI, and the role of PA in the possible association between visual impairment and all-cause mortality. The main findings of this thesis are as follows:

1. *The findings presented in Papers I–III show mostly more symptoms of anxiety and depression and increased all-cause mortality risk among individuals with SRVI than among individuals with SRNI.*
2. *Mixed evidence was found of an association between leisure-time PA and symptoms of anxiety and/or depression symptoms among individuals with SRVI and SRNI (Papers I and II).* Leisure-time PA at baseline was significantly associated with fewer depression symptoms at follow-up among those with SRVI and SRNI. However, in individuals with SRVI, the associations were only statistically significant for adolescents with a more emotionally unstable or introverted personality (Paper I) and for adult women (Paper II). Leisure-time PA was not related to SCL-5 scores among adolescents with SRNI (Paper I) and to anxiety symptoms among adults with SRVI and SRNI (Paper II).
3. *Although the pattern and direction of the association between leisure-time PA and anxiety and/or depression symptoms differed somewhat between individuals with SRVI and SRNI, no significant risk-ratio modifications were observed (Papers I and II).*
4. *Leisure-time PA did not explain the observed association between visual impairment and all-cause mortality (Paper III).*

5. *The increased mortality risk among adults with SRVI was stronger among those who reported no weekly leisure-time PA compared with those who reported weekly hours of leisure-time PA, especially among adults aged < 60 years (Paper III).*

5.2 Methodological considerations

In this thesis, all of the population-based cohort studies had a prospective design, which offered an opportunity to assess the direction of relationships. The underlying goal of epidemiological research is to obtain a precise, valid, and generalizable estimate of the frequency of a disease or the effect of an exposure on the occurrence of a disease. Hence, it is important to minimize the amount of estimation errors. There are two common classes of errors: random errors and systematic errors. The opposite of random error is termed precise, while systematic error is the opposite of validity. In this section, I start by systematically discussing the precision of the estimates, and then discuss the validity of the estimates.

5.2.1 Precision (lack of random error)

To enhance the precision of estimates, it is has been recommended that studies should be designed to assess a large amount of information, distribute the information efficiently across strata of the exposure variable, and statistical analyses such as pooling and regression analyses should be performed (132, 133). Irrespective of the study efficiency, it is common for researchers to present a quantitative assessment of the remaining random error of their estimate. In this thesis, the quantification of random error was carried out by calculating 95% CIs. Hence, a narrow CI indicated a high precision of the estimate, and vice versa.

All three papers in this thesis used data obtained from The HUNT Study, a population-based study with a very large sample size, a relatively heterogeneous population, and a databank

that contains more than 5000 variables. In all three cases, various regression models were used to calculate effect estimates, and reduced study efficiency due to non-responses were handled by multiple imputation. Moreover, the prevalence of SRVI was high in both the adolescent part and the adult part of the HUNT Study. However, for Paper I, the most severe cases of SRVI were selected, leaving only 46 participants in that category.

In all three studies, based on a variety of different reasons, the main analyses were stratified or restricted on specific variables (age, gender, personality). The stratification or restriction resulted in low amount of information for some strata, indicated by wide CIs. Additionally, the mismeasurement of visual impairment, leisure-time PA, anxiety or depression symptoms, and other key variables might have contributed to the overall random inaccuracy. The use of objective methods might have led to greater precision of the estimates.

5.3.2 Validity (lack of systematic error)

In epidemiology, causal effects are commonly described in terms of contrasts of counterfactuals. In the counterfactual framework, population causal effects for a specific target population are defined as 'a contrast of a counterfactual population measure under two exposure conditions' (134).[6] Based on the definition of causal effects, bias is described as 'an expected difference between the estimand and the estimator used to estimate it' (135).

Validity may also be classified as internal validity and external validity. Internal validity is described as making valid inferences about the source population, whereas external validity refers to the extent to which to generalize the observed associations beyond the studied subjects (136). All studies experience threats to the validity of the estimates, and these threats may be

[6] The definition uses a dichotomized exposure, but exposures can be both categorical and continuous.

categorized as selection bias, information bias, and confounding bias. In the following sections, I describe the possible implication of these three types of biases for the effect estimates.

5.3.2.1 Selection bias

Selection bias occurs when the selection of participants depends on both the exposure and the likelihood of an outcome (136). In the research conducted for this thesis, in order to be included in the study population, the individuals had to be living in the county of Nord-Trøndelag and in a certain age group (Young-HUNT1: 13–16 years, HUNT2: ≥ 20 years) during the year of survey. Moreover, for Papers I and II, there were some exclusion criteria. Possible sources of bias are that persons who satisfied the criteria for participation were not enrolled in the study at baseline and that those who were enrolled at baseline later withdrew from the study or refused to provide information in parts of the study.

In all three substudies, the attendance rate was high at baseline (Young-HUNT1: 94.8%, HUNT2: 69.5%). For Papers I and II, even though the attendance rate was lower at follow-up than at baseline, it was still considered acceptable. However, based on the findings from previous studies addressing non-participation in both the adolescent part (113) and the adult part of the HUNT Study (137, 138), as well as on educated guesses, I assume that the associations studied for all the three papers were probably dependent on study participation. The study participants might have been healthier than the source population. in which case the observed associations could be weaker than the true associations.

A further possible source of selection bias is non-response bias. For example, participants with eating disorders may be more reluctant to respond to questions about their eating habits. In all three substudies, MICE was used to examine the possible impact of missing data due to non-response. MICE has been shown to be a more valid procedure than complete case analyses in

most cases, because it uses auxiliary variables (i.e. variables used to predict missing data) to obtain the MAR assumption (139). The estimates from the analyses using MICE resulted in both weaker and stronger associations, but did not affect the study conclusions.

In Paper III, the reported visual impairment may be associated with both survival up to baseline and all-cause mortality. The estimates can be biased (also known as collider bias) if visual impairment and an unmeasured mortality risk factor are both related to survival up to baseline (e.g. Figure 5). Controlling for all mortality risk factors is almost impossible (140), so collider bias is likely to be present in Paper III. However, the magnitude of the possible collider bias may be of less significance given that the effects of each factor in the possible relationship between visual impairment and mortality may be of a low to moderate strength.

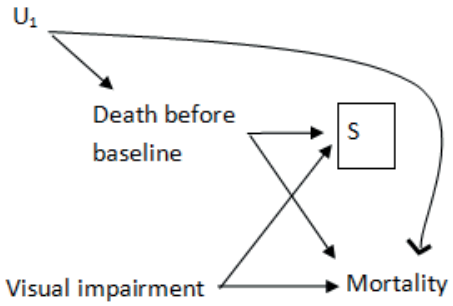


Figure 5. Directed acyclic graph (DAG) showing potential collider bias in the effect of visual impairment on mortality. S indicates selection up to study baseline; U_1 represents uncontrolled risk factor; the box indicates conditioning on that variable

5.3.2.2 Information bias

Information bias occurs when the measured variable deviates from its true value (141). For a categorical variable, measurement error is described as misclassification when the participant is

placed in the wrong category, and the errors could be related to measures of exposure, disease, or covariates. Misclassification may be either differential or non-differential (141). Differential misclassification refers to when the misclassification is dependent on the values of other variables. Otherwise, the classification error is termed non-differential misclassification (141). Most of the information collected during the research for this thesis was self-reported, and the accuracy of self-reported measurements may be dependent on factors such as age, gender, socio-economic status, and cultural background (142, 143).

In this thesis, I assume that participants with SRVI truly perceived that their vision was impaired. However, the questionnaire are not validated, and the way in which questions are constructed and administered may influence the proportion of people categorized as visually impaired (4). Haanes et al. (144) asked their participants to consider whether their eyesight was good, not so good, poor, or very poor/blind, while we asked our participants to describe the degree of their visual impairment. In our study, the SRVI category might have included a high proportion of false-positive cases due to its high prevalence (10.8–33.1%), and asking participants who wore lenses or eyeglasses about their degree of visual impairment might have resulted in a different group of people with SRVI. If a more "stricter" SRVI criterion have been used, a larger difference of the observed associations between individuals with SRVI and SRNI is expected. Nevertheless, sensitivity analyses revealed that using alternative operationalisations of SRVI led to similar results.

Due to the use of self-reported information and lack of diagnostic tools, it is important to emphasize that this study does not represent populations with ICD-defined visual impairment. The prevalence of ICD-defined visual impairment is generally low in Norway (29-31, 37). In this study, since the number of individuals with SRVI was high, I expect that the proportion of people with ICD-defined visual impairment in the SRVI category was generally low.

PA behaviours are notoriously difficult to measure accurately. The PA questionnaires included for Papers I–III assessed the participants' overall numbers of days or hours of leisure-time PA during an average week. Simple global PA questionnaires are concerned about the regularity of an individual's PA behaviours, and do not assess specific PA habits (142). In our study, most items in the PA questionnaires have been shown to have a good reliability and validity compared with other PA instruments and $VO_{2\text{-max}}$ measurements (118, 119). However, poor validity has been found for the LPA item included in the study (Papers II and III) (119). The reasons for the poor validity may be due to hours of LPA being more difficult to recall than hours of MHPA, and a possible ceiling effect due to the narrow range of the ordinal response scale. Based on the results from the validation studies (118, 119), the self-reported leisure-time PA, and especially hours of LPA, is assumed an underestimate of the participants' true weekly amount of leisure-time PA. The misclassification error of PA is expected to be non-differential, which yields in most cases a bias towards the null. In sensitivity analyses, and especially those in Papers II and III, the way in which the PA variables were treated in the analyses (continuous versus categorical, crude items versus PA index) had only a minor influence on the main results.

Anxiety and depression symptoms were assessed by two validated questionnaires, namely SCL-5 (121) and HADS (123). These two questionnaires cover core psychological symptoms of anxiety and depression, yet do not include behavioural and somatic symptoms (122). In Papers I and II, there may be some measurement error due to the episodic nature of some anxiety and depression symptoms. In addition, since anxiety and depression are heterogeneous conditions with a number of different symptoms (89, 145) and that the occurrence of symptoms may vary across subgroups (e.g. women and men), it is plausible that using other types of questionnaires might have resulted in different study results. The analyses including SCL-5 and HADS as categorical variables showed the same overall trend.

5.3.2.3 Confounding

In this thesis, I adopt the following understanding of a confounding factor (from the Latin *confundere*, to mix up): 'assuming that exposure precedes disease, confounding will be present if and only if exposure would remain associated with disease even if all exposure effects were removed, prevented, or blocked' (146). If important confounders have not been accounted for in the analyses, the actual exposure effect may be mixed with the effects of other variables.

In our study, suspected confounders of the association under study were identified from publications and a priori heuristics, (124) which included sociodemographic, psychosocial, lifestyle, health, and clinical characteristics. Variables related to study design were accounted for in sensitivity analyses, but did not affect the estimates. The possible confounding factor was controlled for by regression, restriction, or stratification. In most analyses, adjusting for possible confounding factors turned the association of interest moderately or largely towards the null. Nevertheless, it is plausible that our results were influenced by residual confounding bias due to: (1) the possibility of unknown confounders, (2) the fact that most covariates were based on self-reported data, (3) the problem with time-varying covariates in studies with long follow-up periods, and (4) the fact that there were not enough cases in some strata to perform fully adjusted analyses. If residual confounding was present, this might have made the association appear weaker or stronger than it truly was.

5.3.3 External validity (generalization)

External validity is the possibility to generalize the observed associations beyond the studied subjects (136). The issue of generalization is only important if the results for the restricted study group are valid. One way of making our findings more internally valid is to minimize concerns

about variations in characteristics of the study sample. The HUNT population has been shown to be quite homogeneous in terms of individual, social, cultural, and environmental factors (e.g. most residents live in rural areas and are of Caucasian origin) (112). Moreover, in all the substudies, the sample was restricted to a narrower range of characteristics. Nevertheless, caution should be exercised when drawing causal inferences about the study findings, given the difficulties of eliminating measurement error, selection bias, and residual confounding.

When distinguishing causal from non-causal associations in epidemiology, it is common to use a set of criteria published by Bradford Hill (147). Results with knowledge from diverse branches of evidence support our findings of a relationship between PA and depression symptoms (148, 149), as well as of a relationship between PA and all-cause mortality (90). Moreover, the substudies reported in this thesis have prospective designs, which is valuable for discovering the temporality of relationships. However, due to the descriptive nature of the included substudies, we cannot rule out that the reverse temporal relation may have occurred. Additionally, most of the observed associations were of a low to moderate strength and none of the substudies found any evidence of linear dose-response relationships. Although some of Hill's criteria were not obtained, the causal hypothesis of beneficial effects of leisure-time PA on depression symptoms and all-cause mortality in individuals with visual impairments seems to be a plausible explanation for the results observed in previous studies and in this study.

The setting is Nord-Trøndelag, Norway, in the years between 1995 and 2012. When it comes to generalization, the observed associations may not be generalized beyond those subjects who have been studied. Indeed, this may be relevant for this thesis since populations are more diverse in psychological and social phenomena than in biological phenomena.

5.4 Interpretation of the principle findings

Two substudies respectively reported in Papers I and II investigated the association between PA and symptoms of anxiety and/or depression among individuals with SRVI and SRNI. The third substudy, reported in Paper III, examined the role of PA in the association between visual impairment and all-cause mortality. In the following sections, general interpretations of our main results will be discussed. First, I will discuss the findings reported in Papers I and II, and then discuss of the results presented in Paper III.

5.4.1 Association between physical activity and anxiety or depression symptoms

It is a well-established fact that PA reduces symptoms of depression in general populations (88, 150). Reviews have also supported the notion that PA is associated with fewer anxiety symptoms, but the findings are less consistent than for depressive symptoms (89, 150). However, less is known about whom PA is beneficial for with regard to its possible effects on anxiety and/or depression symptoms (145). Given the differences in physical, psychological, and social factors between individuals with and without self-perceived visual impairment (11, 63), research studies should be conducted before the possible effects of regular PA on anxiety and depression symptoms observed in general populations can be generalized to individuals with SRVI.

In our prospective studies, lower depression scores at follow-up were found associated with leisure-time PA at baseline among individuals with SRVI. However, this association seemed to be complex, in which the observed associations were only statistically significant for adolescents with a more neurotic and introvert personality (Paper I) and for adult women (Paper II). Furthermore, leisure-time PA was not related to anxiety symptoms among adults with SRVI (Paper II). The results from our study are partly in accordance with those from previous studies for depression symptoms (106, 107), but not for anxiety symptoms (107). Nevertheless, due to

the observational nature of previous studies and our study, and the possible bidirectional relationship between PA and depression symptoms (151), it cannot be ruled out that depression symptoms might have caused lower PA.

Capella-McDonnall (106) observed that the associations between PA and depression symptoms were more strongly associated among elderly adults with self-reported dual sensory loss than among elderly adults without self-reported dual sensory loss. The results of the studies included in this thesis show that the strength of the associations between PA and anxiety and/or depression symptoms differed non-significantly between those with SRVI and SRNI, but the direction and pattern of the EMM varied across subgroups (Paper I and II). Thus, based on our study findings, there is no clear evidence that visual impairment modifies the possible effects of leisure-time PA on symptoms of depression.

In Papers I and II, the effect sizes of the relationships are reported as modest in most of the analyses. For example, compared with women with SRVI who reported low baseline PA (Paper II), a 0.80 lower mean HADS-D score at follow-up was observed at for women with SRVI who scored high on the PA index. The fact that the observed associations may be explained by the possibility that depression symptoms caused lower PA, may in turn reduce the public health significance of our study results, since the effect of PA on depression is of greater interest than the possible reverse effect. However, considering the high burden of depression symptoms in the populations experiencing benefits from regular PA (e.g. women with SRVI), even low effect sizes may have public health significance.

To date, no studies have addressed how PA 'dose' is associated with anxiety and/or depression symptoms in populations with visual impairments. In adolescents with severe SRVI and a more emotionally unstable or introvert personality, weekly participation in leisure-time MHPA at baseline was associated with lower SCL-5 scores four years later (Paper I), with few

additional benefits for more weekly days of leisure-time PA (results not shown). Among women with SRVI, high scores on the baseline PA index were associated with fewer depression symptoms at follow-up compared with moderate and low scores on the PA index (Paper II). In Paper II, scoring high on the PA index is comparable with the amount of PA recommended to maintain functioning and health (6). However, if there was an underestimation of leisure-time PA in Papers I and II, higher PA 'dose' may be needed in the real world to obtain reductions in core psychological symptoms of depression.

In Paper II, the reported lack of associations between leisure-time PA and anxiety symptoms among adults with SRVI and SRNI may be related to the observational nature of our study. While randomized controlled trials (RCTs) of adult populations have found that exercise is associated with fewer anxiety symptoms (89), mixed results have been shown in observational studies with prospective designs (152-154). Compared with RCTs, observational studies are less suitable to address cause and effect because the temporal relationship between PA and anxiety symptoms is less clear. Nevertheless, Stonerock et al. (89) stated in their systematic review that there is not enough evidence yet to support the hypothesis of a direct effect of PA on trait anxiety.

The lack of associations between PA and SCL-5 scores among adolescents with SRNI are discussed in the substudy reported in Paper I.

5.4.1.3 The association between visual impairment, physical activity, and all-cause mortality

The second main aim of this thesis was to examine the role of leisure-time PA in the association between SRVI and all-cause mortality. It has already been shown that visual impairment is a significant predictor of premature mortality (77). However, there are indications that the association may be related to the individual's PA levels (109, 110), but no studies have tried to replicate the earlier findings.

The results reported in Paper III show that adults with SRVI had a significantly increased all-cause mortality risk compared with adults with SRNI, and the risk was particularly strong among those in the age group < 60 years. Additionally, adjusting for leisure-time PA changed the risk estimates either further away from the null or no resulted in no changes, implying that PA did not explain the observed association between visual impairment and all-cause mortality. This result is not in line with some of the findings made by Kulmala et al. (109). However, comparison of the results of Kulmala et al.'s study and our study is difficult due to many methodological differences, such as differences in the study size and the assessment of visual impairment. In light of our study results, it could be speculated that other biological, physiological, psychosocial, and behavioural mechanisms that do not involve PA may explain the increased mortality risk of individuals with visual impairments (81, 82). Nevertheless, as well demonstrated by Robins and Greenland (155), statistical mediation analysis requires the fulfilment of very strong underlying assumptions in order to obtain valid estimates.

Low PA in adults with visual impairments may modify their higher risk of mortality-related factors, including functional limitations (48, 63), low physical fitness (11), mental health problems (72, 156), co-morbid somatic conditions (54-58), and social isolation (50). In agreement with the results from a previous study (110), our study findings showed that leisure-time PA is associated with a lower all-cause mortality risk, irrespective of the adult's visual impairment status. Furthermore, our study results add to the current knowledge base by showing an increased mortality risk of SRVI when combined with no leisure-time PA, and especially with no MHPA among those in the age group < 60 years. However, due to the descriptive nature of our study, the observed departure from additivity might have been a consequence of other factors than no leisure-time PA, such as ongoing health problems and biological aging (81, 82).

The results from the study showed that visual impairment was related to some lifestyle-related causes of death (e.g. cancer and cardiovascular diseases). However, because of the close link between visual impairment, PA, and falling (157), it was surprising to find that fatal accidents and sudden deaths, which included deaths from falls and injuries, were not related to visual impairment. Two plausible explanations for the lack of associations may be that there were few deaths from fatal accidents and few sudden deaths and that falls and injuries might have been a part of the etiology, but not the primary cause of death.

5.5 Implications for practice and policy

In this section, some implications for practice and policy are being discussed. Good health is an important feature of the individual's general quality of life. In general populations, increasing individuals' PA levels have been demonstrated as widely applicable, feasible, and effective strategies to modify their functioning, health, and well-being in favourable ways, as well as being associated with a low risk of experiencing adverse events.

The results from our study contribute to the understanding about how leisure-time PA can be used in disease prevention and health promotion among populations of adolescents and adults with visual impairments, and suggest that initiatives aimed at making PA behaviours a general habit may be important for reducing their risk of depression symptoms and premature mortality. Less clear evidence is shown for PA in the reduction of anxiety symptoms. Many factors could possibly influence the health of people with visual impairments. An implication of this may be that rather than targeting specific factors, a more general approach should be considered when designing health strategies and that PA should be an integral part of this approach.

For individuals with vision loss, the greatest obstacles to become physically active are the barriers to participation in organized and unorganized PA. Therefore, strategies that break down

such barriers for individuals with visual impairment are recommended, and the strategies should be made on a national, regional, or community level. Examples of possible initiatives include the following: public sports clubs could include more activities that are adapted for people with visual impairments, education about visual impairment for exercise instructors in school settings and public sports clubs, financial support for the production of vision guides and PA-related assistive devices, transportation to and from exercise facilities, universal designs for exercise facilities, and public awareness campaigns to break down the stigma of visual impairment.

5.6 Implications for future research

To gain more knowledge about how and why PA may improve the health of individuals with visual impairments, the following recommendations for future research are suggested. Future studies should be encouraged to use prospective RCTs in order to identify when and how PA behaviours are initiated and/or maintained, how much PA is performed, and when the intermediate factors occur. Due to the randomization process, the intervention groups should be similar to those in the comparison group, to make it easier to approach cause and effect. Studies should be pragmatic in order for the interventions to be easily implemented in the real world. However, in cases where RCTs are impractical (e.g. examining the association between PA and mortality), observational studies with restricted groups of individuals with visual impairments are needed. Visual impairment is a heterogeneous condition and future studies are encouraged to define the target population clearly, such as by describing the aspect of vision loss being assessed, as well as the onset-age, cause, and severity of vison loss.

Future research should also prioritize obtaining accurate estimates of PA behaviours and various health outcomes in representative populations of individuals with visual impairments (e.g. the percentage of those with visual impairments who meet the PA recommendations).

6.0 CONCLUSIONS

Regular PA is considered a 'best buy' in public health because of its importance for maintaining functioning, good health, quality of life, and longevity. It has also been increasingly recognized that PA may be one out of many factors related to the health of individuals with visual impairments. However, this is a developing research field, and the quality of previous studies including samples of individuals with visual impairments has been low. Therefore, it is difficult to draw strong conclusions, as well to compare the results across the different studies.

Overall, the results from the epidemiological substudies reported in this thesis supported that leisure-time PA may be beneficial for the health of those with visual impairments, as well as being beneficial for both adolescents and adults. More specifically, the findings showed that baseline leisure-time PA was associated with a lower risk of psychological depression symptoms at follow-up, but the associations were present for certain subgroups of SRVI only. Furthermore, in adults with SRVI, the results were less clear of an association between PA and anxiety symptoms. Lastly, it was found that SRVI was significantly associated with an increased all-cause mortality risk when combined with no leisure-time PA, especially among those in the age group < 60 years. No evidence was found of leisure-time PA being a mediating factor of the possible relationship between visual impairment and all-cause mortality.

The results from this thesis indicate that PA may be one of many components to be used in the prevention of depression symptoms and premature mortality among adolescents and adults with visual impairments. Nevertheless, the study findings should be tested by well-designed interventions studies before drawing any causal inferences.

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PAPERS I–III

Research Article

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The effect of physical activity on mental health among adolescents with and without self-reported visual impairment: The Young-HUNT Study, Norway

Audun Brunes
Department of Neuroscience, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

W Dana Flanders
Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA

Liv Berit Augestad
Department of Neuroscience, Norwegian University of Science and Technology (NTNU), Trondheim, Norway;
Department of Visual Impairment, Statped Midt, Melhus, Norway

Abstract
The purpose was to study the effect of physical activity (PA) on mental health according to self-reported vision categories among adolescents. The study was conducted in Nord-Trøndelag, Norway, during the period 1995–1997, with a follow-up 4 years later. Self-reported measurements were used to assess PA and vision at baseline, and mental health problems and well-being at follow-up. The main linear regression analyses included 1417 adolescents between the age of 12 and 17 years, of which 46 had reported visual impairment. Among those reporting no impairment, conducting <1 day per week of PA was significantly associated with having lower levels of well-being at follow-up compared to those conducting ⩾1 day of PA. Among those reporting visual impairment, the mental health benefits of conducting weekly PA compared with conducting non-weekly PA were observed only among those who were more emotionally unstable or introvert at baseline. In conclusion, further longitudinal studies are warranted to examine whether the mental health responses of PA may be dependent on the adolescent's vision status.

Corresponding author:
Audun Brunes, Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), Trondheim NO-7491, Norway.
Email: audun.brunes@ntnu.no

Keywords
Adolescents, mental health problems, physical activity, population-based study, prospective design, vision, visual impairment, well-being

Introduction

Adolescence is a sensitive period of life, and adolescents living with visual impairment not only have to cope with the same developmental challenges as sighted peers but also with difficulties related to visual functioning (Pfeiffer & Pinquart, 2011). Moreover, factors associated with higher risks of lifestyle-related disorders either start or intensify in this life stage, and the way that adolescents handle the challenges may impact health-related outcomes later in life (Sawyer, Drew, Yeo, & Britto, 2007).

One of the major health-related challenges faced during adolescence is the more risk factors related to mental health (e.g. substance abuse), and up to one in five adolescents may have a mental health problem that is severe enough to be classified as a mental disorder (Merikangas, Nakamura, & Kessler, 2009). In the association between vision status and mental health, studies have found that adolescents with visual impairment have reported a lower quality of life compared with sighted adolescents (Chadha & Subramanian, 2011). However, inconsistent results have been found for well-being and symptoms of anxiety and depression (Huurre & Aro, 1998; Kef, & Deković, 2004; Pinquart & Pfeiffer, 2011, 2012).

Another health-related concern is the higher prevalence of physical inactivity in adolescents compared to children in the general population (Armstrong & Welsman, 2006; Kolle, Steene-Johannessen, Andersen, & Anderssen, 2010) and in populations of individuals with visual impairment (Kozub & Oh, 2004). Furthermore, the physical activity (PA) levels of children and adolescents with visual impairment are evidently lower than those of children and adolescents with no visual impairment (Kozub & Oh, 2004; Houwen, Hartman, & Visscher, 2009). The PA levels of adolescents with visual impairment may be explained by the fact that they are likely to experience multiple barriers to their involvement in such activities and some of the barriers stem directly from having a visual impairment (Lieberman, Ponchillia, & Ponchillia, 2013).

The lower levels of PA found among adolescents with visual impairment may be related to their mental health status. The association between PA and mental health has been widely investigated in adolescent populations in general (Ahn & Fedewa, 2011; Camero, Hobbs, Stringer, Branscum, & Taylor, 2012), but has not been studied among adolescents with visual impairment. All studies from Westernized and non-Westernized countries have included adults and used either a cross-sectional design (Di Cagno et al., 2013; Holbrook, Caputo, Perry, Fuller, & Morgan, 2009; Labudzki & Tasiemski, 2013; Valliant, Bezzubyk, Daley, & Asu, 1985) or a qualitative design (Pereira, Osborne, Cabral, & da Silva, 2011). Hence, population-based studies with prospective designs and including a sample of adolescents are needed.

The underlying goal of our study was to examine the effect of leisure-time PA on symptoms of mental health problems and subjective well-being (SWB) among adolescents with self-reported no impairment (SRNI) and self-reported visual impairment (SRVI). The International Classification of Disability and Functioning and Health: Children and Youth Version (ICF-CY) framework was used as a theoretical framework and for terminology (World Health Organization, 2007).

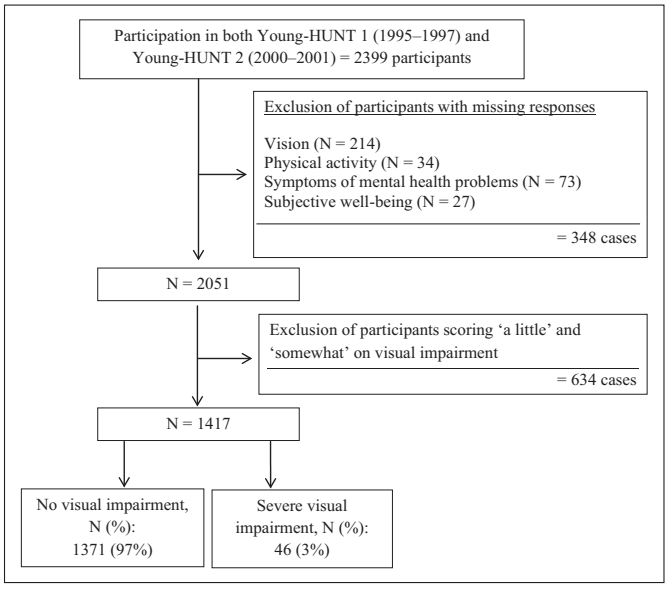

Figure 1. Flow chart of the subject selection and exclusion process.

Materials and methods

Design and sample

Data were collected from the adolescent part, Young-HUNT, of a prospective population-based health study carried out in Central Norway, namely, the Nord-Trøndelag Health Study, also known as the HUNT Study (Holmen et al., 2014). During the period 1995–1997, all students attending middle school (seventh to ninth grade) and high school (first to third grade) were invited to participate in the first wave of the survey (Young-HUNT 1). All students, regardless of any impairment status, were integrated in state schools in Norway at the time of the study. A questionnaire was handed out at school and completed during one school hour. Help was provided by teachers to those struggling with reading the questions. The questions covered public health issues such as mental health, somatic health, and health behaviors. Within one month of the completion of the questionnaire, a medical examination of all eligible students was conducted at the school by a qualified nurse. A total of 8983 (88%) adolescents completed the questionnaire in the first wave of the study.

The second wave of the Young-HUNT Study was conducted in the period 2000–2001, and the study protocol was similar to that of the Young-HUNT 1 Survey. The youngest participants from the first wave of the study were invited (seventh and eighth grade at baseline) to participate in the follow-up. Among the 3124 eligible adolescents, 2399 (77%) completed the questionnaire.

As shown in Figure 1, a total of 348 participants were excluded from the analyses due to missing information on vision, PA, or mental health. A further 634 participants who reported either "a

little" or "somewhat" to the question about vision impairment were excluded in order to include adolescents with the most severe visual impairment and compare them to their contrast, namely, no impairment. Therefore, the main analyses included 1371 adolescents who had reported no impairment and 46 adolescents who had reported severe visual impairment.

Measures

Vision. Self-reported measures of vision have been used more frequently in large studies (Whillans & Nazroo, 2014). Compared to direct measures of vision, self-reported measures have the advantage of low costs, being less prone to oversimplification of vision status, and providing a more complete understanding of an individual's interpretation of visual abilities (Whillans & Nazroo, 2014). In our study, the presence and severity of visual impairment were assessed at baseline by a single question: "How would you describe your visual impairment?" The question had four response alternatives: "no," "a little," "somewhat," and "severely." The study included participants with SRNI with respect to vision and SRVI that was severe.

Physical activity. Leisure-time PA is activity undertaken in the individual's spare time "that leads to any substantial increase in the total daily energy expenditure" (Bouchard, Blair, & Haskell, 2012, p. 12). In Young-HUNT 1 and 2, days and hours of moderate to high intensity of weekly leisure-time PA were measured. The questions were derived from the World Health Organization's Health Behavior in School-aged Children (WHO HBSC) study (King, Wold, Tudor-Smith, & Harel, 1996). For our study, frequency of PA was chosen for the main analyses because the question was found to yield slightly more reliable and accurate responses than the question about hours of PA (Rangul, Holmen, Kurtze, Cuypers, & Midthjell, 2008). Frequency of PA has been found to have a substantial reliability ($r = .73$) and fair validity compared with $VO_{2\text{-peak}}$ ($r = .39$) among Norwegian adolescents (Rangul et al., 2008).

The item includes an 8-point response scale: "never," "less than once a month," "not every 14th day, but more than once a month," "not every week, but at least once every two weeks," "1 day a week," "2–3 days a week," "4–6 days a week," and "every day." For our study, a category named "non-weekly physical activity" was created by including those reporting "not every week, but at least once every two weeks" or being physically active less frequently. The category "weekly physical activity" included those who responded that they were physically active 1 day per week or more frequently.

Mental health. Tudor (1996) claimed that mental health is divided into two separated and correlated dimensions: a mental illness dimension and a mental well-being dimension. In our study, the mental illness dimension of mental health was assessed using the Hopkins Symptom Checklist (SCL). The SCL was used to measure the combined symptoms of anxiety and depression at baseline and follow-up (Strand, Dalgard, Tambs, & Rognerud, 2003). The scale assessed how each participant had felt in the past 14 days and the participant reported on a 4-point Likert scale, ranging from 1 (*not at all bothered*) to 4 (*extremely bothered*). The 25-item version of the checklist (SCL-25) has been found to identify 50% of anxiety and depression cases as to the diagnoses assessed by the Composite International Diagnostic Interview (Tambs & Moum, 2007). For our study, a shortened 5-item version (SCL-5) was included at baseline and follow-up that correlates highly ($r = .92$) with the 25-item scale (Tambs & Moum, 2007). In accordance with a recommendation by Strand et al. (2003), sum scores from the five items were added up and divided by the number of items. The sum score had a Cronbach's alpha of .82.

SWB scale was included at both time points and it assessed the mental well-being dimension of mental health. In accordance with a recommendation by Diener, Oishi, and Lucas (2009), our SWB scale included questions of affect and satisfaction with life. The SWB scale had the following three items: (1) "When you think about the way your life is going at present, would you say that you are by and large satisfied with life or are you mostly dissatisfied?"; (2) "In general, do you feel strong and in a good mood or tired and worn out?"; and (3) "Are you generally happy or sad?" The responses for each item were measured on a 7-point Likert scale. A sum score was created by adding up the scores from the three questions and then the summarized scores were divided by three. A higher score on the sum score indicated higher levels of well-being. The sum score had a Cronbach's alpha of .78.

Covariables. All included covariables were assessed at baseline (1995–1997). Possible confounding were identified from existing literature (Bauman et al., 2012; Diener et al., 2009; Miettinen & Cook, 1981; Sallis, Prochaska, & Taylor, 2000; Strauss, Rodzilsky, Burack, & Colin, 2001) and a priori reasoning. We identified the following variables from the study as potential confounders: gender, age, smoking status, alcohol consumption, age and gender-specific body mass index (Cole, Bellizzi, Flegal, & Dietz, 2000; Cole, Flegal, Nicholls, & Jackson, 2007), personality, self-esteem, self-rated health, feeling lonely, involved in sports, and chronic somatic diseases. Chronic somatic diseases comprised asthma, cardiovascular diseases, kidney disease, pulmonary disease, bowel disease, rheumatism, allergy, epilepsy, musculoskeletal disease, cancer, cerebral palsy, nervous disease, and other unspecified chronic diseases. Those who did not report any diseases were coded as "no."

Statistical methods

Generalized linear models (GLMs) were used to estimate the association between PA levels measured at baseline and the SWB scale measured at follow-up. The estimated beta coefficient and its standard error were used to calculate the 95% confidence interval (CI). Model fit was evaluated using residual plots. The SWB variable had a slightly negatively skewed distribution (−.47), but was used as an untransformed variable in the model since the results were similar to those obtained using SWB as a transformed variable.

A generalized linear regression model with a gamma distribution and log-link relationship was used to estimate associations between the SCL-5 score at follow-up with baseline levels of PA because the SCL-5 scores were right-skewed. Model fit was examined using residual plots.

Treating PA either as a dichotomous variable (<1 day per week, ⩾1 day per week) or as a continuous variable had identical results with the SWB scale. For SCL-5 among those with SRNI, the association was somewhat weaker for PA as a linear term as to PA included as a categorical variable. We chose to report the results of the analyses using PA as a categorical variable and ⩾1 day per week was used as a reference category. All two-way statistical interactions were tested between the exposure and each covariate. Additional analyses were conducted that included vision as a product term with PA in the regression model.

Multiple imputation chained equations (MICE) were used to evaluate potential biases in the main analyses including complete data. The MICE yielded complete data sets for the respondents that had no missing data on primary variables at baseline and were eligible to participate at follow-up ($N = 2028$). In total, 50 data sets were imputed with 10 cycles for each data set in order to fulfill the variability criteria set by White, Royston, and Wood (2011). The imputed data sets were then averaged using Rubin's rules (Rubin, 2004). More details regarding the imputation model are found in Appendix 1.

To check the robustness of the main analyses, three types of sensitivity analyses were conducted. First, since power might have been an issue in the SRVI category, we included all participants who responded "somewhat" to the question about visual impairment at baseline in the SRVI category ($N = 222$). Second, since PA may change in time, the main analyses were supplemented by running PA measured at follow-up (2000–2001). Third, we used a logistic model as an alternative statistical model to study the association of having possible mental health problems or having low levels of well-being with baseline PA category (<1 time per week, ⩾1 time per week). Accordingly, we dichotomized the SCL-5 scale (<2, ⩾2) and the SWB scale (⩾4, <4), based on the coding used in earlier literature (Fløtnes, Nilsen, & Augestad, 2011; Strand et al., 2003).

For most analyses, separate analyses were conducted for those with SRNI and SRVI. An alpha level below .05 or a 95% confidence level that did not include the zero value was considered statistically significant. Statistical Package for the Social Sciences (SPSS) Version 21 (IBM Corp., New York, USA) was used for the main statistical data analyses and sensitivity analyses, while the MICE were carried out using Stata Version 13 (Stata Corp., College Station, TX, USA).

Ethics

All participants gave their written consent to take part in the study. For pupils younger than 16 years, written consent was obtained from one of their parents or guardians. The study was approved by the regional medical ethical committee (Regional Etisk Komite for Medisinsk og Helsefaglig Forskning, REC). The HUNT Research Centre granted us permission to analyze the data from Young-HUNT 1 and 2.

Results

Table 1 lists the numbers and percentages relating to baseline characteristics, mental health, and PA among adolescents with SRNI and SRVI. Results from two-tailed independent *t*-tests showed that those with SRNI had non-significantly fewer symptoms of anxiety and depression at follow-up compared to those with SRVI ($M = 1.49$ vs 1.64, df = 1415, $p = .06$, 95% CI = [−0.30, 0.01]). There was no significant difference in well-being scores measured in Young-HUNT 2 among those with SRNI compared to those with SRVI ($M = 5.25$ vs 5.07, df = 1415, $p = .22$, 95% CI = [−0.11, 0.45]).

In the unadjusted regression analyses of the entire study sample, the associations between PA and mental health were similar within levels of self-reported vision for both symptoms of mental health problems ($\chi^2(1, 1413) = 1.93$, $p = .17$) and well-being ($F(1, 1413) = 0.01$, $p = .91$). In the vision-specific analyses, those with SRNI and reporting non-weekly PA had a significantly higher unadjusted mean score on the SCL-5 ($\beta = .08$, $p = .01$, 95% CI = [0.02, 0.14]) and a significantly lower unadjusted mean score on the SWB scale ($\beta = -.45$, $p < .001$, 95% CI = [−0.61, −0.29]) compared with those with SRNI and reporting weekly PA. Among adolescents with SRVI, similar associations were seen as among adolescents with SRNI for the SCL-5 (unadjusted $\beta = .22$, $p = .04$, 95% CI = [0.02, 0.43]), but for the SWB scale the association was statistically insignificant (unadjusted $\beta = -.41$, $p = .17$, 95% CI = [−1.00, 0.18]).

As shown in Tables 2 and 3, the adjusted betas turned more towards the null compared to the unadjusted betas. Moreover, the association between PA and SCL-5 became non-significant in the adjusted models for those with SRNI and SRVI. There were too few adolescents with SRVI to run full-adjusted models, even in the models using multiple imputations.

Table 1. Number and percentage of baseline characteristics according to self-reported vision categories.

Characteristics	Self-reported no impairment (*N* = 1371)	Missing	Self-reported visual impairment (*N* = 46)	Missing	Pearson's χ^2 test
	N (%)	*N* (%)	*N* (%)	*N* (%)	
Gender: girls/boys	674 (49.2)/697 (50.8)	0 (0.0)	25 (54.3)/21 (45.7)	0 (0.0)	0.48, $p = .49$
Age (years): 12–14/15–17	992 (72.4)/379 (27.6)	0 (0.0)	34 (73.9)/12 (26.1)	0 (0.0)	0.05, $p = .82$
Current smoking status: no/yes	406 (29.6)/133 (9.7)	832 (60.7)	9 (19.5)/9 (19.6)	28 (60.9)	5.88, $p = .02$
Alcohol in past 14 days: no/yes	493 (36.0)/245 (17.9)	633 (46.2)	15 (32.6)/11 (23.9)	20 (43.5)	0.94, $p = .33$
Chronic health problem: no/yes	1196 (87.2)/175 (12.8)	0 (0.0)	38 (82.6)/8 (17.4)	0 (0.0)	0.85, $p = .36$
Living with both parents: no/yes	245 (17.9)/1126 (82.1)	0 (0.0)	12 (16.1)/34 (73.9)	0 (0.0)	0.01, $p = .93$
Reading problems: no/yes	1158 (84.5)/157 (11.5)	56 (4.1)	34 (73.9)/10 (21.7)	2 (4.3)	4.47, $p = .03$
Body mass index:[a] Underweight	73 (5.3)	33 (2.4)	1 (2.2)	0 (0.0)	8.05, $p = .01$
Normal weight	1064 (77.6)		31 (67.4)		
Overweight	201 (14.7)		14 (30.4)		
Feeling lonely: No or rarely	1074 (78.4)	5 (0.4)	25 (54.4)	0 (0.0)	25.25, $p < .001$
Sometimes	249 (18.2)		14 (30.4)		
Often	43 (3.1)		7 (15.2)		
EPQ–Neuroticism scale:[b] <3/≥3	913 (66.6)/358 (26.1)	100 (7.3)	21 (45.7)/21 (45.7)	4 (8.7)	9.44, $p = .002$
EPQ–Extroversion scale:[b] <3/≥3	84 (6.1)/1131 (82.5)	156 (11.4)	6 (13.0)/38 (82.6)	2 (4.3)	2.89, $p = .09$
Rosenberg self-esteem scale:[b] <2.5/≥2.5	255 (18.6)/1076 (78.5)	40 (2.9)	7 (15.2)/38 (82.6)	1 (2.2)	0.37, $p = .55$
Subjective well-being scale:[c] <4.0/≥4.0	98 (7.2)/1273 (92.9)	0 (0.0)	5 (10.9)/41 (89.1)	0 (0.0)	0.92, $p = .34$
Hopkins Symptom Checklist:[d] <2.0/≥2.0	1262 (92.0)/109 (8.0)	0 (0.0)	35 (76.1)/11 (23.9)	0 (0.0)	14.63, $p < .001$
Sports participation: no/yes	426 (31.1)/944 (68.9)	1 (0.1)	23 (50.0)/23 (50.0)	0 (0.0)	7.69, $p = .02$
Weekly MHPA: <1 hr	184 (13.4)	0 (0.0)	11 (23.9)	0 (0.0)	5.96, $p = .05$
1–3 hr	581 (42.4)		23 (50.0)		
≥4 hr	606 (44.2)		12 (26.1)		
Weekly MHPA: <1 day	147 (10.7)	0 (0.0)	14 (30.4)	0 (0.0)	10.91, $p = .004$
1–3 days	777 (56.7)		25 (54.4)		
≥4 days	447 (32.6)		7 (15.2)		

MHPA: moderate-to-high intensity physical activity; EPQ: Eysenck Personality Questionnaire.
[a]Age- and gender-specific cut-offs (Cole, Bellizzi, Flegal, & Dietz, 2000; Cole, Flegal, Nicholls, & Jackson, 2007).
[b]Cut-off at midpoint of the scale and higher scores indicate higher levels of that particular characteristic.
[c]Cut-off according to previous literature (Fløtnes, Nilsen, & Augestad, 2011). Higher scores indicate higher levels of well-being.
[d]Cut-off according to previous literature (Strand, Dalgard, Tambs, & Rognerud, 2003). Higher scores indicate more symptoms of mental health problems.

Table 2. Results of general linear regression analyses for well-being (Young-HUNT 2) in relation to physical activity (Young-HUNT 1) according to self-reported vision categories.

Days of MHPA[a]	Subjective well-being (SWB) scale						
	Self-reported no impairment				Self-reported visual impairment		
	Model I (*N* = 1371)	Model II (*N* = 1173)	Model III (*N* = 1115)	MICE I (*N* = 1963)	Model I (*N* = 46)	Model II (*N* = 40)	MICE II (*N* = 65)
	β [95% CI]	β [95% CI]	β [95% CI]	β [95% CI]	β [95% CI]	β [95% CI]	β [95% CI]
Non-weekly	−.43 [−0.58, −0.27]	−.35 [−0.50, −0.19]	−.21 [−0.39, −0.03]	−.17 [−0.27, −0.06]	−.21 [−0.87, 0.45]	−.11 [−0.78, 0.55]	−.16 [−0.60, 0.32]
Weekly	Reference	Reference	Reference	Reference	Reference	Reference	Reference

CI: confidence interval; MHPA: moderate-to-high intensity physical activity; MICE: multiple imputation chained equations.
[a]Non-weekly PA is coded as less than 1 day per week of MHPA and weekly PA is coded as 1 day per week or more of MHPA.
Model I: adjusted for age and gender.
Model II: Model I + extroversion, neuroticism, chronic somatic diseases (no, yes), and baseline SWB score.
Model III: Model II + body mass index (underweight, normal weight, overweight), feeling lonely (no/rarely, sometimes, often/very often), self-rated health (poor/not so good, good, very good), self-esteem (<2.5, ⩾2.5), and involved in sports (no, yes).
MICE I: Model III.
MICE II: Model II.

Table 3. Results of adjusted gamma regression analyses for symptoms of mental health problems (Young-HUNT 2) in relation to physical activity (Young-HUNT 1) according to self-reported vision categories.

Days of MHPA[a]	Hopkins symptoms checklist (SCL-5)						
	Self-reported no impairment				Self-reported visual impairment		
	Model I (*N* = 1371)	Model II (*N* = 1271)	Model III (*N* = 1115)	MICE I (*N* = 1963)	Model I (*N* = 46)	Model II (*N* = 40)	MICE II (*N* = 65)
	β [95% CI]	β [95% CI]	β [95% CI]	β [95% CI]	β [95% CI]	β [95% CI]	β [95% CI]
Non-weekly	.06 [0.01, 0.12]	.06 [0.01, 0.11]	.05 [−0.01, 0.11]	.03 [−0.01, 0.08]	.10 [−0.08, 0.28]	.09 [−0.06, 0.25]	.18 [−0.02, 0.38]
Weekly	Reference	Reference	Reference	Reference	Reference	Reference	Reference

CI: confidence interval; MHPA: moderate-to-high intensity physical activity; MICE: multiple imputation chained equations.
[a]Non-weekly PA is coded as less than 1 day per week of MHPA and weekly PA is coded as 1 day per week or more of MHPA.
Model I: adjusted for age and gender.
Model II: Model I + extroversion, neuroticism, chronic somatic diseases (no, yes), and baseline SWB score.
Model III: Model II + body mass index (underweight, normal weight, overweight), feeling lonely (no/rarely, sometimes, often), self-rated health (poor/not so good, good, very good), self-esteem (<2.5, ⩾2.5), and involved in sports (no, yes).
MICE I: Model III.
MICE II: Model II.

In this study, personality was measured using the Eysenck Personality Questionnaire–Neuroticism (EPQ-N) scale and Eysenck Personality Questionnaire–Extroversion (EPQ-E) scale. Each scale was dichotomized into a binary variable using the mid-value of the scale (Brunes, Augestad, & Gudmundsdottir, 2013). We observed a two-way statistical interaction between PA and the EPQ-N for both the SCL-5 ($\chi^2(1, 38) = 8.99$, $p = .03$) and the SWB scale ($F(1, 38) = 3.34$, $p = .07$). Moreover, a two-way statistical interaction was found between PA and the EPQ-E with the SCL-5 ($\chi^2(1, 40) = 9.92$, $p = .02$) and the SWB scale ($F(1, 40) = 9.88$, $p = .009$). Among adolescents with SRVI and classified as being more emotionally unstable (EPQ-N score ⩾3) or as being more introverted (EPQ-E score < 3), scoring non-weekly PA was significantly associated with more mental health problems and lower levels of well-being than scoring weekly PA (Figure 2). No other important two-way interactions were observed for SRNI or for SRVI.

We checked the robustness of the results in our sensitivity analyses. First, the association between PA and mental health was not significant after including participants who responded "somewhat" to the question about visual impairment in the SRVI category (results not shown). Second, PA measured in Young-HUNT 2 was significantly associated with concurrent mental

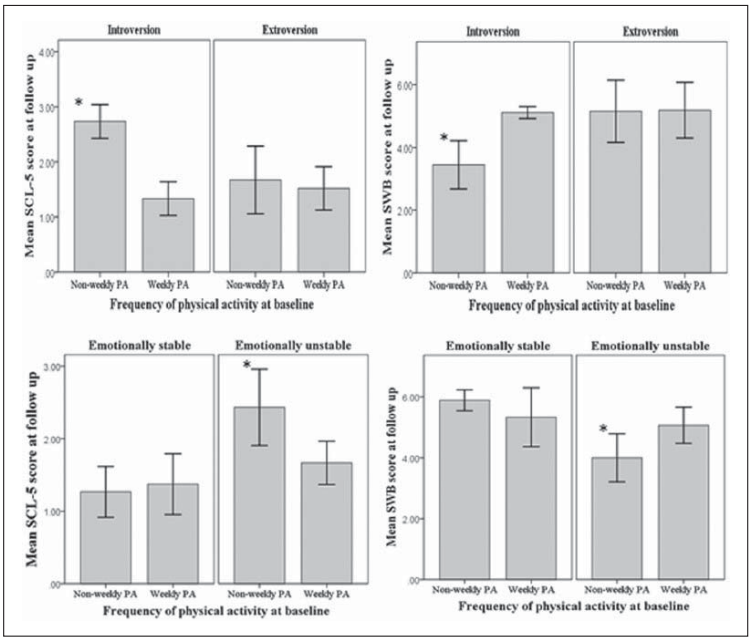

Figure 2. Crude mean mental health scores (SCL-5 and SWB) at follow-up with baseline physical activity according to personality traits among adolescents reporting severe visual impairment.
SCL-5: 5 items from the Hopkins Symptom Checklist; SWB: Subjective Well-Being scale; Introversion: below a score of 3 on the Eysenck Personality Questionnaire (EPQ)–Extroversion scale; Extroversion: EPQ–Extroversion score ⩾3; Emotionally stable: EPQ–Neuroticism score <3; Emotionally unstable: EPQ–Neuroticism score <3; Non-weekly PA: physically active less than 1 day per week; Weekly PA: physically active 1 day or more per week.
Mean value and ±1 standard deviation.
*$p < .05$ and was obtained from linear regression models.

health status (SCL-5 and SWB score) also measured in Young-HUNT 2 only among adolescents with SRNI (results not shown). Third, in the full-adjusted logistic model among those with SRNI, the risk of mental health problems (SCL-5 score ⩾2.0) was 1.31 ($p = .36$, 95% CI = [0.74, 2.30]) and the risk of scoring below <4.0 on the SWB scale was 2.11 ($p = .02$, 95% CI = [1.15, 3.84]) among the non-weekly PA category compared with weekly PA category. For those with SRVI, the age-adjusted risk of a SCL-5 score of 2.0 or higher was 1.91 ($p = .21$, 95% CI = [0.70, 5.21]) among those reporting non-weekly PA compared with those reporting weekly PA. There were too few cases with a SWB score of 4.0 or less to run the age-adjusted logistic model for SWB among those with SRVI (Table 1).

Discussion

The results showed that adolescents with SRNI reported more days a week of PA and fewer symptoms of mental health problems at baseline compared to adolescents with SRVI. Those with SRNI and scoring one day or more per week of PA at baseline had significantly higher levels of well-being at the 4-year follow-up than those scoring lower levels of PA. Among those with SRVI, the mental health benefits of weekly levels of PA compared to non-weekly levels of PA was statistically significant among those scoring as more emotionally unstable or introvert at baseline.

Three of the cross-sectional studies that included adults with visual impairment found that PA was significantly associated with mental health (Di Cagno et al., 2013; Labudzki & Tasiemski, 2013; Valliant et al., 1985), while one study found no association between daily step counts measured by accelerometer and quality of life (Holbrook et al., 2009). Similar to our results, high levels of positive mental health was reported in the studies above (e.g. Labudzki & Tasiemski, 2013). However, we observed that adolescents with SRVI scored high on symptoms of mental health problems at both time points, and our SCL scores are higher than what was observed among 30 Italian male athletes and non-athletes with visual impairment also using the SCL as a measure of mental health problems (Di Cagno et al., 2013). Nevertheless, the higher levels of mental health problems among adolescents with visual impairment may be multifactorial, but some studies have found more problems coping with developmental tasks such as building social relationships (Huurre & Aro, 1998; Kef & Deković, 2004; Pinquart & Pfeiffer, 2012). This corresponds well to our finding that those with SRVI reported more often feelings of loneliness at baseline as to those with SRNI.

We found that baseline PA levels were significantly associated with mental health benefits 4 years later among adolescents with SRVI and scoring to be more emotionally unstable or introvert. Previous studies have shown that positive personal factors are strongly associated with a physically active behavior and mental health of individuals with visual impairment (Garaigordobil & Bernarás, 2009; Saebu & Sørensen, 2011). Moreover, individuals scoring high on neuroticism and low on extroversion have been reported as less physically active and more mentally distressed than their counterparts (Brunes et al., 2013). Among adolescents with SRVI and scoring to have a more stress-reactive personality, PA may have influenced the individual's resilience to stress through emotional or instrumental support from parents, peers, and significant others (Kef & Deković, 2004; Sawyer et al., 2007; Yeung & Towers, 2013). We found that 50% of the adolescents with SRVI reported at baseline to participate in organized sports. Therefore, the experience of social support by being physically active may have been due to the fact that the adolescents practiced organized forms of leisure activities. On the other hand, the lower levels of mental health among adolescents with SRVI who reported a stress-reactive personality and non-weekly activity at baseline may reflect psychosocial barriers to their involvement in leisure-time PA such as overprotection and social isolation (Ayvazoglu,

Oh, & Kozub, 2006; Lieberman et al., 2013). Still, we cannot be cartain of a synergy between PA and personality on mental health because of statistical and methodological issues (Greenland, Lash, & Rothman, 2008).

Adolescents with SRNI and reporting levels of PA of moderate to high intensity were consistently significantly associated with higher levels of well-being. Our finding is comparable with the results from a meta-analysis published by Ahn and Fedewa (2011). They concluded that 1–2 days or more per week of exercise intervention resulted in significant small improvements in mental health scores from baseline to follow-up compared with the control group among children and adolescents. PA of moderate to high intensity may provide adequate physiological responses and psychological rewards to improve well-being (Biddle & Mutrie, 2015). For example, the endorphin hypothesis states that physical exercise results in pleasurable feelings and euphoria due to the release of endogenous opioid peptides (Hoffmann, 1997). PA could also be indirectly related to well-being through fewer passive activities or experiencing positive social interactions (Biddle & Mutrie, 2015). Moreover, there could be a bidirectional association between PA and well-being, such that well-being influences PA level (Biddle & Mutrie, 2015). However, we did not test the possibility of reverse causality in our study.

We did not observe any clear association between PA and mental health problems for adolescents with SRNI. This finding is in contrast to the results from epidemiologic studies and reviews of intervention studies including a population of adolescents (Ahn & Fedewa, 2011; Camero et al., 2012; Fløtnes et al., 2011; Stavrakakis, de Jonge, Ormel, & Oldehinkel, 2012). The increase in SCL-5 scores that we observed from baseline to follow-up in the SRNI category might have been unrelated to their levels of PA, but connected to other biological, social, and environmental factors. Moreover, our results could have been different if we had included specific symptoms of mental health problems (Stavrakakis et al., 2012), carried out gender-specific analyses (Fløtnes et al., 2011), known the total amount and type of PA (Ahn & Fedewa, 2011; Camero et al., 2012), or had information on the social context in which the activity was conducted and the subjective experience of the activity (Whitelaw, Teuton, Swift, & Scobie, 2010).

This reported study is the first prospective population-based study conducted that has examined the long-term effects of PA levels on positive and negative aspects of mental health among adolescents with perceived visual impairment. One of the limitations of the study is confounding. We were unable to adjust for all identified covariates that may be confounding factors because of low sample sizes in the SRVI group and some measured variables had a high number of missing responses (e.g. current smoking status). Including variables that were possible mediators in the regression models may have turned the parameter being estimated more toward the null compared to the true value.

The Young-HUNT Study had a low rate of missing data, but selection bias can occur even with small fractions of missing data (White et al., 2011). However, our multiple imputation analyses were comparable to the results from the complete case analyses. Using information from the invitation list, Holmen et al. (2014) found that non-participants were older, more often boys, and were more often dropouts from upper secondary school compared with the respondents. Moreover, adolescents with mental health problems may be more reluctant to participate in research studies. Finally, non-response may be caused by the embarrassment of answering some of the questions or that adolescents with visual impairment find it difficult to complete a questionnaire. We therefore assume that it was a low to moderate chance that the missing at random (MAR) assumption was obtained for the included variables (Appendix 1).

Since the information on the dependent and independent variables was self-reported, information bias could have influenced the results of the study. The misclassification of PA is expected to be non-differential and the observed association is likely to be more toward the null than the true

effect. Although the accuracy levels of self-reported information among adolescents may be lower than among adults, reliable information regarding self-reported PA and mental health has been found in earlier studies (Haugland & Wold, 2001; Rangul et al., 2008). In addition, adolescence is a sensitive period of life and we cannot rule out fluctuations during the study period in the adolescent's PA levels, mental health status, and self-rated vision status. Finally, based on the findings of a previous study (Whillans & Nazroo, 2014), we expect that the SRVI category included adolescents who corrected their sight with glasses or contact lenses.

When considering the practical implications of the study, it should be borne in mind that the study period ended in 2001 and hence the historical context within which the data were collected might not be completely comparable with the situation today. However, based on the results of this study and more recent study data (Kozub & Oh, 2004; Holbrook et al., 2009; Houwen et al., 2009), efforts are needed to increase participation in leisure-time PA among individuals with visual impairment. Organizing leisure activities for groups of adolescents with visual impairment in Nord-Trøndelag County is challenging because there are very small numbers of such adolescents in the county. Leisure-time PA provides an arena for building friendships and for social interactions. Therefore, in rural areas, it is essential that trainers, parents, and involved others focus on integrating adolescents with visual impairment in leisure activities together with their sighted peers. Furthermore, those in charge of organizing activities including individuals with visual impairment are recommended to modify sports or exercises to the needs of adolescents with visual impairment by taking into consideration visual, personal, social, and environmental factors. This may not only nurture the adolescent's feelings of enjoyment and mastery but could also remove some barriers to participation in regular PA (Lieberman et al., 2013).

Future studies should aim to replicate the findings from our study of vision-specific associations between PA and mental health by including a larger sample of adolescents, using a randomized controlled design, using objective measures of visual impairment, and measuring various aspects of leisure-time PA (e.g. the interpersonal context of the activity). It is also recommended that future studies include a measure of personality when examining the link between PA and mental health in samples of individuals with visual impairment.

Conclusion

Our results showed that adolescents with SRNI had significantly higher levels of moderate-to-high intensity PA and fewer symptoms of mental health problems at baseline than adolescents with SRVI. We found that the association between PA and mental health was dependent on the adolescent's self-reported vision status. Leisure-time PA was only significantly associated with higher levels of well-being among adolescents with SRNI. Among adolescents with SRVI, conducting PA on a weekly basis was associated with fewer mental health problems and higher levels of well-being 4 years later for those who scored having a more stress-reactive personality, probably because of enhanced resilience to stress by participating in organized sports. However, for both vision categories, it is likely that the observed association between PA and mental health does not reflect the true causal relationship and further studies are warranted.

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Declaration of conflicting interests

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Appendix 1

Multiple imputation chained equations (MICE)

Basis of missingness: missing at random. Missing data were due to withdrawal at baseline, withdrawal at follow-up, and non-response either at baseline or at follow-up. We imputed data only for those who participated at baseline and was invited to participate at follow-up in order to obtain stable estimates. Of those, 63% had complete data on all variables. The highest fraction of missing data was for alcohol consumption (44.2%), SCL-5 at follow-up (24.7%), and SWB at follow-up (24.2%). Missing data of <14% were observed for all the other imputed variables.

We tried to obtain the missing at random (MAR) assumption by including a large number of variables in the imputation model that may predict the missingness. We assume that the MAR assumption was moderately probable for PA, mental health at baseline, and most baseline covariates. However, the MAR assumption may be plausible at a low level for missing data on mental health problems at follow-up, subjective well-being at follow-up, baseline smoking status, and baseline alcohol consumption, because missingness may be predicted by unobserved data such as participants' experienced embarrassment at the prospect of answering those questions.

Variable selection and imputation model. All imputed variables and predictors in the imputation model were measured at baseline, while the dependent variables (SCL-5 and SWB) were measured at follow-up (2000–2001).

- Imputed variables using predictive mean matching.
    - EPQ–Neuroticism scale, EPQ–Extroversion scale, mental health problems at baseline and follow-up.

- Imputed variables using linear regression.
  - Subjective well-being at baseline and follow-up.
- Imputed variables using logistic regression.
  - Physical activity, ever tried smoking, parental divorce, and self-esteem.
- Imputed variables using ordinal logistic regression.
  - Self-rated health, body mass index, and feeling lonely.
- Imputed variables using multinomial logistic regression.
  - Cohabitants.
- Variables with complete data:
  - Age, gender, school grade, participation at baseline and follow-up, self-reported vision categories, sports participation, and chronic somatic disease.
- Omitted variables:
  - Other variables were omitted as predictors due to a high fraction of missing data (e.g. alcohol consumption and current smoking status) and hours of physical activity were collinear with days of physical activity.

Model form. Similar variances in the predictions of the imputed data were observed by imputing separate models stratified by age, gender, or self-reported vision categories. We did not check for non-linear terms. To prevent perfect prediction, additional weights were included in the imputation of categorical variables.

Physical activity and symptoms of anxiety and depression in adults with and without visual impairments: The HUNT Study

Audun Brunes[1], W. Dana Flanders[2], Liv Berit Augestad[1,3]

[1] Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology (NTNU), NO-7491 Trondheim, Norway

[2] Departments of Epidemiology and Biostatistics, Rollins School of Public Health, Emory University, Atlanta, GA, 30322 USA

[3] Department of Visual Impairment, Statped Mid-Norway, NO-7224 Melhus, Norway

Corresponding author: Audun Brunes, Department of Neuroscience, Faculty of Medicine, NTNU, NO-7491 Trondheim, Norway. E-mail: audun.brunes@ntnu.no Phone: +47 97578629

ABSTRACT

Purpose: To examine the association of leisure-time physical activity (PA) and symptoms of anxiety and depression among adults with and without self-reported visual impairment.

Methods: A population-based cohort study including 34,393 participants 20–67 years of age from the second wave of the Nord-Trøndelag Health Study (HUNT2, 1995–1997) who also participated in the follow-up (HUNT3, 2006–2008). Of the participants, 3719 (10.8%) had self-reported visual impairment (SRVI). Unadjusted and fully adjusted generalized linear models were used to calculate relative risks (RR) and corresponding 95% confidence intervals (CIs) of PA with anxiety and depression symptoms (Hospital Anxiety and Depression Scale, HADS) separately for visual impairment and gender.

Results: At follow-up, a two-folded higher prevalence of HADS-defined anxiety and depression (a score ≥ 8) was found among adults with SRVI than among adults with self-reported no visual impairment (SRNI). In adults with SRVI and SRNI, fewer depression symptoms at follow-up were significantly associated with high baseline PA scores compared with low PA scores, after adjusting for possible confounders ($p < 0.05$). In adults with SRNI, high baseline PA was related to fewer anxiety symptoms at follow-up compared with their less physically active counterparts, but the associations turned non-significant after adjusting for possible confounders ($p > 0.05$). PA was not significantly related to anxiety symptoms among adults with SRVI ($p > 0.05$).

Conclusions: Regular PA was associated with fewer depression symptoms in adults with SRVI and SRNI, with less clear associations found for anxiety symptoms.

Keywords: anxiety; depression; physical activity; prospective study design; the HUNT Study; visual impairment

1. Introduction

Physical activity (PA) is an inexpensive and accessible tool with few side-effects that may not only be used in the prevention and treatment of some chronic somatic diseases (Warburton, Charlesworth, Ivey, Nettlefold, & Bredin, 2010), but has the potential to reduce the risk of mental health problems (Landers & Arent, 2007). The results of systematic reviews have consistently shown that PA reduces symptoms of depression (Cooney et al., 2013; Herring, Puetz, O'Connor, & Dishman, 2012). Reviews have also supported the notion that PA is associated with fewer anxiety symptoms, but the findings are less consistent than for depressive symptoms (Herring, O'Connor, & Dishman, 2010; Stonerock, Hoffman, Smith & Blumenthal, 2015). However, less is known about whether the possible effects of PA on symptoms of anxiety or depression vary for specific subgroups (Schuch, Morres, Ekkekakis, Rosenbaum, & Stubbs, 2016), including adults with visual impairments.

Visual impairment is a loss in the individual's ability to see, ranging from mild to blindness with no light perception (World Health Organization, 2006). The causes of visual impairment relate to damage, disease, or degeneration in the eyes or its connected nervous system (Congdon, Friedman, & Lietman, 2003). In most cases, vision loss does not affect an individual's exercise capacity (Lieberman, Ponchilla, & Ponchilla, 2013). Despite this, adults with visual impairments are shown to have fewer weekly hours of PA, especially PA of moderate to high intensity, compared with adults without visual impairments (van Landingham, Willis, Vitale, & Ramulu, 2012; Willis, Jefferys, Vitale, & Ramulu, 2012; Augestad & Jiang, 2015). The lower PA levels may be explained by the vicious circle phenomenon. Hence, many adults with visual impairments experience barriers when participating in PA, such as functional limitations, dependency, mobility problems, disabling environments, and fear of injuries (Griffin, Smith, Howe, & Phoenix, 2016). These barriers could decrease an adult's PA,

leading to co-morbid conditions that may function as additional barriers when attempting exercise.

Any degree of visual impairment is found to be a risk factor for mental health problems such as anxiety and depression (Cumberland & Rahi, 2016). The prevalence of subthreshold anxiety and depression in adults with visual impairments have been shown to range between 9.3–15.6% and 11.3–32.2% (Evans, Fletcher, & Wormald, 2007; van der Aa, Comijs, Penninx, van Rens, & van Nispen, 2015, 2015; Zhang et al., 2013), and the estimates are equal or higher than found in general adult populations (Johansson, Carlbring, Heedman, Paxling, & Andersson, 2013; Nes & Clench-Aas, 2011). The aetiology of anxiety and depression among adults with visual impairment is less known, but are suggested to be related to difficulties adjusting to the vision loss, identity problems, dependency, social exclusion, and functional limitations (Senra et al., 2015). If not treated, mental health problems could have additional impact on the health and functioning of individuals with visual impairments (Crews, Jones, & Kim, 2006).

A few studies we know of have examined the relationship between PA and anxiety or depression symptoms in adults with visual impairments (Capella-McDonnall, 2011; Di Cagno et al., 2013). However, only one study had a prospective study design (Capella-McDonnall, 2011). Furthermore, none of the studies assessed the participant's weekly amount of PA. This might be important because the possible effects of PA on anxiety or depression symptoms may be dependent on the PA dose (Schuch et al., 2016).

Therefore, the aim of our prospective cohort study was to examine the association between leisure-time PA and symptoms of anxiety and depression in adults with and without self-reported visual impairments.

2. Method

2.1 Design and participants

The Nord-Trøndelag Health Study (HUNT) is a prospective cohort study including all residents aged ≥ 20 years living in the county of Nord-Trøndelag, Norway (Holmen et al., 2003). Baseline data were collected in the second wave of the HUNT (HUNT2 Survey, 1995–1997), with a follow-up around 11 years later (HUNT3 Survey, 2006–2008). Both surveys had two measurement phases. The first phase included the completion of a postal questionnaire and the second phase included the completion of a clinical examination and a questionnaire. Each of the questionnaires requested information about the participants' demographics, lifestyle behaviours, somatic and mental health.

Of the 92,936 adults who were invited to participate in HUNT2, 65,237 (69.5%) were enrolled in our study by completing and returning the first questionnaire. Of those participating in HUNT2, 37,070 (56.8%) also participated in HUNT3. The main reasons for dropout between HUNT2 and HUNT3 were death, emigration, and non-attendance (Krokstad et al., 2012). Our study was restricted to participants aged < 67 years at HUNT2, which is the ordinary retirement age in Norway. Finally, 34,393 participants were included in the study, of which 3719 (10.8%, mean age: 51.7 years) adults reported visual impairment and 30,674 (89.2%, mean age: 44.2 years) did not report any visual impairment. Most adults described their visual impairment as 'a little', followed by 'some' and 'severe' visual impairment (Figure 1). More details of the sample characteristics are shown in Table 1.

2.2 Measures

2.2.1 Visual impairment

Baseline information on the participants' perceived experience of visual impairment was assessed by a two-item questionnaire. The participants had to first answer the following question: 'Do you have a long-term disease, injury, or condition (at least one year) of a

physical or mental character that impairs your functioning in daily life?' Those who answered 'yes' were asked to describe whether they had a degree of visual impairment. The response alternatives were 'a little impairment', 'some impairment', and 'severe impairment'. Adults who reported that they had a degree of visual impairment were included in the self-reported visual impairment (SRVI) category, while adults who did not report any visual impairment were included in the self-reported no visual impairment (SRNI) category. Not all adults with SRVI scored 'yes' on the first question. We chose to include those adults in the main analysis as it had only a minor impact on our estimates.

2.2.2 Physical activity

In HUNT2 and HUNT3, the participants reported their average weekly hours of low intensity PA (no sweating, not out of breath) and moderate to high intensity PA (sweating, out of breath) during their leisure time and commute time by selecting one of the following response alternatives for hours per week: none, < 1, 1–2, or 3 or more. The PA questionnaire has previously been validated among a sample of Norwegian men in the age group 20–39 years (Kurtze, Rangul, Hustvedt, & Flanders, 2007). Low intensity PA was found to correlate poorly with maximal oxygen consumption ($VO_{2\text{-max}}$) measurements ($r = -0.03$) and the long version of the International Physical Activity Questionnaire (IPAQ-L) ($r = -0.08$). By contrast, moderate to high intensity PA correlated moderately with $VO_{2\text{-max}}$ ($r = 0.46$) and IPAQ-L ($r = 0.31$).

A summary index of PA was created to assess the participants' total amount of PA during leisure time (Augestad, Schei, Forsmo, Langhammer, & Flanders, 2004). Low intensity PA was included as a crude score, while moderate to high intensity PA was weighted 2.5 for each increase in score on that particular variable. Next, the scores were summarized into a PA index, and categorized into low, moderate, and high scores by dividing the index at

the 33.3rd and 66.6th percentiles. The cut-off was 3 and 5.5 points. The PA index had a moderate, linear correlation between HUNT2 and HUNT3 (r = 0.35).

2.2.3 Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) was designed as a survey tool for identifying anxiety and depression for medical hospital patients. At both HUNT2 and HUNT3, the subjects were asked to report the feelings they had experienced during the last week. The questionnaire consisted of two subscales, seven items for anxiety (HADS-A) and seven items for depression (HADS-D). A 4-point Likert scale was used on each question, ranging from 0 (not present) to 3 (maximally present). Therefore, both HADS-A and HADS-D yield a sum score ranging from 0 to 21 points (Zigmond & Snaith, 1983). We found moderate, linear correlations between HUNT2 and HUNT3 for HADS-A (r = 0.54) and for HADS-D (r = 0.58). In our statistical analyses, anxiety and depression symptoms were treated as continuous variables. Both HADS subscales were right skewed, and none of the variables met the normality assumption after data transformation. Therefore, the HADS subscales were treated as untransformed variables in the analyses.

2.2.4 Covariates

Detailed information about the selection procedure, measurement, and study variables can be found using HUNT Databank software, which is currently accessible via the Internet. We identified possible confounding factors from previous publications and a priori reasoning (Miettinen & Cook, 1981). Suspected confounders of the association between PA and HADS-A or HADS-D were: age (linear), smoking status (no, former, current), monthly alcohol consumption (none/teetotaller, 1–4, ≥ 5), education (years: < 10, 10–12, > 12), occupational

status (in work, not in work), and a history of somatic or mental conditions (no, yes). A history of somatic or mental conditions encompassed: angina pectoris, myocardial infarction, stroke, hyperthyroidism, hypothyroidism, asthma, cancer, diabetes, epilepsy, and any mental disorders.

Body mass index (BMI), self-rated health, and life satisfaction were identified as potential confounding or mediating factors in the relationship between PA and anxiety or depression. However, our study is not designed for fulfilling the strong assumptions underlying mediation analyses. Therefore, we chose not to include the variables in order to prevent a possible underestimation of the true associations.

2.3 Missing data

Complete cases were used in the primary statistical analyses, while multiple imputation with chained equations (MICE) was used as a supplementary method to examine the possible impact of missing data. The MICE analyses included all adults who participated in HUNT2 and HUNT3 (N = 34,393). Detailed information of the imputation model and the number of subjects with missing data for each imputed variable are presented in the online supplement. Comparing the results from the complete cases and the MICE revealed similar or slightly stronger associations in favour of the MICE approach (results not shown). If we fulfilled the 'missing at random' assumption of MICE, our results indicate high reliability of the complete case analyses.

2.4 Statistical methods

We calculated descriptive statistics, including numbers and percentages. Generalized linear models (GLMs) with a gamma distribution and log-link function were used to estimate the mean HADS-A or HADS-D scores at follow-up among each category of the baseline PA

index, compared with those in the referent category. The choice of distribution was based on the best fitted model. In all statistical analyses, relative risk (RR) and its corresponding 95% confidence intervals (CIs) were calculated separately for women and men. This choice was based on the notion that previous studies using HUNT data have shown gender-specific associations between PA and symptoms of anxiety and depression (Brunes, Augestad, & Gudmundsdottir, 2013, Brunes, Gundmundsdottir, & Augestad, 2015). Moreover, we tested for effect-measure modification (also called moderation) between visual impairment and PA using the likelihood ratio test to compare models with and without the product term (Greenland, 2008).

Three supplementary analyses were conducted by: (1) including PA measured in HUNT3 in the binomial GLMs because the participant's PA levels might have changed between 1995–1997 and 2006–2008; (2) conducting the main analysis for the crude PA scores instead of the PA index; and (3) adjusting for baseline measures of HADS-A or HADS-D in addition to all indicated covariates because of its possible influence on future PA levels and mental health problems. The results from the supplementary analyses are included in the online supplement.

All analyses were stratified for visual impairment and gender. All analyses were either unadjusted or adjusted for all indicated covariates. The low PA category was the reference category. The significance level was set at $p = 0.05$. The statistical analyses were carried out using Stata Version 13 (Stata Corp., Texas, USA).

2.5 Ethics

The study followed the ethical principles stated by the Declaration of Helsinki. All participants gave their written consent to take part in the study. The study was approved by the Regional Committee for Medical and Health Research Ethics (Regional komitee for

medisinsk og helsefaglig forskningsetikk, avdeling Midt Norge (REK midt)). The HUNT Research Centre gave us permission to analyse the data.

3. Results

The participants' baseline characteristics according to their visual impairments and gender are presented in Table 1. In total, 10.3% of adults with SRVI and 6.0% of adults with SRNI reported that they did not engage in any leisure-time PA at baseline. As shown in Figure 2, the prevalence of HADS-defined anxiety and depression (a score ≥ 8) in adults with SRVI in HUNT3 was almost twice as high as the prevalence for adults with SRNI (Zigmond & Snaith, 1983).

Women with SRVI who scored in the highest tertile on the baseline PA index had a 24% lower risk of depression symptoms at follow-up than women with SRVI who scored low PA, after adjusting for possible confounders. Among men with SRVI, PA was not related to mean HADS-D scores (Table 2). Among women and men with SRNI, significantly fewer symptoms of depression in HUNT3 were found among those with moderate and high baseline PA scores compared with low scores on the PA index. After controlling for possible confounders, the RRs were pulled towards the null, but remained statistically significant for the high PA category. When examining for effect-measure modification in men, we found that the association between PA and depression symptoms was non-significantly weaker among those with SRVI than among those with SRNI. In women, the strength of the association between PA and depressive symptoms across categories of the visual impairment variable was in the opposite direction than to those found among men. However, the effect-measure modification did not reach statistical significance (Table 2).

As shown in Table 3, leisure-time PA was not related to anxiety symptoms in women and men with SRVI. In women and men with SRNI, the mean anxiety symptoms were

somewhat lower among those who scored high baseline PA compared with their less physically active counterparts. However, the associations became non-significant after adjustments for possible confounders (Table 3). In both women and men, the magnitude of the associations was uniform across levels of the visual impairment variable (Table 3).

We conducted three supplementary analyses. First, we observed that the results from the analyses of concurrent associations were similar to those found in the main analyses (Table S1 and S2). Second, among women and men with SRNI, lower HADS-D scores (2006–2008) were shown to be associated with both low intensity PA and moderate to high intensity PA (1995–1997) among women and men with SRVI. Among women with SRVI, those who reported 1–2 hours/week of moderate to high PA at baseline had significantly fewer depression symptoms than those who reported no PA, whereas no significant associations were found between low intensity PA and depression symptoms (Table S3 and S4). Third, after additionally adjusting for baseline depression, the RRs of depression symptoms with high baseline PA index scores were pulled moderately towards the null, and became non-significant for women with SRVI and for women with SRNI (Table S5).

4. Discussion

The primary finding of this prospective cohort study was that high baseline PA scores were significantly associated with fewer depression symptoms at follow-up compared with lower scores among adults with SRVI and SRNI, after controlling for possible confounders. However, among adults with SRVI, the associations were statistically significant for women, but not for men. Furthermore, in the fully adjusted models, leisure-time PA was not found to be related to anxiety symptoms. The strength of the associations between PA and symptoms of anxiety or depression differed non-significantly among adults with SRVI and SRNI.

4.1 Physical activity and depression symptoms

Only two previous studies have examined the association between PA and depression symptoms among adults with visual impairments. In a prospective observational study in the US including 2688 elderly adults, lower depression scores were found among adults with dual sensory loss who maintained ≥ 2–3 times of high-intensity PA per week during the 13-year follow-up than adults with dual sensory loss who had less PA during the same time period (Capella-McDonnall, 2011). In a cross-sectional study including a convenience sample of 30 young Italian adults, Di Cagno et al. (2013) observed significantly fewer depression symptoms in adults with severe visual impairment or blindness playing Torball (a ball game for people with visual impairments) compared with adults with severe visual impairment or blindness not playing any sports. Our study results add to the current knowledge base by showing that high baseline PA scores were more beneficial with regard to depression symptoms at follow-up than moderate and low PA scores, especially for women with SRVI. Although the effect sizes among women with SRVI are generally weak, it is promising in a public health perspective given the high prevalence of subthreshold depression.

We can only guess the possible mechanisms being involved. Scoring high on our PA index is equal to or higher than the 150 minutes of moderate intensity PA/week that is needed to maintain or improve functioning (World Health Organization, 2010). Since visual impairment could limit the adult's functioning and independency (Crews et al., 2006), one possible explanation for our results may be that high PA levels lowers depression symptoms by improving the adult's functioning. Leisure-time PA is related to enjoyable and meaningful activities. Therefore, other potential mechanisms explaining why leisure-time PA can reduce depression symptoms may be through its role of being a mood-regulating tool and replacing passive activities with more enjoyable and pleasurable activities (Craft, 2015). These mechanisms seem plausible given that life dissatisfaction and negative emotions are more

frequently reported in adults with visual impairments than in adults without visual impairments (Fenwick et al., 2012; Senra et al., 2015). Because the relationship between PA and depressive symptoms is complex and reciprocal in nature (Lindwall, Larsman, & Hagger, 2011), we cannot exclude the possibility that depression symptoms led to lower levels of PA.

In our supplementary analysis, we adjusted for baseline depression. It seems reasonable to adjust for baseline differences in HADS-D scores given that depression symptoms may influence PA and depression in the future (Lindwall et al., 2011). However, when there is considerable measurement error of the outcome, adjustment for baseline measures might result in inflated associations (Glymore, Weuve, Berkman, Kawachi, & Robins 2005). In accordance with our expectations, the adjustments led to an attenuation of the associations.

4.2 Physical activity and anxiety symptoms

This is the first prospective study examining the association between PA and anxiety symptoms in a sample of adults with visual impairments. In adults with SRVI and SRNI, after adjusting for possible confounders, cross-sectional and prospective analyses revealed no significant associations of leisure-time PA with anxiety symptoms. Most randomized controlled trials (RCTs) of adult populations have found that exercise is associated with fewer anxiety symptoms (Herring et al., 2010; Stonerock et al., 2015), whereas mixed results have been shown in observational studies with prospective designs (Brunes et al., 2015; de Moor et al., 2008; Jonsdottir et al., 2010). However, observational studies are less suitable than RCTs to address cause and effect because the temporal relationship between PA and anxiety symptoms is less clear. Nevertheless, as stated in a systematic review, there is not enough evidence yet to support a direct effect of PA on anxiety symptoms (Stonerock et al., 2015).

4.3 Visual impairment as a modifying factor

In line with the findings from previous studies (Augestad & Jiang, 2015; Crews et al., 2016; Cumberland & Rahi, 2015; Griffin et al., 2016), we found a higher percentage of adults with SRVI than adults with SRNI having HADS-defined anxiety or depression, poor/not so good self-rated health, a history of somatic and mental conditions, high body mass index, less than 10 years of education. The above-mentioned factors may function as barriers to PA and explain to some extent the lower baseline PA scores among adults with SRVI than among adults with SRNI. Despite the baseline differences, leisure-time PA did not differ significantly between adults with SRVI and SRNI in its association with anxiety or depression symptoms.

Surprisingly, the direction of the effect-measure modification was dependent on the adult's gender. Our findings may be explained by gender-specific differences in how perception of vision loss relates to mental health problems (Zhang et al., 2013). Another possible explanation may be the use of HADS as the outcome measure. We found that men had more depression symptoms than women, which is not in agreement with the scientific literature (Landers & Arent, 2007). HADS assesses psychological and behavioural symptoms (Zigmond & Snaith, 1983), and these symptoms are more common among men than among women (Piccinelli & Wilkson, 2000). Moreover, somatic depression symptoms are found to be closely related to PA (Schuch, Dunn, Kanitz, Delevatti, & Fleck, 2016) and physical impairments (Penninx, Leveille, Ferrucci, Van Eijk, & Guralnik, 1999). Therefore, including measures of somatic depression symptoms may have resulted in different associations.

4.4 Strengths and limitations

The main strengths of our study were the large sample size, the prospective study design, the inclusion of different aspects of PA and mental health problems, restricting our analyses to a

more homogeneous sample with regard to age, and addressing the possible impact of confounding bias and non-response bias.

A number of limitations should be considered. First, our study assessed the adults' own experience of vision impairment, as well as their anxiety and depression symptoms. Therefore, our study sample was not representative of populations with a diagnosis of severe visual impairment, anxiety disorder, or major depressive disorder. We assume that those who reported a degree of SRVI truly experienced a vision impairment. However, our results did not depend on the severity of SRVI or changes in SRVI during the follow-up (results not shown). Second, we expect that the adult's total weekly amount in leisure-time PA was underestimated based on how the response alternatives were constructed and the possibility of recall bias (Kurtze et al., 2007). The PA questionnaire did not distinguish between moderate intensity and high intensity PA. This may have confounded our associations given that moderate intensity activities could have been differently associated with mental health problems than high intensity activities (Lindwall et al., 2011). Third, we may not have taken into account all possible confounding factors (e.g. personality). Fourth, study drop-out and non-participation may have resulted in the inclusion of a healthier study population. We expect that people with visual impairments and mental health problems are more hesitant to participate in population-based studies, such as ours (Langhammer, Krokstad, Romundstad, Heggland, & Holmen, 2012).

5. Conclusion

Our results showed that adults with SRVI and SRNI who reported high leisure-time PA scores at baseline had lower depression symptoms 11 years later, compared with those who scored low PA. The strength of the associations differed non-significantly across the self-reported visual impairment variable, with the largest benefit found among men with SRNI.

Furthermore, leisure-time PA was not significantly related to anxiety symptoms. Our results support the hypothesis that regular PA reduces depression symptoms, also for adult populations with SRVI. Nevertheless, the possible causal relationship between PA and mental health problems in adults with SRVI seems to be complex and needs to be examined further, preferably using randomized controlled designs including interventions with different types, modes, and intensities of activity. Moreover, we encourage future studies to recruit adults with various aspects of vision loss, as well as measuring somatic symptoms of mental health problems.

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Table 1
Baseline characteristics from HUNT2, according to visual impairment and gender.

	Women[a]		Men[a]	
Characteristics	**SRVI (N = 2073) N (%)**	**SRNI (N = 16,826) N (%)**	**SRVI (N = 1646) N (%)**	**SRNI (N = 13,848) N (%)**
Age				
< 50 years	755 (36.4)	11,485 (68.3)	643 (39.1)	9059 (65.4)
50–67 years	1318 (63.6)	5341 (31.7)	1003 (60.9)	4789 (34.6)
Education				
< 10 years	1051 (50.7)	4791 (28.5)	623 (37.9)	3239 (23.4)
10–12 years	677 (32.2)	7661 (45.5)	749 (45.5)	7106 (51.3)
> 12 years	264 (12.7)	4118 (24.5)	226 (13.7)	3323 (24.0)
Missing	91 (4.4)	256 (1.5)	48 (2.9)	180 (1.3)
Smoking status				
No	865 (41.7)	7763 (46.1)	514 (31.2)	6155 (44.5)
Previous	488 (23.5)	4090 (24.3)	606 (36.8)	4266 (30.8)
Current	690 (33.3)	4816 (28.6)	509 (30.9)	3343 (24.1)
Missing	30 (1.5)	157 (0.9)	17 (1.0)	84 (0.6)
Body mass index				
< 25 kg/m^2	758 (36.6)	8286 (49.3)	492 (30.0)	4830 (34.9)
25–29.9 kg/m^2	854 (41.2)	6079 (36.1)	876 (53.2)	7227 (52.2)
≥ 30 kg/m^2	455 (22.0)	2386 (14.2)	268 (16.3)	1751 (12.6)
Missing	6 (0.3)	75 (0.5)	10 (0.6)	40 (0.3)
Alcohol consumption				
None/teetotal	1047 (50.5)	6433 (38.2)	458 (27.8)	2965 (21.4)
1–3 times/month	594 (28.9)	6595 (39.2)	608 (36.9)	5838 (42.2)
≥ 4 times/month	299 (14.4)	3099 (18.4)	520 (31.6)	4656 (33.6)
Missing	133 (6.4)	699 (4.2)	60 (3.7)	389 (2.1)
Chronic diseases				
No	1074 (51.8)	11,898 (70.7)	988 (60.0)	10,817 (78.1)
Yes	795 (38.4)	3938 (23.4)	570 (34.6)	2592 (18.7)
Missing	204 (9.8)	990 (5.9)	88 (5.4)	439 (3.2)
Self-rated health				
Poor/not so good	1056 (50.9)	3243 (19.3)	742 (45.1)	2189 (15.8)
Good/very good	1006 (48.5)	13,424 (79.8)	891 (54.1)	11,574 (83.6)
Missing	11 (0.5)	159 (0.9)	13 (0.8)	85 (0.6)
HADS-depression				
< 8 points	1575 (76.0)	14,683 (87.3)	1279 (77.7)	12,150 (87.7)
≥ 8 points	309 (14.9)	1213 (7.2)	291 (17.7)	1082 (7.8)
Missing	189 (9.1)	930 (5.5)	76 (4.6)	616 (4.5)
HADS-anxiety				
< 8 points	1219 (58.8)	12,618 (75.0)	1179 (71.6)	11,356 (82.0)
≥ 8 points	475 (22.9)	2247 (13.4)	283 (17.2)	1400 (10.1)
Missing	379 (18.3)	1961 (11.7)	184 (11.2)	1092 (7.9)

Table 1 continued

Occupational status				
In work	861 (41.5)	11,084 (65.9)	1033 (62.8)	11,858 (85.6)
Not in work[b]	1173 (56.6)	5514 (32.8)	594 (36.1)	1872 (13.5)
Missing	39 (1.9)	228 (1.4)	19 (1.2)	118 (0.9)
Low intensity PA				
None	149 (7.2)	727 (4.3)	154 (9.4)	896 (6.5)
< 1 hour	358 (17.3)	2566 (15.3)	266 (16.2)	2449 (17.7)
1–2 hours	687 (33.1)	6524 (38.8)	494 (30.0)	4511 (32.6)
≥ 3 hours	593 (28.6)	5360 (31.9)	515 (31.3)	4185 (30.2)
Missing	286 (13.8)	1649 (9.8)	217 (13.2)	1807 (13.1)
Moderate to high intensity PA				
None	698 (33.7)	4742 (28.2)	479 (29.1)	3101 (22.4)
< 1 hour	305 (14.7)	3569 (21.2)	300 (18.2)	3328 (24.0)
1–2 hours	203 (9.8)	3054 (18.2)	273 (16.6)	2992 (21.6)
≥ 3 hours	89 (4.3)	1016 (6.0)	191 (11.6)	1954 (14.1)
Missing	778 (37.5)	4445 (26.4)	403 (24.5)	2473 (17.9)
PA index[b]				
Low	547 (26.4)	3756 (22.3)	383 (23.3)	2591 (18.7)
Moderate	333 (16.1)	3196 (19.0)	304 (18.5)	2774 (20.0)
High	358 (17.3)	4573 (27.2)	452 (27.5)	4624 (33.4)
Missing	835 (40.3)	5301 (31.5)	507 (30.8)	3859 (27.9)

Notes: Anxiety and Depression Scale; PA = physical activity

[a] The results from the Pearson's chi-squared analyses indicated that all characteristics were significantly differently between those with SRVI and those with SRNI ($p < 0.05$), as well as between men and women ($p < 0.05$)

[b] 'not in work' includes being unemployed, retired, homemaker, in education, or in military service

Table 2
Mean HADS depression scores (HUNT3) with physical activity (HUNT2), according to visual impairment and gender.

	HADS depression subscale						Test for EEM[d]
	Self-reported visual impairment (N = 3719)			Self-reported no visual impairment (N = 30,674)			
PA index[c]	Mean (SD)	RR (95% CI)[a]	RR (95% CI)[b]	Mean (SD)	RR (95% CI)[a]	RR (95% CI)[b]	χ^2, p-value
Women							
Low	4.44 (3.17)	Reference	Reference	3.26 (2.87)	Reference	Reference	
Moderate	4.60 (3.10)	1.04 (0.93–1.15)	1.06 (0.94–1.20)	3.06 (2.70)	0.94 (0.90–0.99)	0.99 (0.94–1.04)	
High	3.64 (2.71)	0.82 (0.74–0.91)	0.88 (0.77–0.99)	2.68 (2.66)	0.82 (0.79–0.86)	0.91 (0.87–0.96)	1.22, p=0.54
Men							
Low	4.73 (3.10)	Reference	Reference	3.92 (3.09)	Reference	Reference	
Moderate	4.79 (3.28)	1.01 (0.91–1.14)	1.01 (0.89–1.13)	3.58 (2.84)	0.91 (0.87–0.96)	0.94 (0.89–0.99)	
High	4.38 (3.02)	0.93 (0.84–1.02)	0.95 (0.85–1.06)	3.15 (2.68)	0.83 (0.77–0.84)	0.85 (0.81–0.89)	2.17, p=0.34

Notes: PA = physical activity; HADS = Hospital Anxiety and Depression Scale; RR = relative risks; CI = confidence interval; EEM: effect-measure modification

[a] Unadjusted

[b] Age (linear), smoking status (no, current, present), education (years: < 10, 10–12, > 12), occupational status (in work, not in work), alcohol consumption (no/teetotaller, 1–4, ≥ 5), and a history of somatic or mental conditions (no, yes)

[c] A sum score of low intensity PA and moderate to high intensity PA

[d] Likelihood ratio test comparing the fully adjusted model with main effects and the fully adjusted model including visual impairment and PA as an interaction term

Table 3
Mean HADS anxiety scores (HUNT3) with physical activity (HUNT2), according to visual impairment and gender.

	HADS anxiety subscale						Test for EEM[d]
	Self-reported visual impairment (N = 3719)			Self-reported no visual impairment (N = 30,674)			
PA index[c]	Mean (SD)	RR (95% CI)[a]	RR (95% CI)[b]	Mean (SD)	RR (95% CI)[a]	RR (95% CI)[b]	χ^2, p-value
Women							
Low	5.37 (3.39)	Reference	Reference	4.27 (3.47)	Reference	Reference	
Moderate	5.54 (3.77)	1.03 (0.93–1.15)	1.05 (0.93–1.19)	4.21 (3.26)	0.99 (0.95–1.03)	1.01 (0.97–1.06)	
High	4.98 (3.51)	0.93 (0.83–1.03)	0.95 (0.84–1.07)	4.00 (3.29)	0.94 (0.90–0.98)	0.98 (0.93–1.02)	0.61, p=0.74
Men							
Low	3.95 (3.06)	Reference	Reference	3.53 (3.13)	Reference	Reference	
Moderate	4.34 (3.39)	1.10 (0.96–1.25)	1.10 (0.95–1.26)	3.50 (2.99)	0.99 (0.94–1.04)	1.02 (0.97–1.07)	
High	4.04 (3.17)	1.02 (0.91–1.15)	1.05 (0.92–1.19)	3.33 (2.80)	0.94 (0.90–0.99)	0.97 (0.96–1.05)	0.83, p=0.66

Notes: PA = physical activity; HADS = Hospital Anxiety and Depression Scale; RR = relative risks; CI = confidence interval; EEM: effect-measure modification

[a] Unadjusted

[b] Age (linear), smoking status (no, current, present), education (years: < 10, 10–12, > 12), occupational status (in work, not in work), alcohol consumption (no/teetotaller, 1–4, ≥ 5), and a history of somatic or mental conditions (no, yes)

[c] A sum score of low intensity PA and moderate to high intensity PA

[d] Likelihood ratio test comparing the fully adjusted model with main effects and the fully adjusted model including visual impairment and PA as an interaction term

Table S1

Concurrent assessments of physical activity and HADS-defined depression (HUNT3), according to visual impairment and gender.

	HADS depression subscale					
	Self-reported visual impairment (N = 3719)			Self-reported no visual impairment (N = 30,674)		
PA index[c]	Mean (SD)	RR[a]	RR (95% CI)[b]	Mean (SD)	RR[a]	RR (95% CI)[b]
Women						
Low	4.44 (3.16)	Ref	Ref	3.26 (2.88)	Ref	Ref
Moderate	4.59 (3.11)	1.03	1.07 (0.95–1.20)	3.06 (2.70)	0.94	0.98 (0.93–1.03)
High	3.64 (2.71)	0.82	0.86 (0.77–0.97)	2.68 (2.66)	0.82	0.89 (0.85–0.93)
Men						
Low	4.74 (3.12)	Ref	Ref	3.93 (3.08)	Ref	Ref
Moderate	4.78 (3.27)	1.01	0.99 (0.88–1.11)	3.57 (2.84)	0.91	0.92 (0.87–0.97)
High	4.38 (3.02)	0.92	0.91 (0.82–1.02)	3.15 (2.68)	0.80	0.83 (0.79–0.87)

PA = physical activity; HADS = Hospital Anxiety and Depression Scale; RR: relative risks. CI: confidence interval; Ref: reference

[a] Unadjusted

[b] Age (linear), smoking status (no, current, present), alcohol consumption (no/teetotaller, 1–4, ≥ 5), and a history of somatic or mental conditions (no, yes)

[c] a sum score of low intensity PA and moderate to high intensity PA

Table S2

Concurrent assessments of physical activity and HADS-defined anxiety (HUNT3), according to visual impairment and gender.

	HADS anxiety subscale					
	Self-reported visual impairment (N = 3719)			Self-reported no visual impairment (N = 30,674)		
PA index[c]	Mean SD	RR (95% CI)[a]	RR (95% CI)[b]	Mean SD	RR (95% CI)[a]	RR (95% CI)[b]
Women						
Low	5.37 (3.98)	Ref	Ref	4.27 (3.47)	Ref	Ref
Moderate	5.54 (3.78)	1.03	1.06 (0.93–1.17)	4.21 (3.26)	0.99	1.00 (0.96–1.04)
High	4.98 (3.51)	0.93	0.92 (0.87–1.03)	4.00 (3.28)	0.94	0.96 (0.92–1.00)
Men						
Low	3.98 (3.13)	Ref	Ref	3.54 (3.12)	Ref	Ref
Moderate	4.30 (3.31)	1.08	1.09 (0.95–1.24)	3.49 (3.00)	0.99	1.00 (0.95–1.05)
High	4.04 (3.17)	1.02	1.02 (0.90–1.15)	3.33 (2.80)	0.94	0.95 (0.91–1.00)

Note. PA = physical activity; HADS = Hospital Anxiety and Depression Scale; RR: relative risks; CI: confidence interval; Ref: reference

[a] Unadjusted

[b] Age (linear), smoking status (no, current, present), alcohol consumption (no/teetotaller, 1–4, ≥ 5), and a history of somatic or mental conditions (no, yes)

[c] a sum score of low intensity PA and moderate to high intensity PA

Table S3

Mean HADS scores (HUNT3) with moderate- to high-intensity physical activity (HUNT2), according to visual impairment and gender.

	Self-reported visual impairment (N = 3719)				Self-reported no visual impairment (N = 30,674)			
	HADS-Anxiety		HADS-Depression		HADS-Anxiety		HADS-Depression	
Hours of MHPA	RR[a]	RR (95% CI)[b]	RR[a]	RR (95% CI)[b]	RR[a]	RR (95% CI)[b]	RR[a]	RR (95% CI)[b]
Women								
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
< 1	1.03	1.05 (0.94–1-19)	0.95	1.01 (0.89–1.14)	0.97	1.00 (0.96–1.04)	0.91	0.99 (0.94–1.04)
1–2	0.88	0.90 (0.77–1.03)	0.77	0.85 (0.72–0.96)	0.93	0.97 (0.93–1.02)	0.80	0.89 (0.85–0.94)
≥ 3	0.91	0.92 (0.75–1.12)	0.77	0.85 (0.70–1.05)	0.96	0.97 (0.91–1.04)	0.82	0.91 (0.85–0.98)
Men								
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
< 1	1.05	1.07 (0.94–1.23)	0.98	1.00 (0.89–1.12)	0.98	1.00 (0.96–1.05)	0.88	0.93 (0.88–0.97)
1–2	1.02	1.02 (0.88–1.17)	0.88	0.91 (0.81–1.03)	0.96	0.99 (0.94–1.04)	0.81	0.86 (0.82–0.90)
≥ 3	0.96	1.02 (0.87–1.19)	0.84	0.90 (0.79–1.03)	1.00	1.02 (0.97–1.08)	0.82	0.86 (0.81–0.91)

Note. MHPA = moderate- to high-intensity physical activity; HADS = Hospital Anxiety and Depression Scale; RR = relative risks; CI = confidence interval; Ref = reference

[a] Unadjusted

[b] Age (linear), smoking status (no, current, present), education (years: < 10, 10–12, > 12), occupational status (in work, not in work), alcohol consumption (no/teetotaller, 1–4, ≥ 5), and a history of somatic or mental conditions (no, yes)

Table S4

Mean HADS scores (HUNT3) with low-intensity physical activity (HUNT2), according to visual impairment and gender.

	Self-reported visual impairment (N = 3719)				Self-reported no visual impairment (N = 30,674)			
	HADS-Anxiety		HADS-Depression		HADS-Anxiety		HADS-Depression	
Hours of LPA	RR[a]	RR (95% CI)[b]	RR[a]	RR (95% CI)[b]	RR[a]	RR (95% CI)[b]	RR[a]	RR (95% CI)[b]
Women								
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
< 1	0.96	0.90 (0.76–1.08)	0.88	0.86 (0.71–1.03)	0.98	1.01 (0.93–1.10)	0.93	0.98 (0.89–1.07)
1–2	0.96	0.94 (0.80–1.11)	0.95	0.98 (0.82–1.15)	0.92	0.97 (0.90–1.04)	0.84	0.90 (0.83–0.98)
≥ 3	0.89	0.88 (0.74–1.04)	0.86	0.89 (0.75–1.06)	0.93	0.97 (0.91–1.05)	0.80	0.87 (0.80–0.95)
Men								
None	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
< 1	1.01	1.00 (0.84–1.20)	1.02	1.01 (0.86–1.17)	1.05	1.07 (0.99–1.15)	0.89	0.92 (0.85–0.99)
1–2	0.98	1.03 (0.87–1.22)	0.92	0.91 (0.79–1.05)	1.02	1.05 (0.98–1.13)	0.84	0.85 (0.80–0.92)
≥ 3	1.01	1.05 (0.89–1.24)	0.93	0.92 (0.79–1.05)	0.98	1.02 (0.94–1.09)	0.78	0.80 (0.75–0.86)

Note. LPA = low intensity physical activity; HADS = Hospital Anxiety and Depression Scale; RR = relative risks; CI = confidence interval; Ref = reference

[a] Unadjusted

[b] Age (linear), smoking status (no, current, present), education (years: < 10, 10–12, > 12), occupational status (in work, not in work), alcohol consumption (no/teetotaller, 1–4, ≥ 5), and a history of somatic or mental conditions (no, yes)

Table S5

Associations between mean HADS scores (HUNT3) and physical activity (HUNT2) after additional adjustments for baseline measures of the outcome.

	Self-reported visual impairment (N = 3719)		Self-reported no visual impairment (N = 30,674)	
	HADS-Anxiety	HADS-Depression	HADS-Anxiety	HADS-Depression
PA index[b]	RR (95% CI)[a]	RR (95% CI)[a]	RR (95% CI)[a]	RR (95% CI)[a]
Women				
Low	Ref	Ref	Ref	Ref
Moderate	1.07 (0.95–1.20)	1.13 (1.00–1.27)	1.03 (0.99–1.08)	1.02 (0.97–1.07)
High	0.97 (0.86–1.09)	0.94 (0.84–1.06)	1.00 (0.96–1.04)	0.98 (0.93–1.03)
Men				
Low	Ref	Ref	Ref	Ref
Moderate	1.06 (0.92–1.21)	1.00 (0.89–1.13)	1.04 (0.99–1.10)	0.98 (0.93–1.03)
High	1.00 (0.88–1.13)	0.98 (0.88–1.09)	1.00 (0.96–1.05)	0.92 (0.88–0.96)

Note. MHPA = moderate- to high-intensity physical activity; HADS = Hospital Anxiety and Depression Scale; RR = relative risks; CI = confidence interval; Ref = reference

[a] Age (linear), smoking status (no, current, present), education (years: < 10, 10–12, > 12), occupational status (in work, not in work), alcohol consumption (no/teetotaller, 1–4, ≥ 5), and a history of somatic or mental conditions (no, yes), and baseline HADS anxiety or depression scores (linear)

[b] a sum score of low intensity PA and moderate to high intensity PA

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ORIGINAL ARTICLE

Self-reported visual impairment, physical activity and all-cause mortality: The HUNT Study

AUDUN BRUNES[1], W. DANA FLANDERS[2,3] & LIV BERIT AUGESTAD[1,4]

[1]Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology, Norway, [2]Department of Epidemiology, Rollins School of Public Health, Emory University, USA, [3]Department of Biostatistics, Rollins School of Public Health, Emory University, USA, and [4]Department of Visual Impairment, Statped Mid-Norway, Norway

Abstract

Aims: To examine the associations of self-reported visual impairment and physical activity (PA) with all-cause mortality. **Methods:** This prospective cohort study included 65,236 Norwegians aged ⩾20 years who had participated in the Nord-Trøndelag Health Study (HUNT2, 1995−1997). Of these participants, 11,074 (17.0%) had self-reported visual impairment (SRVI). The participants' data were linked to Norway's Cause of Death Registry and followed throughout 2012. Hazard ratios and 95% confidence intervals (CI) were assessed using Cox regression analyses with age as the time-scale. The Cox models were fitted for restricted age groups (<60, 60−84, ⩾85 years). **Results:** After a mean follow-up of 14.5 years, 13,549 deaths were identified. Compared with adults with self-reported no visual impairment, the multivariable hazard ratios among adults with SRVI were 2.47 (95% CI 1.94–3.13) in those aged <60 years, 1.22 (95% CI 1.13–1.33) in those aged 60–84 years and 1.05 (95% CI 0.96–1.15) in those aged ⩾85 years. The strength of the associations remained similar or stronger after additionally controlling for PA. When examining the joint associations, the all-cause mortality risk of SRVI was higher for those who reported no PA than for those who reported weekly hours of PA. We found a large, positive departure from additivity in adults aged <60 years, whereas the departure from additivity was small for the other age groups. ***Conclusions:*** **Adults with SRVI reporting no PA were associated with an increased all-cause mortality risk. The associations attenuated with age.**

Key Words: *All-cause mortality, physical activity, prospective cohort study, self-reported, HUNT study, visual impairment*

Introduction

An estimated 8.5 million adults in Western Europe were living with visual impairment and blindness in 2010 [1]. As the population ages and the incidence of some chronic diseases increases, visual impairment may have a greater future impact on public health [2]. In a meta-analysis including 29 epidemiological studies [3], adults with visual impairment had a significantly higher risk of all-cause mortality than adults with no visual impairment. This finding persisted across different measures of visual impairment (e.g. self-reported). However, less is known regarding the roles of different risk factors in the possible link between visual impairment and mortality [4]. Physical activity (PA) could be one possible factor, as studies have shown that adults with visual impairment are less engaged in PA than adults without visual impairment [5,6].

Physical inactivity is common in today's modern society, and is a major risk factor for morbidity and premature mortality [7]. In addition, regular PA has been repeatedly shown to be associated with reduced all-cause mortality risk [8,9]. The relationship

Correspondence: Audun Brunes, Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology, NO-7491 Trondheim, Norway. E-mail: audun.brunes@ntnu.no

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between PA and all-cause mortality has been found to be curvelinear, with the largest magnitude of risk reduction between no weekly PA and some weekly PA [8,9]. As a general guideline, the World Health Organization recommends that all adults aged 18 years or older should engage in moderate-intensity aerobic PA of at least 150 minutes per week, high-intensity aerobic PA of at least 75 minutes per week, or a combination of these two intensities [10].

We know of only one study that has examined whether low levels of PA contribute to the association between visual impairment and all-cause mortality risk [11]. As visual impairment and PA are both predictors of all-cause mortality, it is of interest to examine the combination of visual impairment and PA in its association with mortality. To our knowledge, the joint association of visual impairment and PA with all-cause mortality risk has not yet been investigated.

The aim of our prospective population-based cohort study was two-fold: (a) to examine the association between self-reported visual impairment (SRVI) and mortality with and without adjustment for PA; and (b) to analyse the joint associations of SRVI and PA with mortality.

Materials and methods

Design and sample

Our prospective study was based on data from the second wave of the Nord-Trøndelag Health Study (HUNT2, 1995–1997) [12]. The HUNT2 Survey is a large population-based survey including all adults aged ⩾20 years registered as residents in the county of Nord-Trøndelag, Norway. HUNT2 consisted of two subsequent measurement phases. The first phase was carried out by the completion of a postal questionnaire and the second phase was carried out by the completion of a medical examination accompanied by a questionnaire. All baseline data relevant to our study were assessed by the first questionnaire and the medical examination.

A total of 93,898 adults were invited to participate in the study. We excluded 28,662 (30.5%) adults who did not respond to the first questionnaire. This gave a total sample of 65,236 adults. Table I gives the characteristics of the study participants.

Measures

Mortality ascertainment. Data from the National Cause of Death Registry in Norway (currently maintained by the Norwegian Institute of Public Health) and HUNT2 were merged by an external researcher using the participants' national identification numbers. The follow-up time was calculated from baseline (1995–1997) until time of death or at the end of follow-up (31 December 2012), whichever came first. The cause of death was classified in accordance with the tenth revision of the International Classification of Diseases (ICD-10) [13]. Our main analyses included all-cause mortality as an outcome measure. Cause-specific mortality was used in a supplementary analysis and included cardiovascular mortality (codes I00–I99), cancer mortality (codes C00–D48), fatal accident and sudden death (codes V, W and X) and mortality due to other causes specified as not cardiovascular, cancer, or fatal accident and sudden death.

Visual impairment. Information on the participants' perceived experience of visual impairment was assessed by a two-item questionnaire [14]. First, the participants had to answer the following question: 'Do you have a longstanding disease, injury, or condition (at least one year) of physical or mental character that impairs your functioning in daily life?' Those who answered 'yes' were asked to describe whether they had a degree of visual impairment. The response alternatives were 'a little impairment', 'some impairment' and 'severe impairment'. The SRVI category encompassed adults who reported that they had a degree of visual impairment. Those who did not report any visual impairment were included in the self-reported no visual impairment (SRNI) category.

Physical activity. The participants reported their average weekly hours of low-intensity PA (not sweating or being out of breath) and moderate- to high-intensity PA (sweating or being out of breath) during their leisure time and commuting time by selecting one of the following response alternatives for hours per week: none, <1, 1–2 or 3 or more hours per week. The PA questionnaire has previously been validated among a sample of Norwegian men aged 20–39 years [15]. In this validation study, moderate- to high-intensity PA (MHPA) was found to correlate moderately with maximum oxygen consumption ($VO_{2\text{-max}}$) measurements (r=0.46) and the long version of the International Physical Activity Questionnaire (IPAQ-L) (r=0.31). Low-intensity physical activity (LPA) correlated poorly with $VO_{2\text{-max}}$ (r=−0.03) and IPAQ-L (r=−0.08). In our study, the linear dependency between hours of LPA and MHPA was moderate (r=0.44). For the purpose of analyses with dichotomous outcomes, the LPA and MHPA variables were coded into non-weekly (0 hours) and weekly PA (>0 hours).

Table I. Characteristics and standardized mortality rates, according to visual impairment.

Characteristics	SRNI (*n*=54,162)		SRVI (*n*=11,074)	
	Number (%) at risk	Standardized mortality rates[a]	Number (%) at risk	Standardized mortality rates[a]
Age (years)				
<60	41,109 (75.9)	–	4301 (38.8)	–
60–84	12,654 (23.4)	–	6300 (56.9)	–
⩾85	399 (0.7)	–	473 (4.3)	–
Gender				
Women	28,487 (52.6)	17.3	6175 (55.8)	22.9
Men	25,675 (47.4)	22.5	4899 (44.2)	30.0
Smoking status				
None	23,343 (43.1)	16.4	4418 (39.9)	21.0
Previous	14,232 (26.3)	20.2	3278 (29.6)	26.2
Current	15,486 (28.6)	24.2	3049 (27.5)	31.6
Missing	1101 (2.0)	24.5	329 (3.0)	28.7
Body mass index (kg/m^2)				
<25	22,302 (41.2)	20.1	3464 (31.3)	26.6
25–29	23,055 (42.6)	19.1	4917 (44.4)	24.2
⩾30	8315 (15.4)	21.3	2407 (21.7)	27.8
Missing	490 (0.9)	27.3	286 (2.6)	56.5
Marital status				
Unmarried	14,323 (26.4)	22.0	1545 (14.0)	27.3
Married/partner	32,478 (60.0)	19.4	6620 (59.8)	25.5
Widowed	3553 (6.6)	24.4	2119 (19.1)	27.6
Divorced/separated	3678 (6.8)	22.8	776 (7.0)	30.7
Missing	130 (0.2)	19.4	14 (0.1)	–
Education (years)				
<10	16,623 (30.7)	21.7	6064 (54.8)	28.1
⩾10	35,152 (64.9)	18.2	3929 (35.5)	23.6
Missing	2387 (4.4)	26.9	1081 (9.8)	35.6
HADS-D score				
<8	45,027 (83.1)	18.6	7509 (67.8)	24.8
⩾8	4365 (8.1)	23.6	1887 (17.0)	29.3
Missing	4770 (8.8)	24.1	1678 (15.2)	30.4
Diabetes or diagnosed any CVD				
No	49,992 (92.3)	18.4	8443 (76.2)	23.6
Yes	3868 (7.1)	32.3	2509 (22.7)	40.5
Missing	302 (0.6)	26.2	122 (1.1)	37.3
Hours of LPA				
None	3641 (6.7)	23.4	1470 (13.3)	31.7
<1	8104 (15.0)	19.5	1574 (14.2)	26.0
1–2	17,493 (32.3)	18.4	2794 (25.2)	24.4
⩾3	16,595 (30.6)	18.3	2849 (25.7)	23.9
Missing	8329 (15.4)	22.3	2387 (21.6)	28.6
Hours of MHPA				
None	14,887 (27.5)	20.6	4165 (37.6)	28.3
<1	10,563 (19.5)	17.5	1197 (10.8)	23.4
1–2	9085 (16.8)	16.1	899 (8.1)	20.9
⩾3	5130 (9.5)	17.8	572 (5.2)	22.5
Missing	14,497 (26.8)	21.7	4241 (38.3)	27.2

HADS-D: Hospital Anxiety and Depression Scale, depression subscale; LPA: low-intensity physical activity; MHPA: moderate- to high-intensity physical activity; SRNI: self-reported no visual impairment; SRVI: self-reported visual impairment; –: age-standardized mortality rates not calculated.

[a]Direct age-standardized rates multiplied by 100; age coded as <60, 60–74 and ⩾75 years.

Covariates. Detailed information about the selection procedure, measurement and study variables can be found using the HUNT Databank software, currently accessible online. We identified possible confounding factors from previous publications and a priori reasoning [16]. The suspected confounders of the association between visual impairment and mortality were: age (as the time scale), sex, smoking

status (no, previous, current), alcohol consumption (none/teetotal, 1–4, ⩾5 times/month), body mass index (<25, 25–29.9, ⩾30 kg/m^2), marital status (unmarried, married/partnership, widowed, separated/divorced), education (<10, ⩾10 years), diagnosed as having diabetes or any cardiovascular diseases (no, yes) and having adverse biomarkers (no, yes). Adverse biomarkers included hypertension (blood pressure ⩾160/100 mmHg), hyperglycemia (non-fasting glucose ⩾11.0 mmol/L) and high total cholesterol levels (non-fasting levels ⩾7.0 mmol/L).

Missing data

Complete cases were used in the primary statistical analyses and multiple imputation with chained equations (MICE) was used as a supplementary method to impute missing baseline values. The MICE analyses included all participants in HUNT2 (n=65,236). Detailed information about the imputation model and the number of particiants with missing data for each variable included in the imputation model are presented in Table SI (supplementary data, available online).

Statistical methods

Descriptive statistics included cross-tabulations and direct age-standardized mortality rates for each baseline characteristic. The time scale used in the study was age measured in years [17], which in this paper is described as chronological age. Using Kaplan–Meier analysis, we estimated the survival probability as a function of chronological age. Separately, we used data for 2012 obtained from Statistics Norway to plot survival curves for age 20 years to age 105 years for the general Norwegian poluation [18].

Cox regression analyses were carried out to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality and its association with visual impairment. Several subgroup analyses were conducted by including visual impairment and each covariate as an interaction term and then comparing the log-likelihood between models with and without the interaction term. In a separate analysis we examined whether PA contributed to the association between visual impairment and all-cause mortality by adding LPA and MHPA to the model (model III in Table II). By doing this, we could test the hypothesis of PA being a mediator in the possible relationship between visual impairment and mortality.

To estimate the joint associations, we created a categorical variable with four categories and added the variable to the Cox model. The four categories were: (a) SRNI and LPA or MHPA (reference); (b) SRNI and no LPA or MHPA; (c) SRVI and LPA or MHPA; and (d) SRVI and no LPA or MHPA. We also tested for effect-measure modification on multiplicative and additive scales. The test of departure from multiplicativity was determined by including a product term of visual impairment and LPA or MHPA in the Cox model. The test of effect-measure modification on an additive scale was carried out by calculating relative excess risk due to interaction (RERI). The RERI values were derived from the β coefficients and covariance matrix obtained from the regression models [19]. Departure from additivity is considered valuable to public health because it identifies the excess risk if two factors are working in combination rather than each factor working alone.

To check the proportional hazards assumption, the visual impairment variable was included in the Cox models as an interaction term with a linear or a logarithmic function of time [20]. We accounted for a violation of the proportional hazards for visual impairment with all-cause mortality by fitting Cox models separately for restricted groups of chronological age (<60, 60–84, ⩾85 years). The model fit was found to be satisfactory after restricting for chronological age.

We conducted two supplementary analyses. First, a test for linear trend across visual impairment categories (none, a little, some and severe visual impairment) was conducted by comparing the log-likelihood between the models treating visual impairment as a continuous variable and as a categorical variable. Second, visual impairment was examined in its association with specific causes of death (cancer, cardiovascular diseases, fatal accident and sudden death, and other causes) (Table SII, supplementary data, available online).

The Cox models were either age- and sex-adjusted or adjusted for all indicated covariates. p<0.05 indicated statistical significance. Stata Version 13.0 was used for the statistical analyses.

Ethics

The study followed the ethical principles stated by the Declaration of Helsinki. All participants gave their written consent to take part in the study. The study was approved by the Regional Committee for Medical and Health Research Ethics (Regional komitee for medisinsk og helsefaglig forskningsetikk). The HUNT Research Centre and the Norwegian Institute of Public Health gave permission to analyse their data.

Results

Table I shows the characteristics and standardized mortality rates according to visual impairment of the

study participants. Of the sample, 11,074 (17.0%, mean age 62.6 years) had SRVI and 54,162 (83.0%, mean age 47.6 years) had SRNI. Of the study participants, a higher percentage described their visual impairment as 'a little' (9.6%) rather than 'some' (5.4%) or 'severe' (2.0%).

The mean follow-up time was 14.5 years (range 0–17 years) with a total of 947,031 person-years. In total, 44.3% of adults with SRVI died during the 17 year follow-up period, whereas 16.0% of adults with SRNI died during the same time period. The median age at death for those with SRVI was two years lower than those with SRNI (83 vs. 85 years). In the Kaplan–Meier analysis, we found that the survival probability was lower for adults with SRVI than for adults with SRNI and the plotted data from Statistics Norway. The gap in survival gradually decreased for adults with SRVI surviving beyond the age of 70 years (Figure 1).

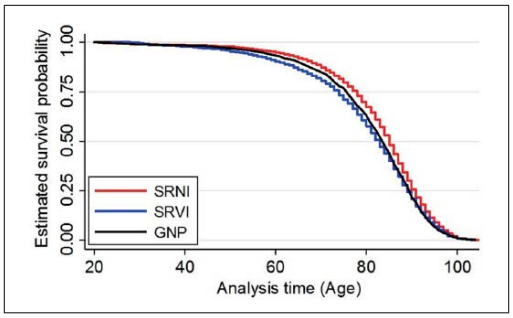

Figure 1. Kaplan–Meier survival curves showing survival probability for self-reported vision categories and the general Norwegian population. GNP: general Norwegian population; SRNI: self-reported no visual impairment; SRVI; self-reported visual impairment.

Table II shows that adults with SRVI had significantly higher HRs than adults with SRNI in the age groups <60 years and 60–84 years after adjustment for age and sex, as well as after adjustment for all indicated confounding factors. However, we did not find any statistically significant association for adults aged ⩾85 years. Additional adjustments for LPA and MHPA resulted in an increased relative risk in the age group <60 years, whereas minor changes were observed in the age group 60–84 years and ⩾85 years (Table II). No two-way interaction between visual impairment and other covariates reached statistical significance ($p>0.05$).

Tables III and IV show the joint associations of visual impairment and PA with mortality. When the reference category was adults with SRNI reporting weekly hours of PA, significantly higher mortality risks were found for SRVI alone, no LPA or MHPA alone, and the combination of SRVI and no LPA or MHPA. In the age group < 60 years, the increased mortality risk associated with SRVI was found to be stronger among those who reported no LPA or MHPA than those who reported LPA or MHPA. However, the large, positive risk-difference modification reached statistical significance for MHPA only (RERI 1.80, 95% CI 0.85–2.75). No other effect-measure modification was observed on additive or multipliciative scales.

In the supplementary analysis, for the age groups having significant associations between visual impairment and all-cause mortality, the results from the log-likelihood test showed that there were no significant differences between the models treating the visual impairment variable as continuous or categorical (60 years: χ^2 9.5, $p=0.01$; 60–84 years: 14.8, $p<0.001$). This means that there were no evidence of a linear trend. In the cause-specific analyses, adults

Table II. Hazard ratios for all-cause mortality with visual impairment, according to restricted age groups.

Visual impairment status	Number of deaths (person-years)	Model I	Model II	Model III
		Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
<60 years				
SRNI	721 (384,274)	1.00 (reference)	1.00 (reference)	1.00 (reference)
SRVI	153 (23,040)	3.12 (2.61–3.73)	2.17 (1.77–2.66)	2.47 (1.94–3.13)
60–84 years				
SRNI	4810 (357,641)	1.00 (reference)	1.00 (reference)	1.00 (reference)
SRVI	2493 (79,810)	1.37 (1.30–1.43)	1.25 (1.17–1.32)	1.22 (1.13–1.31)
⩾85 years				
SRNI	3114 (65,254)	1.00 (reference)	1.00 (reference)	1.00 (reference)
SRVI	2258 (37,012)	1.05 (0.99–1.11)	1.03 (0.96–1.10)	1.05 (0.96–1.15)

SRNI: self-reported no visual impairment; SRVI: self-reported visual impairment.
Model I: adjusted for age (as time-scale) and sex. Model II: adjusted for age (as time-scale), sex, body mass index (<25, 25–29.9, ⩾30 kg/m^2), diagnosed as having diabetes or diagnosed any cardiovascular diseases (no, yes), education (<10, ⩾10 years), marital status (married/partner, unmarried, widowed, divorced/separated), adverse biomarkers (no, yes), smoking status (no, previous, current) and alcohol consumption (none/teetotal, 1–4, ⩾5 times/month). Model III: model II + low- and moderate- to high-intensity physical activity (0, >0 hours).

Table III. Joint associations of visual impairment and low-intensity physical activity (LPA) with all-cause mortality risk, according to restricted age groups.

Hours of LPA	SRNI		SRVI		Hazard ratio (95% CI) for SRVI within strata of LPA
	Number of deaths (person-years)	Hazard ratio (95% CI)	Number of deaths (person-years)	Hazard ratio (95% CI)	
<60 years[a]					
0	66 (23,145)	1.48 (1.14–1.93)	23 (2254)	5.51 (3.63–8.37)	4.47 (3.13–6.40)
>0	548 (321,958)	1.00 (reference)	107 (18,229)	3.02 (2.05–3.73)	3.02 (2.05–3.73)
60–84 years[b]					
0	501 (22,644)	1.41 (1.26–1.57)	425 (8334)	1.67 (1.48–1.89)	1.79 (1.55–2.06)
>0	3016 (281,051)	1.00 (reference)	1476 (57,815)	1.27 (1.18–1.36)	1.27 (1.18–1.36)
⩾85 years[b]					
0	346 (4995)	1.13 (0.98–1.30)	446 (5162)	1.17 (1.02–1.33)	1.18 (0.98–1.42)
>0	1556 (38,342)	1.00 (reference)	1054 (20,089)	1.05 (0.96–1.14)	1.05 (0.96–1.14)

SRNI: self-reported no visual impairment; SRVI: self-reported visual impairment.
Measure of effect modification on an additive scale: RERI (95% CI): <60 years, 2.02 (−0.45 to 4.48); 60–84 years, 0.01 (−0.24 to 0.25); ⩾85 years, −0.01 (−0.21 to 0.20).
Measure of effect modification on a multiplicative scale: Hazard ratio (95% CI): <60 years, 1.23 (0.73–2.08); 60–84 years, 0.94 (0.79–1.11); ⩾85 years, 0.99 (0.81–1.20).
[a]Adjusted for age (as time-scale) and sex.
[b]Adjusted for age (as time-scale), sex, body mass index (<25, 25–29.9, ⩾30 kg/m^2), diagnosed as having diabetes or cardiovascular diseases (no, yes), education (<10, ⩾10 years), marital status (married/partner, unmarried, widowed, divorced/separated), adverse biomarkers (no, yes), smoking status (no, previous, current) and alcohol consumption (none/teetotal, 1–4, ⩾5 times/month).

Table IV. Joint associations of visual impairment and moderate- to high-intensity physical activity (MHPA) with all-cause mortality risk according to restricted age groups.

Hours of MHPA	SRNI		SRVI		Hazard ratio (95% CI) for SRVI within strata of MHPA
	Number of deaths (person-years)	Hazard ratio (95% CI)	Number of deaths (person-years)	Hazard ratio (95% CI)	
<60 years[a]					
0	214 (98,663)	1.43 (1.20–1.71)	63 (7273)	4.95 (3.76–6.51)	3.93 (2.67–5.77)
>0	322 (232,263)	1.00 (reference)	47 (11,860)	2.74 (2.02–3.71)	2.74 (2.02–3.71)
60–84 years[b]					
0	1547 (99,426)	1.35 (1.24–1.48)	1046 (28,332)	1.67 (1.51–1.85)	1.71 (1.43–2.06)
>0	1004 (143,239)	1.00 (reference)	395 (21,950)	1.26 (1.11–1.43)	1.26 (1.11–1.43)
⩾85 years[b]					
0	1041 (19,394)	1.14 (1.00–1.31)	985 (14,111)	1.17 (1.01–1.35)	1.28 (0.96–1.71)
>0	347 (10,527)	1.00 (reference)	196 (4479)	1.12 (0.93–1.36)	1.12 (0.93–1.36)

SRNI: self-reported no visual impairment; SRVI: self-reported visual impairment.
Measure of effect modification on an additive scale: RERI (95% CI): <60 years, 1.80 (0.85–2.75); 60–84 years, 0.07 (−0.15 to 0.30); ⩾85 years, −0.09 (−0.33 to 0.14).
Measure of effect modification on a multiplicative scale: Hazard ratio (95% CI): <60 years, 1.26 (0.83–1.92); 60–84 years, 0.98 (0.84–1.14); ⩾85 years, 0.91 (0.74–1.13).
[a]Adjusted for age (as time-scale) and sex.
[b]Adjusted for age (as time-scale), sex, body mass index (<25, 25–29.9, ⩾30 kg/m^2), diagnosed as having diabetes or cardiovascular diseases (no, yes), education (<10, ⩾10 years), marital status (married/partner, unmarried, widowed, divorced/separated), adverse biomarkers (no, yes), smoking status (no, previous, current) and alcohol consumption (none/teetotal, 1–4, ⩾5 times/month).

with SRVI were more likely to die from cancer, cardiovascular disease and other causes than adults with SRNI (Table SII, supplementary data, available online). The risk of mortality due to fatal accident and sudden death was similar for adults with SRVI and SRNI (results not shown). Compared with the full-adjusted analyses presented in Table II, the associations between visual impairment and all-cause mortality remained similar in the supplementary analyses handling missing data using MICE, except for a moderate decrease in the risk estimates for adults in the age group <60 years (results not shown).

Discussion

In this large population-based study, adults with SRVI had a significantly increased all-cause mortality

risk and the associations remained similar or stronger after controlling for LPA and MHPA. Moreover, we found that the higher all-cause mortality risk associated with SRVI was stronger for adults who reported no LPA or MHPA than for adults who reported weekly hours in LPA or MHPA. The strength of all statistical associations decreased with increasing chronological age.

Our results showed that adults with SRVI were associated with an increased risk of all-cause mortality and that the strength of the association decreased with age. This finding is consistent with a recently published meta-analysis [3]. The results from previous publications show that increased severity of visual impairment is associated with a higher risk of some adverse health outcomes [21,22] and all-cause mortality [3]. The lack of a linear dose–response relationship in our study cannot be readily explained and should be addressed in future studies.

It has been hypothesized that PA could mediate the possible link between visual impairment and mortality [11]. In a study including 416 Finnish adults aged 75 or 80 years at baseline, Kulmala et al. [11] found that PA accounted for 20% of the association between visual acuity loss and all-cause mortality among adults aged 75 years at baseline, whereas PA did not explain the association between visual acuity loss and all-cause mortality among adults aged 80 years at baseline. In our study, we found no evidence of leisure-time PA contributing to the increased risk of all-cause mortality among adults with SRVI. However, comparing the results of the study of Kulmala et al. [11] and our study are difficult as a result of many methodological differences. In light of our study results, we could speculate that other biological, physiological, psychosocial and behavioural mechanisms that do not involve PA may explain the increased mortality risk of adults with visual impairment [23]. Nevertheless, as demonstrated by Robins and Greenland [24], mediation analysis requires very strong underlying assumptions to obtain valid estimates. Further studies are therefore needed.

The results from the joint associations showed that the increased mortality risk of SRVI was stronger for those who reported no PA than for those who reported weekly hours of PA. This result was found irrespective of the intensity of leisure time PA, probably because 95% of those who reported no LPA also reported no MHPA (results not shown). It is possible that low PA in adults with visual impairment may be one of many factors related to their high prevalence of functional limitations [22], low physical fitness [25], disability [22], mental health problems [21,22], co-morbid somatic conditions [21,22] and social isolation [21]. This could explain why adults with SRVI had an increased risk of some lifestyle-related causes of death in our study (e.g. cardiovascular diseases). However, due to the descriptive nature of our study, the observed departure from additivity may have been a consequence of other mortality-related factors than low PA, such as ongoing health problems and biological ageing [4,23].

Because of the close link between visual impairment, PA and falls [26], we were surprised to find that fatal accidents and sudden deaths, which included deaths from falls and injuries, were not related to visual impairment. Some plausible explanations for the lack of association may be that there were few deaths from fatal accidents and sudden deaths (n=547) and that falls and injuries may have been a part of the aetiology, but not the underlying cause of death.

The major strengths of our study were its prospective study design with a large sample of non-institutionalized participants, the high participation rate, using data from a national registry for endpoint and censoring, and the long follow-up period.

Our study had several limitations. First, the measure of visual impairment in our study reflects the participant's own experiences of visual functions and does not represent a clinical diagnosis of severe visual impairment or blindness. We assumed that those who reported a degree of vision impairment truly experienced that their vision was impaired. The percentage of adults with SRVI in our study was comparable with the percentages reported in a representative sample of US adults that measured visual impairment using one-item questions [27]. Second, we expect that the hours in leisure time PA were under-reported based on how the questionnaire was constructed and the possibility of recall bias [15]. It is likely that the misclassification of PA was non-differential, resulting in conservative estimates of relative risk. Third, SRVI and PA were only measured once and we did not know the participants' vision or PA levels in the years prior to our study or in the years from HUNT2 to censoring or death. As the population ages, we expect a higher number of adults with SRNI or reporting hours of PA at baseline to develop SRVI and become physically inactive during the study period. Fourth, we could not exclude the possibility of residual confounding bias. Fifth, the generalizability of our findings may have been hampered because 30% of the participants were excluded from our study. This may increase the possibility of

survival bias and a healthy worker effect [28,29]. We expect that adults with SRVI are healthier than the target population of adults who experience visual impairment, given that the participants had to travel to the health station and to complete and return questionnaires. The results from the statistical analyses using MICE were comparable with the analyses using complete cases, which increased our confidence that our results were not biased as a result of item non-response.

In conclusion, our results showed that adults with SRVI were associated with an increased risk of all-cause mortality. We found some evidence that the all-cause mortality risk of SRVI was dependent on their engagement in leisure-time PA, with a higher risk observed among adults with SRVI who reported no PA. As physical inactivity is common in today's society, our findings support the public health importance of promoting regular PA in the population and for those who experience a degree of visual impairment. However, more high-quality studies are needed to understand the causal nature of this relationship, probably by recruiting adults at the time of vision loss, having a shorter follow-up period, and assessing visual impairment and PA objectively.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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APPENDICES

I Questions used from the Young-HUNT Studies

II Questions used from the HUNT Studies

APPENDIX I

Questions used from the Young-HUNT Studies

OM HELSA DI

10. **Hvordan er helsa di nå ?** (Sett ett kryss for det som passer for deg)

- * Dårlig ..... ☐
- * Ikke helt god ..... ☐
- * God ..... ☐
- * Svært god ..... ☐

11. **Er du funksjonshemmet på noen av disse måtene ?**
(Sett ett kryss på hver linje)

	Nei	Litt	Middels	Mye
* Er bevegelseshemmet	☐	☐	☐	☐
* Har nedsatt syn	☐	☐	☐	☐
* Har nedsatt hørsel	☐	☐	☐	☐
* Hemmet pga. kroppslig sykdom	☐	☐	☐	☐
* Hemmet pga. psykiske plager	☐	☐	☐	☐

OM IDRETT OG MOSJON

50. Utenom skoletida: **Hvor mange dager i uka driver du idrett, eller mosjonerer du så mye at du blir andpusten og/eller svett?**
(Sett bare ett kryss)

- * Hver dag ..... ☐
- * 4-6 dager i uka .. ☐
- * 2-3 dager i uka ... ☐
- * 1 dag uka ..... ☐
- * Ikke hver uke, men minst en dag hver 14.dag . ☐
- * Ikke hver 14.dag, men minst en dag i måneden ☐
- * Sjeldnere enn en dag i måneden ..... ☐
- * Aldri ..... ☐

51. Utenom skoletida: **Til sammen hvor mange timer i uka driver du idrett eller mosjonerer du så mye at du blir andpusten og/eller svett?**
(Sett bare ett kryss)

- * Ingen ..... ☐
- * Omtrent ½ time .. ☐
- * Omtrent 1 time ... ☐
- * Omtrent 2-3 timer ..... ☐
- * Omtrent 4-6 timer ..... ☐
- * 7 timer eller mer ..... ☐

HVORDAN DU HAR DET

59. **Når du tenker på hvordan du har det for tida, er du stort sett fornøyd eller er du stort sett misfornøyd ?** (Sett bare ett kryss)

- * *Svært fornøyd* ..... ☐
- * *Meget fornøyd* ..... ☐
- * *Ganske fornøyd* ..... ☐
- * *Både og* ..... ☐
- * *Nokså misfornøyd* ..... ☐
- * *Meget misfornøyd* ..... ☐
- * *Svært misfornøyd* ..... ☐

60. **Føler du deg stort sett sterk og opplagt eller trøtt og sliten ?** (Sett bare ett kryss)

- * *Meget sterk og opplagt* . ☐
- * *Sterk og opplagt* ..... ☐
- * *Ganske sterk og opplagt.* ☐
- * *Både og* ..... ☐
- * *Ganske trøtt og sliten* ... ☐
- * *Trøtt og sliten* ..... ☐
- * *Svært trøtt og sliten* ..... ☐

61. **Er du vanligvis glad eller nedstemt (trist) ?** (Sett bare ett kryss)

- * *Svært nedstemt* (trist) .... ☐
- * *Nedstemt* (trist) ..... ☐
- * *Nokså nedstemt* (trist) .. ☐
- * *Både og* ..... ☐
- * *Nokså glad* ..... ☐
- * *Glad* ..... ☐
- * *Svært glad* ..... ☐

65. **Nedenfor er en liste over noen problemer eller plager. Har du vært plaget av noe av dette de siste 14 dagene ?** (Sett ett kryss for hver linje)

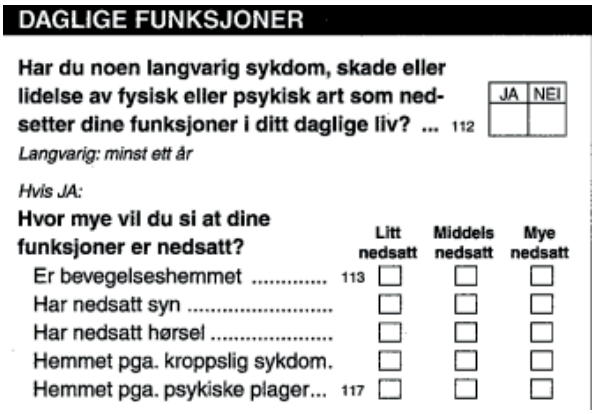
	Ikke plaget	Litt plaget	Ganske plaget	Veldig plaget
* *Vært stadig redd og engstelig*	☐	☐	☐	☐
* *Følt deg anspent eller urolig*	☐	☐	☐	☐
* *Følt håpløshet når du tenker på framtida*	☐	☐	☐	☐
* *Følt deg nedfor eller trist*	☐	☐	☐	☐
* *Bekymret deg for mye om forskjellige ting*	☐	☐	☐	☐

66. **Har du i løpet av den siste måneden vært plaget av nervøsitet (irritabel, urolig, anspent eller rastløs) ?**

Nesten hele tida ☐ *Ofte* ☐ *Av og til* ☐ *Aldri* ☐

APPENDIX II

Questions used from the HUNT Studies



DAGLIGE FUNKSJONER

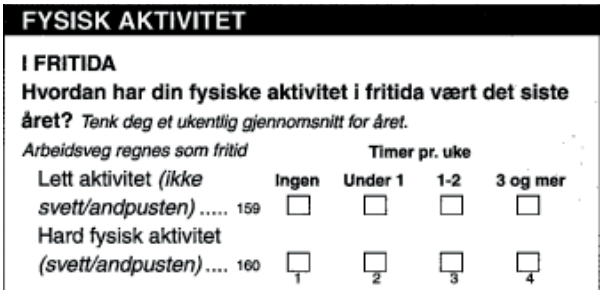
Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? ... 112

JA	NEI
☐	☐

Langvarig: minst ett år

Hvis JA:

Hvor mye vil du si at dine funksjoner er nedsatt?		**Litt nedsatt**	**Middels nedsatt**	**Mye nedsatt**
Er bevegelseshemmet	113	☐	☐	☐
Har nedsatt syn		☐	☐	☐
Har nedsatt hørsel		☐	☐	☐
Hemmet pga. kroppslig sykdom.		☐	☐	☐
Hemmet pga. psykiske plager...	117	☐	☐	☐



FYSISK AKTIVITET

I FRITIDA

Hvordan har din fysiske aktivitet i fritida vært det siste året? *Tenk deg et ukentlig gjennomsnitt for året.*

Arbeidsveg regnes som fritid

		Timer pr. uke			
		Ingen	**Under 1**	**1-2**	**3 og mer**
Lett aktivitet *(ikke svett/andpusten)*	159	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)*	160	☐ 1	☐ 2	☐ 3	☐ 4

HVORLEDES FØLER DU DEG?

Har du de siste to ukene følt deg:

	Nei	Litt	En god del	Svært mye
Trygg og rolig? 162	☐	☐	☐	☐
Glad og optimistisk?	☐	☐	☐	☐
Har du følt deg:				
Nervøs og urolig?	☐	☐	☐	☐
Plaget av angst? 165	☐	☐	☐	☐
Irritabel?	☐	☐	☐	☐
Nedfor/deprimert?	☐	☐	☐	☐
Ensom? 168	☐ 1	☐ 2	☐ 3	☐ 4

*Her kommer noen flere spørsmål om hvorledes du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser **den siste uka.** Ikke tenk for lenge på svaret - de spontane svarene er best*

Jeg gleder meg fortsatt over ting slik jeg pleide før 169

Avgjort like mye ..... ☐ 1 Bare lite grann ..... ☐ 3
Ikke fullt så mye ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg har en urofølelse som om noe forferdelig vil skje 170

Ja, og noe svært ille .... ☐ 1 Litt, bekymrer meg lite . ☐ 3
Ja, ikke så veldig ille ... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg kan le og se det morsomme i situasjoner 171

Like mye nå som før .... ☐ 1 Avgjort ikke som før .... ☐ 3
Ikke like mye nå som før ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg har hodet fullt av bekymringer 172

Veldig ofte ..... ☐ 1 Av og til ..... ☐ 3
Ganske ofte ..... ☐ 2 En gang i blant ..... ☐ 4

Jeg er i godt humør 173

Aldri ..... ☐ 1 Ganske ofte ..... ☐ 3
Noen ganger ..... ☐ 2 For det meste ..... ☐ 4

Jeg kan sitte i fred og ro og kjenne meg avslappet 174

Ja, helt klart ..... ☐ 1 Ikke så ofte ..... ☐ 3
Vanligvis ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg føler meg som om alt går langsommere 175

Nesten hele tiden ..... ☐ 1 Fra tid til annen ..... ☐ 3
Svært ofte ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg føler meg urolig som om jeg har sommerfugler i magen 176

Ikke i det hele tatt ..... ☐ 1 Ganske ofte ..... ☐ 3
Fra tid til annen ..... ☐ 2 Svært ofte ..... ☐ 4

Jeg bryr meg ikke lenger om hvordan jeg ser ut 177

Ja, har sluttet å bry meg ☐ 1 Kan hende ikke nok .... ☐ 3
Ikke som jeg burde ..... ☐ 2 Bryr meg som før ..... ☐ 4

Jeg er rastløs som om jeg stadig må være aktiv 178

Uten tvil svært mye ..... ☐ 1 Ikke så veldig mye ..... ☐ 3
Ganske mye ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg ser med glede frem til hendelser og ting 179

Like mye som før ..... ☐ 1 Avgjort mindre enn før . ☐ 3
Heller mindre enn før ... ☐ 2 Nesten ikke i det hele tatt ☐ 4

Jeg kan plutselig få en følelse av panikk 180

Uten tvil svært ofte ..... ☐ 1 Ikke så veldig ofte ..... ☐ 3
Ganske ofte ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg kan glede meg over gode bøker, radio og TV 181

Ofte ..... ☐ 1 Ikke så ofte ..... ☐ 3
Fra tid til annen ..... ☐ 2 Svært sjelden ..... ☐ 4