Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

Runi Elise Ertsås Nilsen

A cross-sectional study on the relationship between BMI and cognition

Master's thesis in Clinical health science - obesity and health
Supervisor: Asta K. Håberg
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Acknowledgements

I have been fortunate enough to have written in consultation with the fMRI group at the Norwegian University of Science and Technology (NTNU).

This past year has been both eventful and insightful. I have learned a lot about myself and it has been an interesting experience to be a part of the academic world. It has been challenging at times, but I would not have been without.

I would like to thank my supervisor Asta K. Håberg for all the support throughout the entire study and writing process, with grate guidance and patience this last year. I would also like to thank the fMRI group at the MR-center for welcoming me in their work environment.

Finally, I would thank my friends and family for mental support throughout this whole year.

Trondheim, June 2020

Runi Elise Ertsås Nilsen

Contents

Abstract

Introduction: Previous research has shown association between overweight/obesity and pathologies connected to overweight/obesity and cognition, indicated that mid-life obese individuals could have lower cognitive function compared to normal weight individuals.
The first aim of this study will investigate if BMI (body mass index) is associated with self-perceived memory and objectively measured cognition in a population from 50 to 66 years of age. The second aim is to find out if a change in BMI from Nord-Trøndelag health survey (HUNT) 2 to 3, i.e. approximately 10 years, is likewise associated with the same measures as in aim one.

Method: A cross-sectional design was employed including participant from the studies HUNT MR, HUNT Memoro and HUNT 2 in the adults from the general population in the age range 50-66 years of age. Cognition in relation to BMI was assessed by examining associations between demographic and clinical variables and self-perceived memory and objective cognitive tests. BMI was used to stratify the participants into groups by normal weight, overweight and obese, and for the HUNT 2 to HUNT 3 measures into stable BMI and increased BMI. Demographic and clinical variables was extracted from the HUNT database, self-perceived memory from the HUNT MR database and objective cognitive tests from Memoro, the web-based neuropsychological test battery.

Results: This study found a significant ($p= 0.015$) interaction effect were men in the obese group performed better in the Object in Grid (OiG) test, which was one of the objectively measured cognition tests. This significant interaction was also found in the increased BMI groups for men ($p= 0.032$) when looking at BMI change from HUNT 2 to 3 in relation to the cognition variables. No other associations between BMI group and self-perceived memory and objective cognitive tests were uncovered.

Conclusion: This study did not find any association between overweight and obesity and reduced cognition in a general population of middle-aged adults, which do not concur with previous studies on these relations and their influence on each other within middle-age people. Further research is needed to understand to potential associations between cognition and obesity to help optimizing treatment for people with obesity.

Abstrakt (norsk)

Introduksjon: Tidligere forskning har vist sammenheng mellom overvekt/ fedme og patologier knyttet til overvekt/fedme og kognisjon, indikerte at individer med fedme i midten av livet kunne ha lavere kognitiv funksjon sammenlignet med normalvektige individer.

Det første målet med denne studien vil undersøke om KMI (kroppsmasseindeks) er assosiert med selvopplevd hukommelse og objektivt målt kognisjon i en populasjon fra 50 til 66 år. Det andre målet er å finne ut om en endring i KMI fra Helseundersøkelsen i Nord-Trøndelag (HUNT) 2 til 3, dvs. omtrentlig 10 år, også er assosiert med de samme tiltakene som i mål én.

Metode: Det ble benyttet et tverrsnitts design som inkluderte deltager fra studiene HUNT MR, HUNT Memoro og HUNT 2 hos voksne fra den generelle befolkningen i aldersgruppen 50-66 år. Kognisjon i forhold til KMI ble vurdert ved å undersøke assosiasjoner mellom demografiske og kliniske variabler og selvopplevd hukommelse og objektive kognitive tester. KMI ble brukt til å stratifisere deltakerne i grupper etter normalvekt, overvekt og fedme, og for HUNT 2 til HUNT 3 målene til stabil KMI og økt KMI. Demografiske og kliniske variabler ble uthentet fra HUNT-databasen, selvopplevd hukommelse fra HUNT MR-databasen og objektive kognitive tester fra Memoro, det nettbaserte nevropsykologiske testbatteriet.

Resultat: Denne studien fant en signifikant ($p = 0,015$) interaksjonseffekt der menn i fedme gruppen presterte bedre i Object in Grid (OiG) -testen, som var en av de objektivt målte kognisjonstestene. Denne signifikante interaksjonen ble også funnet i den økte KMI-gruppen for menn ($p = 0,032$) når man så på KMI-endring fra HUNT 2 til 3 i forhold til kognisjonsvariablene. Ingen andre assosiasjoner mellom KMI-gruppe og selvopplevd hukommelse og objektive kognitive tester ble avdekket.

Konklusjon: Denne studien fant ingen sammenheng mellom overvekt og fedme og redusert kognisjon hos en generell populasjon av middelaldrende voksne, som ikke stemmer overens med tidligere studier om disse forholdene og deres innflytelse på hverandre hos middelalderske mennesker. Ytterligere forskning er nødvendig for å forstå potensielle assosiasjoner mellom kognisjon og fedme for å bidra til å optimalisere behandlingen for personer med fedme.

Introduction

General background

It is well established that it is a high and increasing prevalence of overweight and obesity among all age groups today (1). The Word Health Organization (WHO) describes this as an obesity epidemic, and regards it as one of the most severe health issue in developed and developing countries (2). WHO classifies overweight with cut-off points in body mass index (BMI) of ≥25 and obesity as ≥ 30, and are defined as *"a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired"* (3). They define a heathy BMI (kg/m^2) within the range 18.5 to 24.9 for adults, with regards to reduced mortality risk. On a world basis, over 1.9 billion adults are overweight, and among those 650 million people have obesity (4). In line with this, the prevalence of obesity is raising also in Norway, were men increased from 7.7% to 22.1%, and women from 13.3% to 23.1% between the years 1984/86 to 2006/8 (5), were men had a higher increase in obesity than women.

Stigmatization of people with obesity is a well-known issue (6), and many believe obesity is a result of lack of willpower, and eating too much energy dense food and perform too little activity. However, obesity is now categorized as a complex chronic disease which includes multifactorial interrelationship between genes and environment (7). The cause of obesity is multifactorial related to external factors such as types of food available and their costs, level of physical activity, social rules regarding eating etc., and individual factors such as genetic makeup, interest in food, appetite regulation, hunger mechanisms, ability to defer immediate gratification etc. Importantly, overweight and obesity are linked to increased risk of several serious diseases such as type 2 diabetes, metabolic syndrome, cardiovascular disease, several types of cancer, muscle and joint diseases and a number of psychosocial problems (8). The metabolic syndrome is a complex of interrelated risk factors for various chronic and acute diseases. These factors include dysglycemia, raised blood pressure, elevated triglyceride levels, low high-density lipoprotein cholesterol levels, blood glucose and obesity (particularly central adiposity) among more (9). Reducing obesity is therefore also important for improving the general health of people.

Diet in general is based on satiety and hunger, they are influenced by the quantity (energy content and density), and quality (macronutrient composition), this may further on affect the regulation of the periodicity of eating (10). Some studies have showed associations with reduced body fat (in humans) when meals are smaller and more frequent (10–12). This is based on that obesity is an appetite dysfunction, where one may think that people with overweight and obesity eat bigger meals, less frequent.

Certain personality characteristics and psychological profiles have been connected to overweight and obesity including increased impulsivity, more reward seeking and poorer decision-making and executive functioning (13,14). However, the studies have conflicting results (15,16). Importantly, studies of cognition in the overweight/obese population have not been performed according to standards of clinical neuropsychology across all cognitive domains with recognized standard tests (17).

Uncovering underlying differences in cognition to detect the increasing the risk of and/or resulting from overweight/obesity is vital to establish efficient measures to avoid overweight/obesity and limit the consequences of overweight/obesity on cognition.

Theoretical background, Obesity and cognition

Cognition

Cognition encompasses several functions such as perception, thought, language and memory which are usually divided into subfunctions or domains, for example short- and long-term memory, working memory, attention, visual-spatial perception, and executive function. These domains can be assessed by a wide variety of neuropsychological tests (18).

It is suggested both that poor frontal lobe function, i.e. greater impulsivity, reduced planning ability, impaired executive function and decision making, as well as poor working memory and episodic memory (frontal and temporal lobe functions) are involved in the pathogenesis of overweight and obesity (15). Evidence supporting this theory has been variable, but a recent meta-analysis and data from the large-scale UK biobank study (19), corroborate this notion. It is possible that the variable findings stem from differences in cohorts included in the different studies.

Cognition and body composition

High BMI, overweigh, obesity and undesirable elevated waist circumference have been associated with impairments in planning, impulsivity decision making, working memory and episodic memory (20). These two memory-components are core cognitive processes that are critical for food-related decision-making. Problems with appetite control and weight gain can therefore have been disrupted by impairments in working memory and episodic memory.

In relation to the feelings of uncertainty towards availability and planning of food it is looked at this impaired episodic memory (20). This can give a chain reaction with regard to an increment of food intake, who can lead to increased fat storage and result in a probability of becoming overweight and obesity. In support of this, it is reported that satiation to a variety of stimuli is faster for those with larger working memory capacity (20–22).
In extent of this there can be said that decisions regarding eating is an outcome of a cognitive process that involves integrating a range of inputs in memory, including sensory, somatic, affective, socio-cultural and contextual information (23). By consuming energy dense foods, it can have harmful effects on the hippocampus.

A systematic literature review by Prickett and colleagues (2015) revealed that mid-life obese adults (18-65 years) had impairments in almost all cognitive domains that they investigated, this was shown in complex attention, verbal and visual memory and decision making (24). Although, in that study, as in other studies on this topic, there were identified numerus methodological limitations which have to be taken into consideration when interpreting the results.

There has been a very strong focus on impairments in frontal functions (i.e. impulsivity, decision-making and reward processing) in the overweight and obesity research, and these functions are usually investigated using material with food stimuli in the overweight and obesity literature (17,25–28). This makes it difficult to draw general conclusion about cognition in people whit overweight and obesity.

In previous research it has been found links in the relation between cognition, body composition and somatic diseases and its association with increased BMI. The hypothesis that obesity, especially abdominal which is associated with metabolic syndrome and diabetes type 2, is associated with poorer cognition seems to be correlated with smaller hippocampi (29). The hippocampus supports long-term memory, and it is critically involved with cognitive processes such as memory and decision-making (30). Both spatial and several nonspatial forms of memory is encoded and regained from the hippocampus (31).

When looking at vascular risk factor in relation to cognition there has been seen that diabetes type 2, hypertension, hypercholesterolemia and obesity is connected to the development of mild cognitive impairment (MCI) (32,33) and dementia (34). Moreover, the association between obesity and age there are some findings pointing to increased risk of developing dementia, in middle-age people (35).

Furthermore, when it has been looked at psychosomatic distress there have been found a link between self-perceived memory decline with depression (36,37), but by adjusting for mood it were no longer associated to objective memory deficits (38,39).

Subjective cognitive function

A previous HUNT study have looked at impairments in subjective memory were they found relations such as neuroticism (personality traits), heart disease and stroke (vascular factors), white matter hyperintensities (brain changes), brain metabolic dysfunction and structural changes and psychosocial stress (40). It has also been found that decline in subjective cognition is linked to risk of developing preclinical Alzheimer's disease (AD).

Project aims

The first aim of this study will investigate if BMI is associated with self-perceived memory and objectively measured cognition in a population from 50 to 66 years of age. The second aim is to find out if a change in BMI from HUNT 2 to 3 is likewise associated with the same measures as in aim one.

The relationship between cognition and obesity remains undetermined, however previous studies on obesity has shown that it has detrimental effects on cognition (41–43). Apparently, effects are shown to arise in earlier stages, and not only mediated by clinical consequences of obesity (44). It is likely that differences are already there or developed due to BMI changes. The role of cognition in people with overweight and obesity needs to be understood to design optimal personalized and effective treatment to combat the obesity epidemic. This thesis will therefore include demographic and clinical variables to look at differences between BMI groups in self-perceived memory and cognitive measured cognition.

The prediction is that overweight and obese individuals in the general population will show decreased cognitive abilities compared to normal weight individuals, and further the population will increase their BMI-score from HUNT 2 till HUNT 3 which will affect the distribution of self-perceived memory and performance on the objectively measured cognition tests.

Material and method

Participants

The HUNT study is one of the world's largest prospective population-based studies and comprises health information, clinical data and biobank material from the population in Trøndelag, Norway, that consented to participate. The first data collection started in 1984 (HUNT 1) and have until now had four collections (HUNT 4, 2019).

This thesis used participants from the HUNT population between 50 and 66 years who were included in HUNT 3 (July 2007 - December 2009) HUNT-MRI (n= 1006, 52.7% females) who also had participated in HUNT 2 (1995-1997), and a subset of these participants who performed the web-based cognitive test battery Memoro (45).

All of the variables concerning anthropometric measures, blood variables and psychological health from both HUNT 2 and 3 were measured in the same manner. Other variables were taken from HUNT 3 (see specifications in the sections below).

Demographic variable

From the HUNT questionnaires the following variables were obtained: education level from HUNT 2 (46) while relationship status, age and sex were obtained from HUNT 3 (47). Level of education was divided into five categories, 1 = completed secondary school, 2 = completed technical college, 3 = completed high school, 4 = completed three or fewer years of college or university education, 5 = more than three years of college or university education. Relationship status was divided into ten categories, 0 = undisclosed, 1 = unmarried, 2 = married, 3 = widow, 4 = divorced, 5 = separated, 6 = registered partner, 7 = separated partner, 8 = divorced partner 9 = surviving partner.

Anthropometric measures

Body weight and height were from the clinical HUNT 3 and 2 measures acquired using manual measuring standard practices. Weight were measured without shoes and with a light layer of clothes. Registered weight was rounded to nearest half kilo. Height was measured wearing the same "outfit" as during weighing, and the registered centimeter were given without decimals.

Body Mass Index (BMI) are calculated as weight in kilograms divided by height in meters squared (kg/m2) (48). In this thesis the BMI was classified into three standardized categories, where a BMI values ≤ 24.9 are in the category "normal weight", the BMI values between 25 and 29.9 as "overweight", and ≥ 30.0 as "obese" (3).

Blood variables

From HUNT 3 and 2 non-fasting blood samples, triglycerides, cholesterol and glucose were obtained.

Blood glucose level was tested with a drop of blood obtained by pricking the finger with a sharp needle or an aperture. All variables were using Architect ci8200 in HUNT 3 and Hitachi 911 Autoanalyzer in HUNT 2 as instruments. In glucose tests were analyzed used Hexokinase/G-6-PDH methodology in HUNT 3 and an enzymatic hexokinase method in HUNT 2. The concentration of glucose in the blood to humans is normally 4-6 mmol/l. All the values were given in non-fasting serum samples. Cholesterol were analyzed by enzymatic cholesterol esterase methodology in HUNT 3 and measured by applying an enzymatic colorimetric cholesterol esterase method in HUNT 2 (49). Cholesterol is grouped into a total cholesterol variable where between 5-6 mmol/l is satisfying, and values above are undesirably elevated (50). Triglycerides were analyzed by Glyserol Phosphate Oxidase methodology in HUNT 3 and using an enzymatic coulometric method in HUNT 2. Triglycerides is "regular fat" dissolved in the blood and should be ≤ than 0.66 mmol/l (51).

Psychological health

Previous research have shown that disorders related to brain atrophy such as reduced brain volumes and increased risk of dementia are linked to anxiety and depression, and as they are common among middle-age and older adults it is important to understand the role of these disorders impact also in cognition (52).

The Hospital anxiety and depression questionnaire (HADS) (53–55) was used in HUNT 3 and 2 (56). HADS is an instrument for self-report of anxiety and depression in people with both somatic and/or mental problems (57). It is developed by Zigmond and Snaith in 1983 and is an instrument which is reliable for detecting and assessing anxiety and depression symptoms in patients in somatic, psychiatric and primary care, as well as the general population (used here) (53,54).

This self-reported questionnaire measures the frequency of anxiety and depression during the last week (55). This questionnaire used a 14-item version where participants rated their symptoms using a 4-point Likert scale where 0 is "no symptom", and 3 corresponds to "highest symptom level". The items are equally divided, seven about anxiety (HADS-A) and seven about depression (HADS-D) (see appendix A1). The maximum score of the test is 21 on each scale indicating the highest symptom load. A HADS-A or HADS-D score of 0-7 is considered normal, while 8-10 mild-, 11-14 moderate- and 15-21 severe symptoms (58). A score of ≥8 on either scale is often treated as an indication of clinically relevant for symptoms of anxiety or depression, here the score have to be doubled to find the corresponding symptom group (52,54). In this thesis the scores were combined into a total score for both anxiety and depression, this makes a maximum score of 42.

Self- perceived cognition

It has been found that a subjective perceived reduction in cognition is strongly associated with age (59) and in extension of this it is interesting to look at what the participant think about their memory. And by further looking at the spectra of reduction in memory, there may also be an underlaying pathological basis or a reflection of psychosomatic distress. Comparing self-perceived and objectively measured memory has not shown that self-perceived memory reflects objective memory function (60).

In HUNT 3 participants answered nine questions (Meta Memory Questionnaire) concerning their self-perceived cognition (56,58). The questions included current memory problems and change in memory function concerning short time, names, dates, plans, medium time, long time and talking.

Scoring of self-perceived memory is done in two ways: the first and last question is scaled; 1 = No, 2 = Yes, some, 3 = Yes, a lot. The rest is scaled; 1 = Never, 2 = Sometimes, 3 = often (see table 2 and 5). The lower score the better self-perceived memory.

Objective Cognitive testes

A subset of participants in HUNT 3 MRI performed cognitive testing with Memoro (45,61,62), a web based cognitive testing system developed in the fMRI group.

The participants had to perform the tasks on their own without taking any notes during the tests. The subjects performed the tests either in their own home, at work or at a dedicated room at the MR-center. The participant was not informed of their results on each test, except the "pre-test trial" to ensure compliance with test instructions.

Four tests assessing different cognitive abilities were performed, and the participants filled in a questionnaire on self-rating their computer familiarity. All test instructions were given both orally and written on the screen.

Episodic memory: Processing speed

Processing speed (PS) is often investigated with briefly presented visual or auditory stimuli (63). In this thesis, visual stimuli were used. The PS reflects speed of perception and selection of appropriate response and as such includes an executive function.
Age plays a significant role in PS performance were the PS decreases with increasing age. Most other cognitive tasks rely on processing speed. Because age is strongly related to heath status it has been suggested that health problems in general might affect an individual's PS (63). There is still uncertainty as to which health-related issues can affect PS (64). Another variable that may moderate PS is the amount of experience and/or practice with the test.

Test description:

The participants were instructed to judge if pairs of geometrical shapes (block 1, 3, 5) or numbers (block 2, 4, 6) were identical or different from each other. They started with four pre-test trials before the test started, here they were given feedback on their performance. They were asked to respond as fast as possible, without making mistakes. To indicate if they thought the pair was identical or different, they pressed the keys "L" for identical (Norwegian L = like) and "F" for different (Norwegian F = forskjellig) on their keyboard. The entire test contained six blocks, each lasting 30 seconds. The complexity in the geometrical shapes and the amount of numbers increased in difficulty with each block completed. Performance was scored as number of correct responses minus the number of erroneous responses. The total score varies from 0 to 150 points.

Working memory: Letter-number sequencing

Working memory is responsible for mental manipulation of information and problem solving during a short time period (65). It is restricted in its capability and only allows retention from a limited number of items to be manipulated (66). This specific brain function may be affected in many different disorders like ADHD (Attention Deficit Hyperactivity Disorder), learning disabilities, anxiety disorder, depression and bipolar disorder to mention some (67,68).

Test description:

The subjects were presented with a string of single letters and numbers from 2 to 8. Each letter/ number was shown for 2 seconds on the screen. This test started with three practice trials with feedback on responses. Afterwards the test started. There were in total 14 trials, and the number and letters increased from two to eight digits with consecutive trials. After stimulus presentation in a trial, participants were to recall and type all the numbers in ascending order and then all the letters in alphabetical order. The test stopped automatically if there were three consecutive erroneous trials. Scoring was given by the number of correct trials. Test scores for both immediate recall and delayed recall was added together to make a maximum score of 32.

Verbal memory: Word list learning and memory

This memory test measures the ability of an individual to both encode and store a list of words short and long term (69), here it is looked at short-term memory (70). This test is a combination of the California Verbal Learning test (CVLT) (71) and the Word List Test (WLT) (72). Word list learning and memory becomes reduced with age-difference, schizophrenia (73) and early stages of dementia (69).

Test description:

The participant listens to a voice presenting a main list of 16 words and a distraction list of 16 words. The words in the main list were from four semantic categories; furniture, fruits/vegetables, animals and means of transportation. The 16 words were presented in a random order to each participant. The main world list was presented a total of 4 times. After that a "distraction list" which contained the same number of words, but from the categories;

furniture, body parts, fruits/vegetables and animals, was presented. After the distraction list the main lest was to be recalled, the immediate free recall test. The participants typed in the words they remembered from the main wordlist.

Next there where a 20 minutes delay of nonverbal test tasks. The participants then performed delay free recall of the main list where they again typed the words they membered.

The Memoro system was used to score the participants responds from the test, except the incorrect ones. Before the final score was given the incorrect responses were manually evaluated. This because words could be misheard, misspelled or sounded phonologically similar to another word. If the control person saw that an "error" was clearly meant as a correct response it was changed manually. Final scoring of the test was graded as number of correctly recalled words on immediate free recall test, VM (imm.rec), and on the delayed free recall test, VM (late.rec). The score was 16 words for both VM imm.rec. and VB late.rec, making the maximum score 32 words.

Spatial memory: Objects in Grid

Spatial memory is memory for location of for instance objects in a specific environment (74). Here, short-term or immediate spatial memory was investigated. The test used here is similar to the Silverman and Eals Location Memory test which are used in other studies (75). Spatial short-term or immediate memory is also sensitive to age affects, and impairments are seen to relate to Alzheimer`s disease (AD) (76).

Test description:

The participant is task with remembering the location of objects (lifelike drawings) located to different squares in a grid. It stated with a practice test which contained dragging and dropping objects on the screen.

The participant was showed 18 items to remember. Each item was located randomly in a square within a 6 x 6 grid. The grid with the images were presented for 90 seconds. Immediately after the grid and objects disappeared, the participants were presented with an empty grid and were required to drag the objects now posited to the side of the grid to their correct place. They could replace the objects until they thought they had placed them correctly. Scoring were done as the number of correctly placed objects. The score on this test were 18 (objects) for each immediate and delayed, making it a maximum score of 36 objects.

Computer familiarity assessment

Performance on computerized test batteries may depend on the participants familiarity with computers and the use of it (77). It has been shown that computer familiarity may in some cases influence validity of test results, and can be associated with performance on tests (78). A better performance on a cognitive test is also associated computer familiarity is general, regardless of whether the test is computerized or traditional (79). Age also plays a role here. Performance on computerized tests can decreas due to inexperience, but not in all cases, some studies shows that the seniors are able to follow the instruction regardless because instructions often are simplified to all “levels” of familiarity (80,81). Another issues that may affect performance is technical aspects of the computer, especially hardware or user interface (82).

The participant were asked to rate their own computer familiarity with six questions (three on computer usage, three on computer skill), the Memoro Short Computer Questionnaire (see appendix A2) (78). Low computer familiarity can influence performance on the Memoro tests. Computer usage gave a maximum of 15 points, and computer skill gave 20 points maximum, making it a maximum score of 35 points.

Statistical analyses

IBM SPSS Statistics (version 25) was used to analyze the data. Data from the same participants in HUNT 3 MR cohort, Memoro, and HUNT 2 were used in the analyses.

Project aim 1

The BMI values were categorized in to three groups, normal weight, overweight and obese, and these three BMI groups were used in the analyses.
Demographic and clinical variables were all normally distributed and therefor given in mean and standard deviation (SD).

Difference between the tree BMI groups (normal, overweight and obese) with regard to the demographic and clinical variables, self-perceived memory and objective measured cognitive test scores were compared. A chi-square test was performed to investigate if the level of educations differed between the three BMI groups. For the categorical and ordinal data, HADS and relationship status, a Mann-Whitney U test was used to examine presence of differences

between BMI groups. For the continuous data (scalar data) (age, blood glucose, cholesterol and triglycerides) an ANOVA was used, if it was significant difference in mean, this was further looked into with the Post Hoc test. A bar chart was made for the variables that were significant different to visualize the differences.
P-values ≤ 0.05 (two-tailed) were considered statistically significant.

Self-perceived memory

The response to each memory question was analyzed by a Pearson chi-squared test using the tree BMI groups. Values were skewed and therefore given in median and range.
One missing value (women) on BMI-value and thereby taken out of analysis.

Objective cognitive tests

The scores from the Memoro tests were compared between the tree BMI groups in a two-way ANCOVA after assessing that the group variances are equal and the assumption of homogeneity of variance fulfilled. The outcome/dependent variables were total score of processing speed, letter-number sequencing, word list learning, objects in grid and computer familiarity.

Cofounding factors were age and education, and fixed factors were BMI and sex. Looking at the interaction between BMI and gender (group*sex interaction) by doing a post hoc test (Tests of Between-Subjects effects).

Project aim 2

To examine the influence of change in BMI from HUNT 2 to HUNT 3 on self-perceived memory and objective measured cognition from HUNT 3, a new the BMI-change value was calculated. The HUNT 2-3 BMI change value was stratified into a stable group which included those who had decreased or no change in BMI from HUNT 2 to HUNT 3. While the increasing BMI group included those who had increased their BMI with ≥0.01 BMI-points in the same period.

Difference between the two BMI groups (stable and increased) with regard to the demographic and clinical variables, self-perceived memory and objective cognitive tests were compared with similar methods as in aim 1.

P-values ≤ 0.05 (two-tailed) were considered statistically significant.

Self-perceived memory

The response to each memory question was analyzed by a Pearson chi-squared test comparing the two BMI groups. Values were skewed and therefore given in median and range.
Seven missing values (four women, tree men) on BMI value and thereby taken out of analysis.

Objective cognitive tests

Similar ANCOVA analysis was used as in project aim 1, but in the two BMI group (stable and increased).

Ethics

All the participants in the HUNT studies were aware and content with that their data on weight and other personal variables are being used as reaches data. Data are approved for extraction from both HUNT and REK (regional ethics committee). This study has not endangered any of the participants.
The study was approved by the regional ethics committee (reference number 166559) and HUNT board of directors.

Results

Demographic and clinical variables

Table 1 shows the distribution of the demographic and clinical variables in the three BMI groups in project aim 1.

Table 1: Descriptive measures of the different BMI groups.

Measure	Normal weight (n = 311)	Overweight (n= 491)	Obesity (n= 203)
Age (a)	57.3 ±4.21	57.8 ±4.13	58.2 ±4.29*
Education (range 1-5) (b)	2.9 ±1.41*	2.6 ±1.33	2.5 ±1.37

Relationship status (range 0-9 (c)	2.3 ±0.81	2.3 ±0.82	2.2 ±0.79
HADS total score (c)	6.8 ±5.42	6.7 ±5.11	7.1 ±5.55
Blood glucose (mmol/l) (a)	5.3 ±1.17	5.7 ±1.62	5.9 ±2.26*
Cholesterol (mmol/l) (a)	5.8 ±1.06	5.7 ±1.05	5.9 ±0.97
Triglycerides (mmol/l) (a)	1.6 ±0.85	1.7 ±0.91	1.7 ±0.90

Values are given as mean and ± SD. Age in years old, Education range from lower (1) to highest (5), for relationship status categories see Material and Methods, HADS is the total score including anxiety and depression, Blood glucose. n = number of participants. Statistical tests used were a, ANOVA. b, *chi-squared test.* c, *Mann-Whitney U test. * marks significant difference.*

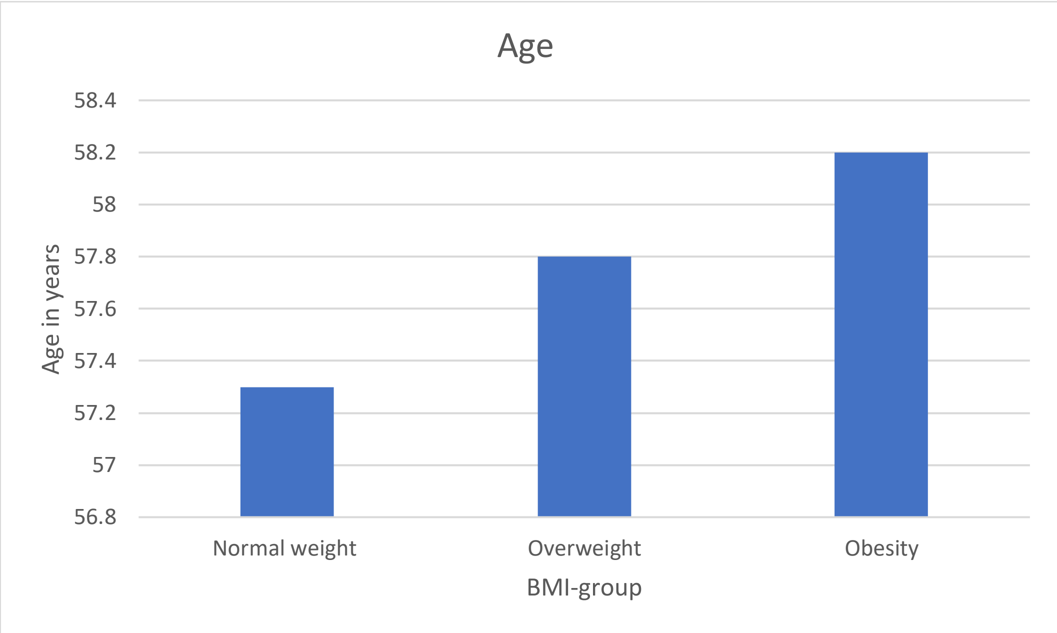

Figure 1: Overview of mean differences in age between the BMI groups.

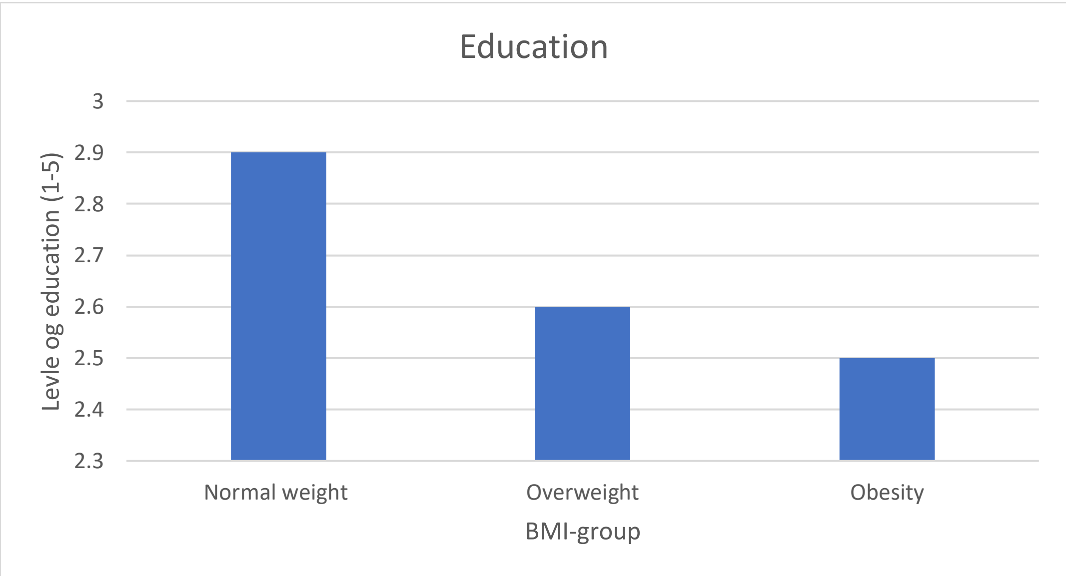

Figure 2: Overview of the mean differences in education level going from 1-5 (lowest to highest) between the BMI groups.

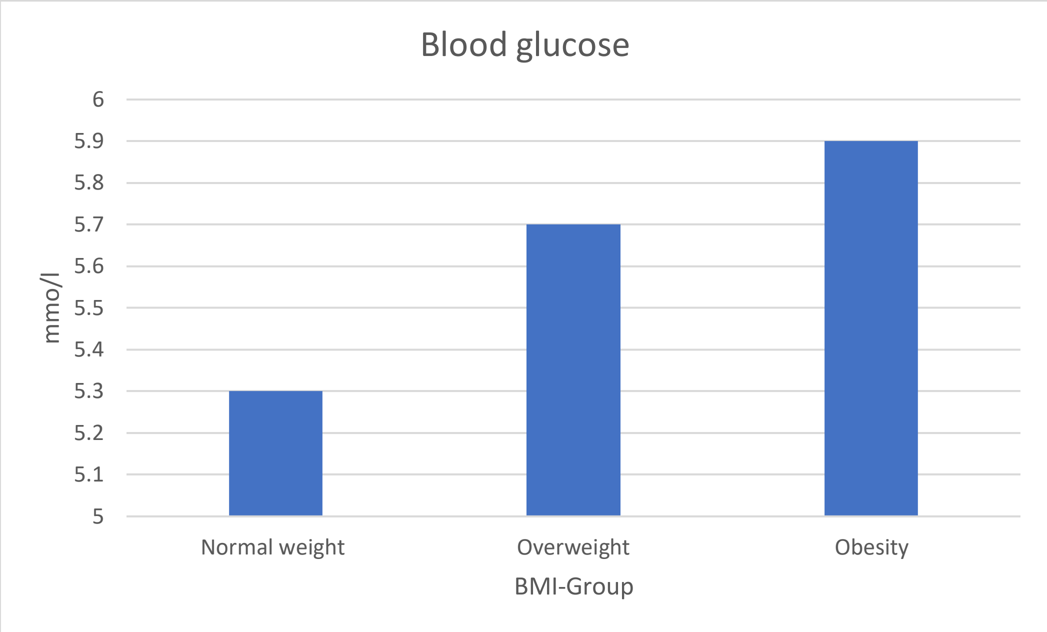

Figure 3: Overview of mean differences in blood glucose shown in mmo/l between the BMI groups.

The three groups differed on age, education and blood glucose levels (Table 1). A significant (p-value 0.046) higher age were found in the obese group compare to the normal weight group (Figure 1). Whiles education was significantly (p-value 0.02) lower in the obese group compared to the normal weight group (Figure 2). Blood glucose was significantly (p-value 0.00) higher in the obesity group compare to the normal weight group.

Project aim 1 (PA1):

Self-perceived memory

Table 2 shows that the participants think in general their memory is god and have just some problems remembering certain things. For the memory they have some trouble with is question 1, 3, 4 and 7, these ones mainly comprise the long-term memory.

Table 2: Descriptive of self-perceived memory in the tree BMI groups.

Question	Normal weight (n = 311)	Overweight (n= 491)	Obesity (n= 203)
1. Has your memory changed since you were younger?	2 (2)	2 (2)	2 (2)
2. Do you have trouble remembering events a few minutes ago?	1 (2)	1 (2)	1 (2)

3. Do you have trouble remembering names of other people?	2 (2)	2 (2)	2 (2)
4. Do you have trouble remembering dates?	2 (2)	2 (2)	2 (2)
5. Do you have trouble remembering to do what you have planned?	1 (2)	1 (2)	1 (1)
6. Do you have trouble remembering events that happened a few days ago?	1 (2)	1 (2)	1 (2)
7. Do you have trouble remembering events that happened a year ago?	2 (2)	2 (2)	2 (2)
8. Do you have trouble keeping the thread in conversations?	1 (2)	1 (2)	1 (2)
9. Do you have trouble whit your memory?	1 (2)	1 (2)	1 (2)

Values are given in median and (range). The first and last question is scaled; 1 = No, 2 = Yes, some, 3 = Yes, a lot. The rest is scaled; 1 = Never, 2 = Sometimes, 3 = often. n = number of participants. Tested with chi-squared test.

There was no significant difference in self–perceived memory score between the three BMI groups on any of the questions (Appendix A3 for p-values). This means that every question on self-perceived memory is independent from the BMI groups, which shows no association.

Objective cognitive tests

An overview of the scores on the four cognitive tests and computer familiarity questionnaire for the three BMI groups is presented in table 3.

Table 3: Descriptive of the objective cognitive tests divided into the tree BMI groups.

Test	Normal weight (n= 311)	Overweight (n= 491)	Obesity (n= 203)
Processing speed	50 ±12.4	50 ±12.9	47 ±12.9
Letter-number sequencing	8 ±2.7	8 ±2.9	8 ±3.3
Verbal memory test	26 ±5.6	26 ±4.9	25 ±5.7
Object in Grid	15 ±6.9	17 ±7.6	17 ±7.7
Computer familiarity	23 ±5.3	24 ±5.3	24 ±5.8

Presented in mean and ± SD. See M&M for scoring of each test. Values rounded up to the nearest decimal or hole number. n = number of participants.

Processing Speed

In this test there were no variable that was significant associated with performance. When looking at the scores, the normal weight group scored 49.8 ±1.51, overweight group 49.9 ±1.10 and obese group 46.8 ± 1.51 on PS. A slight reduced performance on the test was seen among the obese participants, but no significant effect was found ($p = 0.203$ for BMI group).

Looking at gender differences we also can see a small difference with women scoring slightly better with a mean of 49.3 ± 1.07 than men 48.5 ± 1.18, but no significant effect of gender was found (p = 0.608). There was no interaction effect between BMI group and gender (p = 0.340).

Letter-Number Sequencing

In this test there were no variable that was significantly explained the score on the Letter-Number Sequencing test. All BMI groups have very similar mean values on the test, with the normal weight group scoring 7.7 ±0.35, overweight group 7.9 ±0.26 and obese group 7.7 ± 0.37. This emphasize that all of the BMI groups perform approximately the same on the test which was also reflected in the significant level with p-value is 0.930 for the BMI groups.
Looking at gender differences we also can see almost no difference where women have a mean of 7.6 ±0. 26, and men 7.9 ±0.28, which means there is a very slight advantage to be a man in performance in this test, but p- value 0.349 showing no significant gender difference.
There was no interaction between BMI group and gender (p = 0.293).

Verbal Memory Test (word list)

In this test there were no variable that was significant associated with the score, when looking at test scores, all BMI groups had very similar mean values on the test, normal weight group scored 25.9 ±0.66, overweight group 25.6 ±0.49 and obese group 25.3 ± 0.67. This emphasize that all of the BMI groups perform approximately at the same level on this test with the p-value of 0.776 confirms that the BMI groups performed similarly.
Looking at gender differences we find just a small difference where women have a mean of 25.1 ±0.47, and men 26.1 ±0.52, which means there is a very slight advantage to be a man in performance in this test. There was no interaction between BMI group and gender (p-value = 0.136).

Objects in Grid (OiG)

In this test there was one variable that was significantly associated with test performance; age (p = 0.025). This shows that there are an association between what age the participants are and the BMI group they are in. There was also a significant interaction between BMI group and gender (p = 0.015).

When looking at the performance data the normal weight participants had a mean score of 14.9 ±0.86, the overweight participants a mean of 16.8 ±0.64, and the obese participants a mean score of 17.1 ±0.89. This shows a slight difference with the obese participants placing approximately three more objects than the normal weight participants in their correct position in the grid, which means that there was a slight advantage to be obese in performance in this test. But there was no significant effect of group (p = 0.153). Looking at gender differences we can see a small difference where women have a mean of 15.7 ± 0.62, and men 16.9 ± 0.68, which means there is a slight advantage to be a man in performance in this test, but this was no significant (p = 0.177).

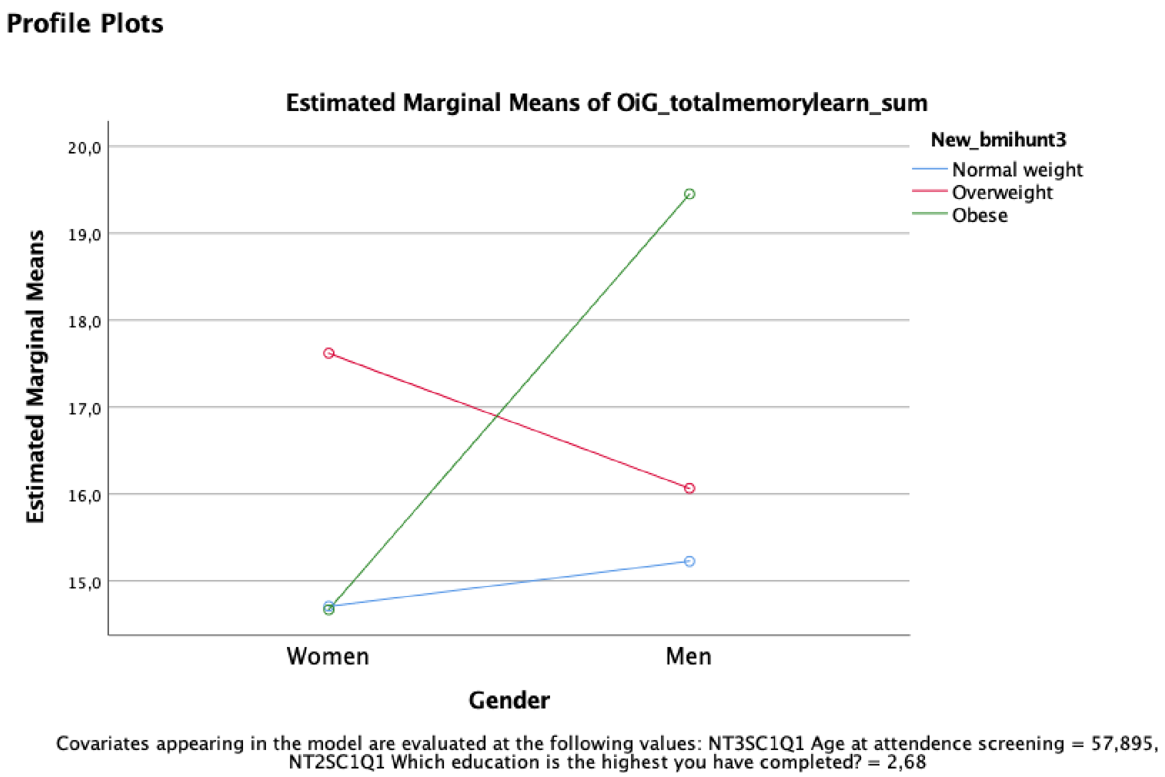

Figure 4: Illustrates the association in BMI groups and gender in the Objects in Grid test.

Computer familiarity

There was no variable that was significant associated with total score on computer familiarity questionnaire. When looking closer at the data all BMI groups have scored themselves very similarly with the normal weight group having 22.7 ±0.64, overweight group 24.4 ±0.47 and obese group 23.9 ± 0.65 points. This emphasize that all of the BMI groups scored themselves very similarly. When looked just at BMI differences, it is as also shown no significant p-value of 0.120 for BMI group.

Looking at gender differences we can see almost the exact same self-rating where women score themselves to a mean of 23.7 ±0.45, and men 23.7 ±0.50, and again the p-value = 0.995, is none significant. There was no interaction between BMI group and gender (p = 0.751).

Project aim 2 (PA2):

From HUNT 2 to 3 most participants increased their BMI leading 746 participants in the increasing BMI group and 253 in the stable BMI group. BMI increased from a mean of 25.70 in HUNT 2 to 26.96 in HUNT 3, which is 1.3 BMI-points, most of the participants remained in the category «overweight» from HUNT 2 to 3. The demographic characteristics and blood measures in the stable and increasing BMI groups are shown in Table 4.

Table 4: Descriptive of the stable and increasing BMI groups.

Measure	Stable BMI group (n= 253)	Increasing BMI group (n= 746)
Age	58.1 ±4.24	57.6 ±4.17
Education (range 1-5)	2.7 ±1.39	2.7 ±1.36
Relationship status (range 0-9)	2.3 ±0.77	2.3 ±0.82
HADS total score	7.1 ±5.52	6.6 ±5.14
Blood glucose (mmol/l)	5.6 ±1.82	5.6 ±1.61
Cholesterol (mmol/l)	5.5 ±0.99	5.8 ±1.04
Triglycerides (mmol/l)	1.6 ±0.91	1.7 ±0.88

Values are given as mean and ± SD. Age in years old, Education range from lower (1) to highest (5), for relationship status categories see Material and Methods, HADS is the total score including anxiety and depression, Blood measures are in the same forms of measure. n = number of participants. BMI-change from HUNT 2 to 3.

Self-perceived memory

None of the questions on self-perceived memory were significantly different between the two BMI groups. This means that every question on self-perceived memory is independent from which of the BMI groups the participants belonged to.

The score on the different questions are presented in Table 5 and the statistical results in Appendix B1.

Table 5: Descriptive for self-perceived memory questions divided in the two BMI groups.

Question	Sable BMI (n= 253)	Increased BMI (n= 746)
1. Has your memory changed since you were younger?	2 (2)	2 (2)
2. Do you have trouble remembering events a few minutes ago?	1 (2)	1 (2)
3. Do you have trouble remembering names of other people?	2 (2)	2 (2)
4. Do you have trouble remembering dates?	2 (2)	2 (2)
5. Do you have trouble remembering to do what you have planned?	1 (2)	1 (2)
6. Do you have trouble remembering events that happened a few days ago?	1 (2)	1 (2)
7. Do you have trouble remembering events that happened a year ago?	2 (2)	2 (2)
8. Do you have trouble keeping the thread in conversations?	1 (2)	1 (2)
9. Do you have trouble whit your memory?	2 (2)	1 (2)

Values are given in median and (range). The first and last question is scaled; 1 = No, 2 = Yes, some, 3 = Yes, a lot. The rest is scaled; 1 = Never, 2 = Sometimes, 3 = often. n = number of participants. Tested with chi-squared test.

Objective cognitive tests

An overview of the scores on the four cognitive tests and computer familiarity questionnaire for the two BMI groups is presented in table 6.

Table 6: Scores on the different cognitive tests and self-reported computer familiarity questionnaire in the two BMI groups.

Test	Sable BMI (n= 253)	Increased BMI (n= 746)
Processing speed	49 ±12.5	49 ±12.9
Letter-number sequencing	8 ±2.6	8 ±3.0
Verbal memory test	26 ±4.9	25 ±5.4
Object in Grid	16 ±7.5	16 ±7.5

Computer familiarity	24 ±5.2	24 ±5.5

Presented in mean and ± SD. See M&M for scoring of each test. Values rounded up to the nearest decimal or hole number. n = number of participants.

Processing speed

In this test there are no variable that was significant associated with performance.
When looking at the BMI groups scores the stable group has a mean score of 49.4 ±1.54, and the increase group a mean of 48.7 ±0.86 which is very similar as also shown by the lack of significant difference (p = 0.689). Looking at gender differences we also can see a small difference where women have a mean of 49.8 ± 1.30, and men 48.4 ± 1.18, which means there is a slight advantage to be a woman in performance in this test, but this was not significant (p = 0.422).
Also, when comparing the groups up to the genders we find only a small difference. In both groups there was an advantage to be a woman with stable BMI group woman having a mean of 50.2 ± 2.32, increased BMI group women a mean of 49.4 ± 1.20, while stable group men had 48.1 ± 1.23 and increasing BMI men 48.7 ± 2.01, but there was no significant interaction between BMI group and gender (p = 0.939).

Letter-number sequencing

In this test there are no variable that was significantly associated with performance. When looking at BMI groups, the stable BMI group had a mean of 7.5 ±0.36, and the increasing BMI group a mean of 7.8 ±0.20 which is shows a slight advantage of a higher BMI in performance in this test, but this was not significant (p = 0.540).
Looking at gender differences were no real difference with women having a mean of 7.72 ± 0.308, and men 7.61 ± 0.276, was not significantly different (p = 0.797).
Also, when examining the interaction between BMI group and genders no significant interaction effect was found (p = 0.118). It seems that there is an advantage to have a stable BMI for women compared to men, and the opposite for the increasing BMI group where men have a better performance in the test. Stable group woman has a mean of 7.9 ± 0.55, and men 7.2 ± 0.47, and increased group have a mean of 7.5 ± 0.29 for women and 8.1 ± 0.29 for men. Still this effect was not significant.

Verbal memory test (word list)

In this test there are no variable that was significant associated with performance. When looking at the performance in the stable BMI group with a mean of 26.36 ± 0.665, and that in the increasing BMI group with a mean of 25.2 ±0.37 there is no significant differences reflected in the p-value 0.121.

Looking at gender differences we see find women to score a mean of 25.6 ± 0.56, and men 25.9 ± 0.52, which is almost similar and a non-significant p-value of 0.683.

There was also no significant interaction between BMI group and gender for performance on the verbal memory test. There seemed to be an advantage to be a woman compared to man in the stable BMI group, and the opposite for the increasing BMI group, but there was no significant interaction present, p-value = 0.557.

Object in Grid

In this test there were two variables that were significantly associated with performance, age (p = 0.041) and the interaction between BMI group and gender (p = 0.032), which means that increasing age is associated with the Object in Grid performance.

When looking at scores in the BMI groups, the stable group had a mean score of 15.8 ± 0.89, and the increasing BMI group a mean score of 16.4 ± 0.50 which is not a great difference but can indicate slight advantage of being in the increasing BMI group on performance in this test, the p-value 0.539 was not significant.

Looking at gender differences we see a small difference where women have a mean score of 16.2 ± 0.75, and men 15.9 ± 0.68, but there was no significant effect with a p-value 0.805.

The interaction between BMI groups and genders was significant. There was an advantage to have a stable BMI for women, and the opposite for the increasing BMI group where men had a better performance.

Profile Plots

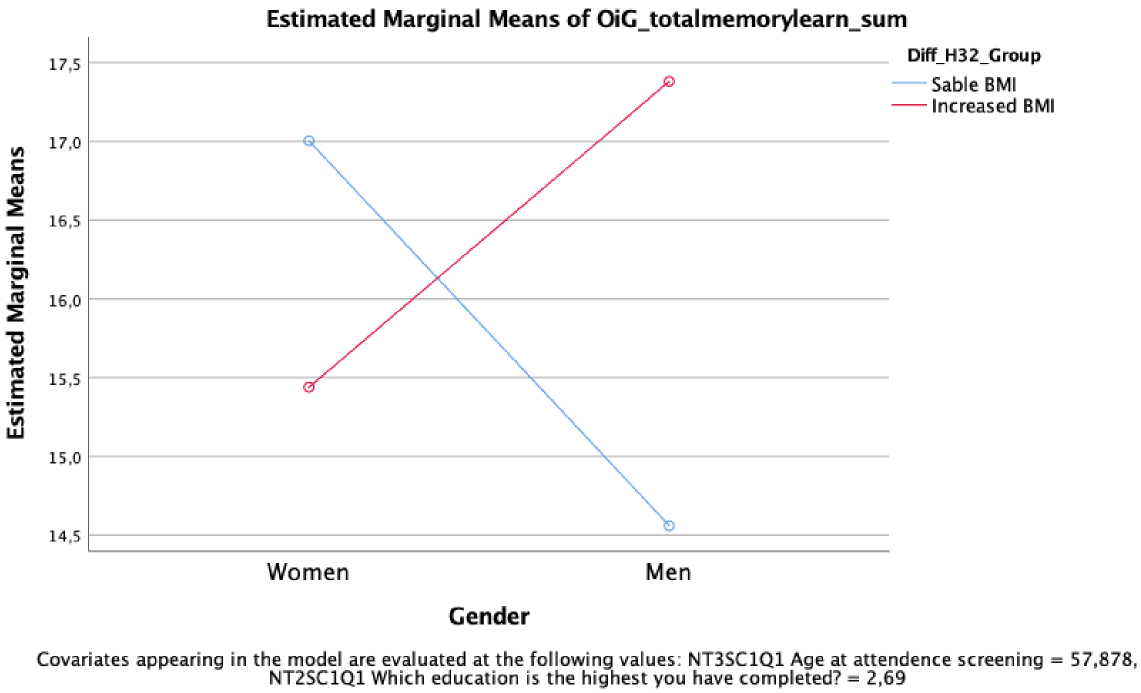

Figure 5: Shows the performance in the Object in Grid test divided into gender and BMI group.

Computer familiarity

There was no variable that was significant associated with self-rating of computer familiarity. When looking at the scores, the stable BMI group had a mean score of 23.9 ± 0.66, and the increasing BMI group a mean of 23.7 ±0.36 which were not significantly different (p = 0.768). Looking at gender differences we see a small difference where women have a mean of 23.6 ± 0.56, and men 24.1 ± 0.51, but this was also not significant with a p value of 0.434.

There was no interaction between BMI group and gender (p = 0.404).

Discussion

Aim and result

The first aim of this study was to investigate if BMI was associated with self-perceived memory and objectively measured cognition in a population from 50 to 66 years of age. The second aim was to find out if a change in BMI from HUNT 2 to 3 was likewise associated with the same measures as in aim one.

This study did not find any association between overweight and obesity and reduced cognition, which do not concur with previous studies which finds relations between undesired elevated BMI its relation to decrement in cognition, within adults (24).

For aim one it showed no decreased self-perceived memory nor in objectively measured cognition, but contrary to the expectation OiG performance was better in obese men. For aim two the same results with regard to self-perceived memory and objectively measured cognition were showed. On the OiG test performance was best in men with increasing BMI from HUNT 2 to HUNT 3. This study showed an interaction in performance on the OiG test, which was one of the objectively measures of memory. The significant interaction was between BMI group and gender, with obese men having the highest performance score. Higher performance on OiG was also found for the group with increasing BMI from HUNT 2 to HUNT 3, and a significant interaction between BMI group and gender was present with the men with an increasing BMI scoring best on the OiG test.

Demographics and clinical variables

As showed in the distribution of participants in each BMI group the number participants with normal weight was 311, overweight was 491 and obese was 203 at time of HUNT 3. This shows that the number of participants in the normal weight group is lower compared to the overweight group. This is in line with the global explosive evolution of the obesity problem. Today the increase in number of overweight and obese individuals is dramatic in the whole world and with this increase follows numerous diseases which further aggravates the effects of overweight and obesity. The amount of overweight and obese individuals have increased the with time, in all ages and social groups, concerning the whole world (83)(s. 466-471).

When it comes to the demographic and clinical variables, there was a significant difference between the tree BMI groups in HUNT 3 in the variables age, education and non-fasting blood glucose (see table 1 and figure 1-3).

Since BMI increases with age (84), this might explain that the obese group had the highest age, but the differences was so small that in practice it does not make a difference despite that it is significant. Looking at the global prevalence in Chooi and colleagues (2018) study on the epidemiology of obesity, the age group 50-64 years, which is quite similar to the HUNT 3 age range, has the highest percent of 47% (women 50%, men 45%) of people with overweight, in people with obesity, in the same age group, with a percent of 16% (women 20%, men 12%) of the whole population (85). These global numbers are almost identical to the present results in HUNT 3 where the overweight group was 48.9% of the total, and the obesity group counted for 20.2%.

Education was lower in both the overweight and obese group compared to the normal weight BMI group. Similar results have also be published in a larger HUNT study by Sund and colleagues (2010) who reported that higher BMI was found in those of lower education (86). The number and frequency of good health choices are associate with education level (87). Those with higher education have better lifestyle behaviors such as exercise more often, have a healthier diet and receive preventative medical care. This can facilitate and create environmental or social networks that can influence favorable behavioral health habits, it can also lead to better nutrition and an general increased opportunity to make more health-promoting choices (88,89), which can counteract a obesogenic environment. A HUNT study by Krokstad and colleagues (2013) showed that a low level of education in HUNT 1 was most related to women with obesity and in HUNT 3 the same was mostly seen among men (90). It is often seen that people with obesity are in social networks where higher education is less frequent. In industrialized countries, it is seen that low socioeconomic status is associated with obesity, while it is the other way in developing countries (91). This makes the relationship between education level and overweight/obesity divers based on with country a person is from, and the expectation towards education as well as the economical availability to take higher education. In some countries, unhealthy food and beverages may be less expensive which may be a cause for overweight/obesity and further education may also be expensive, so, then looked at these factors together one may see a relationship between low education and high BMI.

In general, there is a clear advantage to have a higher level of education on the development of a healthy lifestyle and further on the preserving a healthy BMI.

There was no difference in relationship status between the BMI groups in this study. This is partly in line with a study by Averett and colleagues (2008) who looked at relationship status and BMI (92). They look at four hypotheses regarding the topic of marriage from the following point of views; selection, protection, marital obligation and marriage market. The key points they found were that social obligation in a marriage lead to socializing within networks which may eat more unhealthy food etc., and that individuals on the marriage market increase their chances by losing weight and those married no longer maintaining healthy BMI. They found that BMI increased for both men and women during marriage and in the course of a cohabiting relationship. I did not investigate if those married in HUNT 3 were married to people who had the same BMI class or not. But this could have been investigated with more variables from the HUNT databank. The results did show that BMI class did not influence relationship status, which means that relationships are built on other aspects than BMI.

The obese and overweight groups also had higher blood glucose levels than the normal BMI group, but the mean value was within normal range (between 4-6mmol/l) in all groups. The obese group had a mean value of 5.9 mmol/l and the normal weight group had 5.3 mmol/l, this shows that both of groups had values in the upper half of the scale. Since obesity is a major component of metabolic syndrome it is also strongly associated with other components involved in metabolic syndrome such as elevated glucose levels (93). It is therefore not surprising that the obese group is in the upper range of normal blood glucose levels. Since the HUNT blood glucose measure was not obtained in in the fasting state, it might also be that those in the obese/overweight groups had eaten or drank closer to the time of the blood test.

Results from this study showed that cholesterol and triglycerides were similar in the normal weight, overweight and obese groups. This is not in line with another studie that show total serum cholesterol to be positively associated with increased BMI, participants in that study from Finland were a 6.6% random sample of the population within the age range 30 to 59 years (94). It is also shown that higher BMI is associated with higher serum triglyceride level, and also, as discussed in the above section, higher blood glucose levels compared to normal weight individuals (94–96).

From HUNT 2 to HUNT 3, 74.7% of the participants increased their BMI which is in line with similar data from the rest of the world, and also the association with the participants higher age (85,97). The BMI increased from a mean of 25.7 in HUNT 2 to 27.0 in HUNT 3, which is 1.3 BMI-points. This reinforces the reality of the accelerating BMI development among the population today in Norway, as in the rest of the world. Some of the reasons for the increase in BMI over time can be explained by a combination of energy-rich food intake and minimal energy consumption, and also since basal metabolism decreases with 1% each year after the age of 20 (83), this age group is 50-66 years old, it can explain some of the BMI gain from HUNT 2 to 3.

The group that increased their BMI from HUNT 2 to HUNT 3 was no significant different with regard to the demographic, clinical or psychological measures. It is therefore not possible to explain the belonging to either group stable or increasing BMI as related to age, education or poorer psychological health, for example. Also, it did not seem that having increasing BMI had a negative effect on blood glucose, triglycerides and cholesterol. This can be interpreted as that this population from HUNT is too “healthy” to find any differences between the BMI groups in health variables.

Self-perceived cognition and BMI

Participants in all three BMI groups in HUNT 3 scored themselves similarly and reported on median to have no problems with cognition (score of 1) on all questions expect those pertaining to experiencing decline in memory, having difficulty remembering names and dates, and remerging things that happened a year ago. They scored themselves as having some problems on the latter four questions, with a median score of 2. Although some of the participants scored themselves to a 2, it is still a low score and very unlikely that they are having trouble with their memory. My results are similar to that in the study by Almkvist and colleagues (2017) on self-reported memory in a larger sample in HUNT 3 in the same age group. Almkvist and colleagues showed that higher scores were more common for questions associated with long-term memory components (40), which is similar to what was found here. Other studies have shown that subjective memory complains are associated with higher age, female sex and are more frequent in highly educated people (98). Some studies have found a relationship between depressing feelings and memory complaints rather than actual memory performance (99,100). On interpretation of our results is that the HUNT study participants had a “too good” overall somatic and psychological health and not too high educational to experience any complaints in cognition. With regard to the age of the participant it may be thought that they were to “young” to find any relationship with self-perceived memory complaint because a number of studies have found that self-perceived memory complains are most pronounced in people over the age of 65 years (101,102). In difference here to other studies on this topic who have shown that higher age is relate to more pronounced memory complaint, did we not here find these relations. So, unlike this study, other studies could indicate a relation between age, memory complaints and higher BMI. When it comes to the level of education, the overall level might be too low and the variation in level was low as well, to find any relationship between self-perceived memory and education level. Most of the participants were between levels “completed technical college” and “completed high school,”. This makes the variation too small to find any difference between the groups to see if education level affects memory complaints/subjective cognition. Here it was not found any effect of gender on self-perceived memory.

Further, Small and colleagues (2013) disclosed that self-report of a healthy lifestyle in middle- and older age was associated with better self-perceived memory abilities, and therefor suggest that lifestyle behavior habits may protect brain health and possibly protect against the ageing factor of memory symptoms (103).

There was no indication in my results of self-perceived cognitive function being affected by BMI since overweight and obese individuals rate themselves similarly as those with normal BMI. Thus, in this study there were not extracted any data on the participants lifestyle habits, but it would have been beneficial to look at, in hindsight, to see if variations in lifestyle could have affected these results.

There was also no significant difference in self-reported cognitive function between the group with stable BMI and the group with increasing BMI from HUNT 2 to HUNT 3. The scores are quite similar with mostly scores of 1 and scores of 2 found for the same questions as for the tree BMI groups in HUNT 3. This means that also those who perhaps had a less healthy lifestyle over time report similar self-perceived cognitive abilities which is contrary to what Small and colleagues reported (103). Their study selection was 18 552 US residents ranging from 18 to 99 years, were 6 356 of them were middle-aged (40-59 years). A reason for that this study did not find no significant difference may be due to a smaller study selection or that our participants are taken from the general healthy population and therefor do not have distinct troubles with their memory.

In summary, self-perceived cognition was in general very good in all BMI groups at time of HUNT 3 and increasing BMI from HUNT 2 to HUNT 3 also did not influence it.

Objective cognitive measures and BMI

Overall, the three BMI groups performed very similarly on the objective cognitive tests (table 3 and 6, figure 4 and 5). Objects in Grid was the only objective cognitive test that showed an interaction effect with gender. The analysis showed that there was a great advantage to be an obese man for remembering and placing the most objects correctly in the Object in Grid task. The effect of gender is in line with research that reveal that men and women perform differently on cognitive tests (104,105). Further, it is shown in some studies that men perform better on most spatial tasks (which this test assesses), but it is important to investigate and evaluate task complexity, stimulus familiarity and the nature of the precise processes tested to understand gender advantages (106–108). My results in HUNT 3 concur with results from the Baltimore Longitudinal Study of Aging which showed that people with obesity actually performed better on tests of visuospatial skills and attention/psychomotor speed. The Object in Grid test is a test that also relies on visuospatial skills. The Baltimore Longitudinal Study of Aging also showed a more rapid decline in obese people on measures of global functioning, executive function, and memory over time, which are consistent with past studies who finds that having obesity for a longer period of time is unfortunate, both for mental functions and physical function (84). However, my study found that being a middle-aged man with obesity was an advantage in performance in the Object in Grid test.

Gender differences in cognition with relation to BMI are an interesting subject to investigate because there are gender differences in cognition (104), and there are differences between men and women with regard to BMI cut-offs and frequency of difference diseases. This makes it important to understand how gender could underlay pathophysiological mechanisms leading to differences between men and women.

Also, age affected how many objects participants were able to place in Object in Grid test. A study looking at age differences in spatial memory showed that older participants made significantly more spatial memory errors than younger participants, where only 24% of the elderly participants were able to locate the goal without error (109). These age-related deficits are seen in both place and route learning tasks (110).

Computer familiarity

Computer familiarity scores in HUNT were lower than in previous studies in people around the same age range as here, middle-age (45,61,62). All of the participant had scored around the same, making them equally good. Also, there were no differences between sable BMI and increased BMI. In this test the reason for no significant may have been the same as in other variables where it is pointed out that the selection is too “healthy” in general. This was also found in the HUNT MR study were it was investigated if health differed between participants and non-participants in the timespan between 1984-2009 (111).

There was no difference in performance on the objective cognitive test between the stable and increasing BMI groups from HUNT 2 to HUNT 3, expect for a significant interaction between increasing BMI and gender, with men in the increasing BMI group scoring significantly higher. There was also a significant effect of gender on Object in Grid performance. This is very similar to the results for the cross-sectional BMI groups in HUNT 3, where obese men performed the best.

There are studies that show that intentional weight loss in people with obesity/overweight is associated with improvements in performance across various cognitive domains (112). Here we showed that gaining BMI was associated with better spatial memory performance. Why this is, is unclear since most papers find that obesity impairs cognitive functions such as spatial memory, particularly in middle-aged and old-aged individuals (113). However, men who were in the obese groups showed a better performance in the OiG test in this study which someway could be explained by that BMI is better on indicating health risk factor than body composition, and in that way the men may have had more lean tissue than though from the BMI value. Also, biologically there is a difference between men and women in distribution of fat and lean tissue, were men have more muscle mass compared to their body weight than women.

The objective measures of cognition showed that the participants rated themselves in line with their actual performance. This indicates good concurrence between the two measures. Previous studies have shown that most people who report subjective memory decline perform normally on neuropsychological tests (114).

In summary, being an obese man in HUNT 3, and being a man whose BMI increased from HUNT 2 to HUNT 3 were shown to be associated with better performance on the Object in Grid test. There was no evidence for BMI or increasing BMI being connected to poorer cognitive performance. This is not in line with previous research which either tend to find better performance in people with normal weight than those with obesity, or they find no differences between the BMI groups (24). But these results may now indicate that there is an advantage among the men who have obesity in cognitive function whit regard to spatial memory and should create further research on this topic.

Certain personality characteristics and psychological profiles have previously been connected to overweight and obesity including increased impulsivity, more reward seeking and poorer decision-making and executive functioning (13,14). Impulsivity and reward and decision making were not investigated here, but working memory is an executive function, and that was “similar” in all groups.

As mentioned earlier it is suggested both that poor frontal lobe function, i.e. greater impulsivity, reduced planning ability, impaired decision making, as well as poor working memory and episodic memory (frontal and temporal lobe functions) are involved in the pathogenesis of overweight and obesity (15). Evidence supporting this theory has been variable, but a recent meta-analysis and data from the large-scale UK biobank study (115), corroborate this notion. This UK Biobank study showed that short-term memory was associated with overweight and obesity, and reduced executive function was associated with only obesity. It is possible that the variable findings stem from differences in cohorts included in the different studies. Here this possibility was assessed by examining cognitive profile in people of all weight classes in the general population by using different anthropomorphic methods for assessing body mass index, and somatic measures and their associations with cognitive performance. In this study it has been looked at several episodic memory tests (verbal, pattern separation, OiG), and found improved function and not reduced.

High BMI, overweigh, obesity and undesirable elevated waist circumference have been associated with impairments in planning, impulsivity decision making, working memory and episodic memory (20). These memory-components are core cognitive processes that are critical for food-related decision-making. Problems with appetite control and weight gain can therefore have been disrupted by impairments in working memory and episodic memory. However, here there are found no differences in working memory or episodic memory, between BMI groups the findings do not support the notion that these functions are associated being obese or becoming obese.

There has been a very strong focus on impairments in frontal functions (i.e. impulsivity, decision-making and reward processing) in the overweight/obesity research, and these functions are usually investigated using material with food stimuli in the overweight/obesity literature. This makes it difficult to draw general conclusion about cognition in people who are overweight/obese. Thus, the stimuli used here were not food related.

Strengths and limitations

Participants

All of the participants from both HUNT 2 and 3 were from the general population and therefor it may have been difficult to find differences or associations among the BMI groups and test performance. The participants in the HUNT MRI study were a "healthy" selection of the population. As briefly touched on earlier in the discussing, there was a HUNT-MRI study by Honningsvåg and colleagues (2012) that found that those who participated in the study overall had a higher education level, were less likely to be obese (111), so, here as well as in other sections, the selection had an overall good health and in that way did not show any significant differences.

This could indicate that other factors than BMI are important for the effect of BMI on cognition as reported previously. These factors in combination with other previous mentioned factor (thorough the discussion) may have contributed to BMI not being associated with performance in this study regardless of what is shown in previous studies.

Moreover, the distribution of participants in the three BMI groups was more even between the groups than between the stable BMI group and the increased BMI group. In aim two, the increased BMI group accounts for 74.7% of the total selection which makes it an extremely uneven distribution of participants.

In previous studies on the effect of BMI on cognition participants came most often from a general population or form a selection of people who already have a disease (with a relation to BMI and cognition). However, if one may have been looking at subjects who are a part of treatment in/from the hospital, one may see more severe health problems compared to the HUNT population looked at here. People getting help from the hospital often have more severe obesity which comes with more risk factors for other health issues.

In summary, in this HUNT sample compared to other studies on cognition in relation to BMI it seems that the sample here are “healthier” than those other studies, also this sample does not have the most severe cases of obesity since no one is over 150 kilograms. Further, the distribution of BMI groups is similar, so in that way they should be similar in other measures as well.

BMI measure

One of the exclusion criteria for the HUNT MR study was a maximum weight of 150 kilograms which is a limiting factor for this thesis since many of potential participants who could contribute to get a more insightful result regarding the project aims were excluded. It is possible that more associations between BMI group and cognition could have been found with more participants in the higher BMI categories. Also, those who gain the most weight, from HUNT 2 to HUNT 3 would be excluded. Including this group could have changed the results as a higher increase in BMI is related to a further decrease in cognition (112). But, it should be noted that the research on BMI`s relation to cognition is limited and there is uncertainty of whether trouble with cognition came before the increased BMI or after, this is a difficult question to study considering that one may have to follow individuals a whole lifetime to answers “what came first”.

The normal weight group was younger and had higher educational attainment than the overweight and obese groups. Previous research also show that higher education level is associated with a lower BMI and decreased cognition (79,111,116), which is not shown in the results here. This underscores the importance of including educating in the ANCOVA analyses. However, education was not found to be significantly associated with performance on any test in this study.

Some studies find that education can act as a protective factor in cognitive aging, this type of cognitive reserve is thought to reflect high neuroplasticity (i.e. *the brain`s ability to reorganize itself by forming new neural connections throughout life*) within an individual (88,116,117). These studies suggest that having a stable, normal weight, BMI throughout life preserves cognition better with age than having a higher BMI. This emphasize the importance of keeping a normal BMI also early in life to prevent health complications later in life. But mine result indicate that being a man with obesity might be best for some cognitive functions.

Since BMI fails to capture multiple important physiological factors such as muscle mass, distribution of adipose tissue and ethnicity differences there are other measures of desirable/undesirable body compositions which also are cost- and time effective like BMI. These include waist circumference, waist to hip ratio, bioelectrical impedance, and skinfold thickness. However, like BMI they also have limitations (118). The gold standards for measuring body composition are dual energy X-ray absorptiometry, magnetic resonance imaging (MRI), and computerized tomography (CT). But all these methods are expensive and used mostly in research and difficult to use in people with BMI ≥35. So, other measures would also have been good alternatives to find the participants body composition in HUNT, but BMI is a valuable measure when it comes to bigger groups of peoples, also there have been done more studies on BMI, which make it is better to compare the results with.

There is some evidence of central obesity in particular coupled to insulin resistance, being associated with altered cognitive performance in particular more severe memory problems and risk of dementia (2,17,28). Studies have also found that presence of insulin resistance mediates a further performance reduction. Thus, we predicted that anthropomorphic measures reflecting increased risk of insulin resistance are associated with poorer performance in particular on frontal (working memory and executive function) and medial temporal lobe (episodic memory) tests, we found no significant difference.

However, the results may have been different if we did not categorize BMI groups, but used other body composition measures to stratify into groups. Another alternative would have been to use BMI, or another measure of body composition, as a continues variable in the statistical models.

Age range

Since the age group in this study was limited to middle aged adults between 50-66 years, it may have contributed to less findings. It could have given a better insight if we had included a wider age range. This is because a lot of phycological variables change with age, and some variables may affect the body harder in some age than others. An older body can withstand less strain than a younger body that is constantly changing and repairing itself.

Other demographic and clinical variables

From the HUNT database there were a lot of variables to choose from and look at in relation to BMI. I ended up choosing age, education, relationship status, HADS total score, blood glucose, cholesterol and triglycerides because these factors are seen to be related to what BMI a person have. In hindsight, it would probably been beneficial to have included variables such as LDL-cholesterol, blood pressure and maybe waist-to-hip-ratio now (with regard to central obesity) as they are seen to have a strong correlation with BMI (9,118,119). Another variable that could have been looked are c-reactive protein (CRP) which is an inflammatory marker, this have been looked at in a previous HUNT study in relation to obesity and its pro-inflammatory release from visceral- and subcutaneous fat (120).

Internet testing: Computer and online administration

By using web-based cognitive testing a truly standard administration is achieved, which is the clearest advantage here. The computer gives the exact same instructions each time, and the answers are recorded without the possibility of human error (121). But when you have an online administrated test, the examiners do not have control over whether the subjects follow the instructions or cheats, for example. This is an uncertain factor that may impact the results of the tests, because we can never really know if the participants actually did the tests on their own or under the same circumstances.

The participant either completed the tests on a computer at home, or in a dedicated room at the MR-center. They received both a username and password to log into the test. Instructions were given both written on the screen and verbally. The test was identical for all participants, and the test-battery included six cognitive tests. This type of testing also allows a large amount of people being tested at the same time and is cost effective in the sense of traveling to be tested.

A factor that can influence the participants performance on the Memoro test is the type of equipment they use to do the tests, for example, PC, iPad/tablet, external mouse, internal mouse and more. Since all the tests used in HUNT MRI group was accuracy tests, where time or speed are not important, equipment used have limited effects on performance.

The subjects' experience and/or familiarity with technology and computer specifically, can also affect the performance. Furthermore, participants may have a reduced hearing which makes it difficult for them to hear the verbal instructions given from the computer this might influence the verbal memory test. All other tests were presented both verbally and in writing on the screen. Also, everyday disturbances from the household can affect performance (this was eliminated if taken at the MR-center). Nevertheless, this cannot be controlled for.

Ethics

The development and implementation of new technologies in clinical practice and research bring with it several ethical aspects in need of consideration (122–124). These challenges are relevant for test developers, test administrators and test takers (125). For web based cognitive testing, it is vital that the platforms on which the tests are administrated protects the privacy of the users. This includes mechanisms for securing the transfer, handling, and storing of data. Memoro implements 256 bits encryption (same as "nettbank") which means that data is encrypted in the user's computer before transfer over the web. All data on the server is encrypted. No person identifiable data is stored together with the cognitive performance data.

A possible downside to investigating potential associations between cognition and overweight/obesity is further stigmatizing a group already stigmatized by society (1,8). For instance, it could be perceived by some that the study wants to show that people who are overweight/obesity also are less intelligent than normal weight people. It is therefore important to emphasis that this study is uncovering cognitive mechanisms related to overweight/obesity, which in turn can be targeted or strengthened to help people achieve a more health body weight.

Conclusion

In this selection of a general population between 50 and 66 years stratified by BMI into normal weight, overweight and obese groups or increasing their BMI or not from HUNT 2 to HUNT

3, there was no effect of BMI group on self-perceived cognition or objective performance on cognitive tests, except for a better performance for obese men in HUNT 3 and men who increased their BMI from HUNT 2 to HUNT 3 on the Object in Grid.

These results are surprising as they do not concur with previous studies which looked at BMI and cognition and found either decreased performance among people with obesity or no difference between BMI groups. However, clear differences are difficult to find due to methodical differences between the studies.

Further work is much needed to better delineate the association between obesity and cognitive function with a more standardized methodology, to then look at meaning of this towards bettering of treatment strategies.

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Appendix

Appendix A1

The HADS questioner scale:

Table 3 The Hospital Anxiety and Depression (HAD) scale item numbers and texts

Scale/item number	Item text
A/1	I feel tense or wound up
A/3	I get a sort of frightened feeling as if something awful is about to happen
A/5	Worrying thoughts go through my mind
A/7	I can sit at ease and feel relaxed
A/9	I get a sort of frightened feeling like 'butterflies' in the stomach
A/11	I feel restless as if I have to be on the move
A/13	I get sudden feelings of panic
D/2	I still enjoy the things I used to enjoy
D/4	I can laugh and see the funny side of things
D/6	I feel cheerful
D/8	I feel as if I am slowed down
D/10	I have lost interest in my appearance
D/12	I look forward with enjoyment to things
D/14	I can enjoy a good book or TV programme

Questions are answered on a four-point scale from 0 to 3.
Items 2, 4, 6, 7, 12 and 14 are reversed before summation.

Appendix A2

Questions on computer familiarity.

There were presented three which was assessing computer usage;

- "Where have you used a computer during the last 6 months?" alternatives (score): "Home (2), Work (2), Other (1),"

- "What activities have you done on a computer during the last 6 months?" alternatives: "Paying bills (1), E-mail (1), Browsing (1), Office (1), Multimedia (1),"

- "How often do you use a computer?" alternatives: "Daily (5), Several times a week (4), Once a week (3), More than once a month (2), Less than once a month (1)."

Then there was tree who were assessing computer skill;

- "How comfortable are you in using a computer mouse?" alternatives: Very uncomfortable (1), Uncomfortable (2), Neither nor (3), Comfortable (4), Very comfortable (5).

- "How comfortable are you using a computer keyboard?" same alternatives as previous question.

- "How comfortable are you using computers on a scale from 1 to 10 with 1 being 'only experience problems' and 10 'no problems at all'?".

Appendix A3

Table A: Significant level for each memory question in the tree BMI-groups.

Question	p-value *(n = 1005)*
Has your memory changed since you were younger?	0.583
Do you have trouble remembering events a few minutes ago?	0.390
Do you have trouble remembering names of other people?	0.141
Do you have trouble remembering dates?	0.074
Do you have trouble remembering to do what you have planned?	0.826
Do you have trouble remembering events that happened a few days ago?	0.290
Do you have trouble remembering events that happened a year ago?	0.587
Do you have trouble keeping the thread in conversations?	0.336
Do you have trouble whit your memory?	0.388

Pearson Chi-square significant value (p-value) on each self-perceived cognition questions.

Appendix B1

Table B: Significant level for each memory question in the two BMI-groups.

Question	p-value *(n = 999)*
Has your memory changed since you were younger?	0.251
Do you have trouble remembering events a few minutes ago?	0.487
Do you have trouble remembering names of other people?	0.861
Do you have trouble remembering dates?	0.300
Do you have trouble remembering to do what you have planned?	0.432
Do you have trouble remembering events that happened a few days ago?	0.780
Do you have trouble remembering events that happened a year ago?	0.898
Do you have trouble keeping the thread in conversations?	0.391
Do you have trouble whit your memory?	0.161

Pearson Chi-square significant value (p-value) on each self-perceived cognition questions

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