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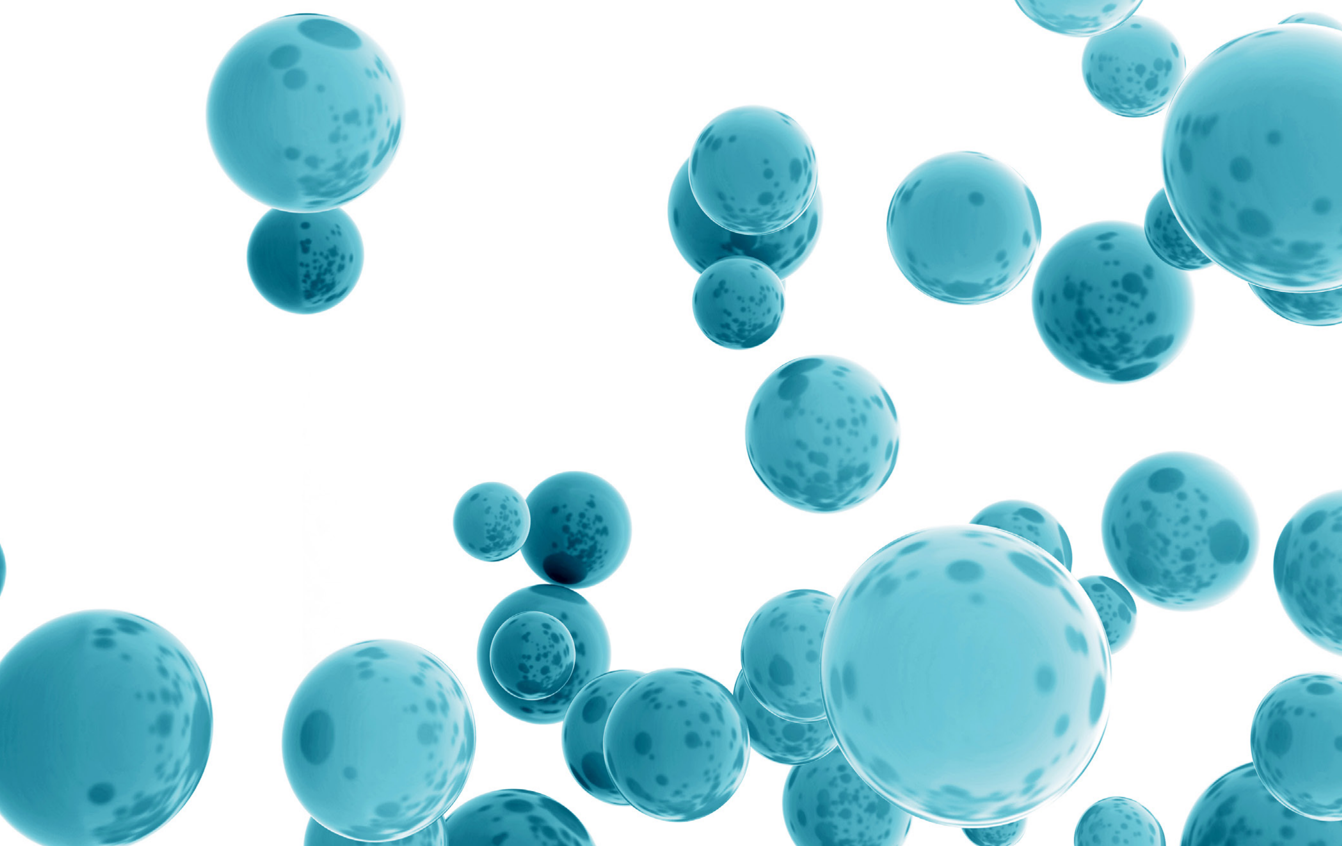
INNA LISKO

Obesity in the Oldest Old

Associations of body mass index and waist circumference with physical functioning and mortality



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ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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I wish to express my gratitude to my beloved late grandparents
Elli & Vilho Koivisto and Alina & Mauri Lisko
for all the strength, determination and joy you have passed on to me.

Contents

Abbreviations

ADL	Activities of daily living
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
HR	Hazard ratio
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability and Health
IL-1RA	Interleukin-1 receptor antagonist
IL-6	Interleukin-6
IU	International Units
MMSE	Mini-Mental State Examination
MNA	Mini Nutritional Assessment
NA	Not applicable
OR	Odds ratio
TNF-α	Tumor necrosis factor alpha
WC	Waist circumference
WHR	Waist-to-hip ratio
WHO	World Health Organization

List of original publications

I Lisko I, Stenholm S, Raitanen J, Hurme M., Hervonen A, Jylhä M, Tiainen K. Association of body mass index and waist circumference with physical functioning: The Vitality 90+ Study. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 70(7): 885–891, 2015. doi: 10.1093/gerona/glu202

II Lisko I, Tiainen K, Raitanen J, Jylhävä J, Hurme M Hervonen A, Jylhä M, Stenholm S. Body mass index and waist circumference as predictors of disability in nonagenarians: The Vitality 90+ Study. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. Epub 14 March 2017. doi:10.1093/gerona/glx032

III Lisko I, Tiainen K, Stenholm S, Luukkaala T, Hervonen A, Jylhä M. Body mass index, waist circumference, and waist-to-hip ratio as predictors of mortality in nonagenarians: The Vitality 90+ Study. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences 66A(11): 1244–1250, 2011.doi: 10.1093/gerona/glr147

IV Lisko I, Tiainen K, Stenholm S, Luukkaala T, Hurme M, Lehtimäki T, Hervonen A, Jylhä M. Inflammation, adiposity and mortality in the oldest old. Rejuvenation Research 15(5): 445–452, 2012. doi: 10.1089/rej.2011.1310

Abstract

Obesity and underweight increase the likelihood of poor physical functioning in both middle and old age, but the association between obesity and mortality has been found to be weaker or non-existent in older adults. However, the associations between obesity and physical functioning, as well as obesity and mortality, have been scarcely studied in the oldest old, i.e., people aged 85 years and older, who are the fastest-growing population group in developed countries. From a biological viewpoint, obesity is associated with low-grade inflammation, which in turn indicates an increased mortality risk. The relationships between body weight, inflammatory status and mortality have also been scantly studied, and related studies on the oldest old are lacking.

The aim of this study was to examine the associations of both low and high body weight with physical functioning and mortality in the oldest old, with body mass index (BMI) indicating general obesity and waist circumference (WC) indicating abdominal obesity. Furthermore, the aim was to investigate the combined associations of BMI and WC, and inflammatory status on mortality in the oldest old.

The study is based on the Vitality 90+ Study, conducted in the city of Tampere, Finland. Cross-sectional data are derived from health examinations collected in the years 2000, 2001, 2003 and 2010. All home-dwelling and institutionalized persons aged 90 years were invited to participate (n=1,827). The participants (n=209–569 in sub-studies) were measured for BMI, WC, physical performance and activities of daily living (ADL) disability. Additionally, blood was drawn in the year 2000, and concentrations of four inflammatory markers were subsequently analyzed. The longitudinal data for physical functioning are derived from mailed questionnaires gathered in 2001, 2003, 2007, 2010 and 2014. The incidence of mobility and ADL disability was examined, with a median follow-up of 3.6 years (range 0.6–7.8 years). For mortality, four-year and eight-year follow-ups were used.

Women with low WC had higher physical performance and less ADL disability in the cross-sectional setting when compared to those with high WC. Women with low WC also had low mortality risk when the low WC was combined with overweight or low inflammation (low disease burden). However, in the longitudinal setting, low WC in women predicted the development of ADL disability. From the

viewpoint of obesity, neither high WC nor high BMI were associated with an increased mortality risk in women or men. Moreover, men with low WC or low BMI had an increased mortality risk regardless of inflammatory status. Men with low WC and high BMI had less ADL disability compared to those with low WC and low BMI in the cross-sectional setting, but neither low nor high WC or BMI predicted incident mobility or ADL disability.

In conclusion, this population-based study suggests that in the oldest old, a low body weight is a greater concern in terms of mortality than general obesity. However, abdominal obesity has adverse consequences in terms of both mortality and physical functioning, especially in women. The results also indicate that WC and BMI are more informative when considered together rather than separately. It should be recognized better in the health care and health services that low weight is an important indicator of declining health in old age. To improve existing practices, malnutrition and low protein intake should be screened more and nutritional care provided when needed. Future studies should explore the associations of body composition and physical fitness on physical functioning and mortality at different stages of the aging process by taking weight history and nutritional intake into account.

Keywords: body mass index, waist circumference, underweight, body composition, physical performance, disability, nonagenarians, inflammation

Tiivistelmä

Lihavuus ja alipaino ovat yhteydessä heikkoon toimintakykyyn niin keski-ikäisillä kuin ikääntyneillä, mutta ikääntyneillä lihavuuden yhteys kuolleisuuteen on lievempi. Lihavuuden yhteyksiä toimintakykyyn ja kuolleisuuteen on tutkittu vain vähän vanhoista vanhimmilla eli yli 85-vuotiailla ja sitä vanhemmilla, jotka ovat länsimaissa nopeimmin kasvava väestöryhmä. Biologiselta kannalta tarkasteltuna lihavuus on yhteydessä matala-asteiseen tulehdukseen, joka puolestaan lisää kuolleisuusriskiä. Lihavuuden, kuolleisuuden ja tulehdustason välisiä yhteyksiä on tutkittu vain vähän ja vanhoista vanhimmilla yhteyksiä ei ole aiemmin selvitetty.

Tämän tutkimuksen tavoitteena on selvittää alhaisen ja korkean kehonpainon yhteyttä toimintakykyyn ja kuolleisuuteen vanhoista vanhimmilla käyttäen mittareina yleistä lihavuutta kuvaavaa painoindeksiä ja keskivartalolihavuutta kuvaavaa vyötärönympärystä. Lisäksi tavoitteena on selvittää painoindeksin, vyötärönympäryksen ja tulehdustason yhteisiä yhteyksiä kuolleisuuteen vanhoista vanhimmilla.

Tutkimuksessa käytetään Tampereella kerättyä Tervaskannot 90+ -tutkimuksen aineistoa. Tutkimuksen poikkileikkausaineisto koostuu vuosina 2000, 2001, 2003 ja 2010 kerätyistä terveystarkastustiedoista. Terveystarkastuksiin kutsuttiin kaikki 90-vuotiaat sekä kotona että laitoksessa asuvat asukkaat (n=1 827). Tutkittavilta (n=209–569) mitattiin painoindeksi, vyötärönympärys, fyysinen suorituskyky ja päivittäistoiminnoista selviytyminen. Vuonna 2000 tutkittavilta otettiin myös verinäytteet, joista määritettiin neljän tulehdustekijän tasot. Pitkittäisasetelmassa toimintakykyä seurattiin postikyselyillä vuosina 2001, 2003, 2007 ja 2014. Seurannan kohteena oli rajoitteiden ilmaantuminen liikkumisessa ja päivittäistoiminnoissa. Seuranta-ajan mediaani oli 3,6 vuotta (vaihteluväli 0,6–7,8 vuotta). Kuolleisuusseurantana käytettiin neljän ja kahdeksan vuoden seurantaa.

Naisilla, joilla oli alhainen vyötärönympärys, oli poikkileikkausasetelmassa parempi fyysinen suorituskyky ja vähemmän ongelmia päivittäistoiminnoissa verrattuna niihin, joilla oli korkea vyötärönympärys. Alhainen vyötärönympärys naisilla yhdistettynä joko ylipainoon tai vähäiseen tulehdustasoon oli myös yhteydessä matalampaan kuolleisuusriskiin. Kuitenkin kun toimintakykyä seurattiin pitkittäisasetelmassa, alhainen vyötärönympärys naisilla ennusti rajoitteiden ilmaantumista päivittäistoiminnoissa. Lihavuuden näkökulmasta suuri vyötärönympärys tai korkea painoindeksi eivät olleet yhteydessä kohonneeseen kuolleisuusriskiin naisilla tai miehillä. Sen sijaan miehillä, joilla oli alhainen vyötärönympärys tai matala painoindeksi, oli kohonnut kuolleisuusriski tulehdustasosta riippumatta. Alhaisen vyötärönympäryksen ja korkean painoindeksin omaavilla miehillä oli poikkileikkausasetelmassa vähemmän ongelmia päivittäistoiminnoissa. Pitkittäisasetelmassa miesten vyötärönympäryksellä tai painoindeksillä ei kuitenkaan ollut merkitystä liikkumisrajoitteiden tai päivittäistoiminto-ongelmien ilmaantumisen kannalta.

Tämä tutkimus osoittaa, että vanhoista vanhimmilla alhainen kehonpaino on suurempi huolenaihe kuolleisuuden kannalta kuin yleinen lihavuus. Keskivartalolihavuus oli kuitenkin yhteydessä niin kuolleisuuteen kuin heikompaan toimintakykyyn etenkin naisilla. Painoindeksi ja vyötärönympärys näyttävät myös olevan informatiivisempia yhdessä kuin erikseen. Vanhojen ihmisten alhaiseen kehonpainoon liittyvät riskit tulisi nykyistä paremmin tunnistaa terveydenhuollossa ja sosiaalipalveluissa. Verrattuna nykyisiin käytänteisiin aliravitsemusta ja alhaista proteiininsaantia tulisi seuloa aktiivisemmin ja ravitsemuksellista tukea tulisi tarjota herkemmin. Jatkotutkimuksissa olisi syytä tutkia kehonkoostumuksen ja fyysisen kunnon välisiä yhteyksiä toimintakykyyn ja kuolleisuuteen vanhenemisprosessin eri vaiheissa ottaen huomioon myös painohistoria ja ravinnonsaanti.

Avainsanat: kehon painoindeksi, vyötärönympärys, alipaino, kehon koostumus, fyysinen suorituskyky, toimintakyky, toiminnanvajaus, 90-vuotiaat, inflammaatio

1 Introduction

Obesity is recognized as a major global health challenge (Ng et al. 2014). It is associated with various diseases, as well as decreased functioning and quality of life (Withrow & Alter 2011). A recent study that included as many as 30.3 million participants demonstrated the deleterious effects of obesity by showing that in the general population, obesity increases mortality risk (Aune et al. 2016). However, with increasing age, the association between obesity and mortality weakens (Winter et al. 2014), and for many older adults, low weight and malnutrition comprise a more pronounced problem than obesity. Indeed, both low weight and obesity are important risk factors in the decline of physical functioning, and these associations seem to be similar in both middle-aged and older adults (Backholer et al. 2012, Ferraro et al. 2002). But is it a good or a bad thing to be obese at the age of 90 years, in a population who on average have several diseases and have a high risk of mortality?

The prevalence of obesity has increased markedly during the past four decades in both younger and older adults worldwide (Villareal et al. 2005, Ng et al. 2014). Combined with an aging population (United Nations 2013), this has led to a substantial increase in the number of older adults who are obese. The fastest-growing segment of the population in developed countries in recent years has been the oldest old, i.e., people aged 85 years and older (Christensen et al. 2009). However, very little data exists regarding the associations of obesity with physical functioning and mortality in the oldest old.

Obesity may be measured in various ways (Duren et al. 2008). The most commonly used method is body mass index (BMI), in which body weight in kilograms is divided by the square of height in meters (kg/m^2). Another widely used method is waist circumference (WC). This method provides a more accurate estimate of the amount of harmful visceral fat in the abdominal region as compared to BMI (Despres 2012). Yet neither BMI nor WC distingueshes between fat mass and muscle mass. Muscle mass is closely associated with muscle strength, which plays a crucial role in maintaining physical functioning (Barbat-Artigas et al. 2013). This association is highlighted in aging when muscle mass and strength decrease (Goodpaster et al. 2006). However, in light of their simplistic ability to predict health risks at a population level (Pischon et al. 2008), BMI and WC have justified their use. Again, however, scant information is provided on the association of BMI and especially WC with physical functioning or mortality in the oldest old.

From a biological viewpoint, in obese individuals, the body carries an excessive amount of body fat (Balistreri, Caruso & Candore 2010). Fat stores, especially when they are located viscerally in the abdominal region, are metabolically very active and promote a pro-inflammatory status (Licastro et al. 2005, Exley et al. 2014). This low-grade inflammation is associated with various chronic diseases such as cardiovascular disease, cancer, and Alzheimer's disease (Coussens & Werb 2002, Cesari et al. 2003, Glass et al. 2010), as well as an increased mortality risk (Harris et al. 1999). However, low weight and disease-related malnutrition are also associated with inflammation and mortality (Jensen et al. 2013). The relationships between obesity, inflammatory status and mortality are scantly studied, and related studies on the oldest old are lacking.

This study aims to examine the associations of high and low body weight with physical functioning and mortality in the oldest old. The focus is on two of the most commonly used indicators of general and abdominal obesity: BMI and WC. Furthermore, the aim is to investigate the combined associations of BMI and WC and inflammatory status on mortality in the oldest old. Population-based data from the Vitality 90+ Study, which includes persons aged 90 years and older living in the city of Tampere, Finland, was used in the study.

2 Characteristics of the oldest old

2.1 Demographics

The world has witnessed remarkable growth in life expectancy since the 19th century (Christensen et al. 2009, United Nations 2013). Not only has life expectancy at birth increased but also the life expectancy at older ages (Rau et al. 2008, Christensen et al. 2009, United Nations 2013). In Finland, between 1980 and 2014 life expectancy at the age of 65 years increased from 17.0 years to 21.7 years in women and from 12.6 years to 18.2 years in men (European Union 1995-2016). Concurrently, the life expectancy of an 84-year-old Finn increased approximately two years to 7.6 in women and 6.5 in men in 2014 (European Union 1995-2016). The life expectancy for a 90-year-old in 2014 was 4.4 years for women and 3.8 years for men (Statistics Finland 2015a).

The aging of the population has primarily been a consequence of decreasing mortality and declining fertility, and as a result, the number of old people is now at an unprecedented high level (Christensen et al. 2009, United Nations 2013). The fastest-growing segment of the population in developed countries is the oldest old, often defined as people aged 85 years and older (Christensen et al. 2009). Over the last 25 years (1990–2015) the population in Finland has grown 10%, from approximately 5.0 million inhabitants to 5.5 million (Statistics Finland 2016). Concurrently, the number of older adults, people aged ≥65 years, has grown 67%, and the number of oldest old has grown by as much as 168%. In 2015, older adults represented 20% of the population in Finland and the oldest old represented 2.5% (Statistics Finland 2016), and the numbers are still increasing. It is forecast that in 2030, older adults will represent a fourth (25.6%) of Finland's population and the oldest old will represent 3.8% of the population (Statistics Finland 2015b).

A distinctive demographic feature in the oldest old is that the number of women clearly outweighs the number of men (United Nations 2013). In Finland, for every 100 oldest old women, there are only 42 men (Statistics Finland 2015b).

2.2 Health status

Many health aspects change with aging, and factors associated with health in younger people or in younger old age may no longer apply in the oldest old (Forette 1999, Nybo et al. 2003, Ben-Ezra & Shmotkin 2006). Generally speaking, the oldest old are a heterogeneous population group. Some are bedridden with multiple comorbidities, while others are physically active and have a high quality of life with only a few diseases and a limited number of medications (Jylhä & Hervonen 1999, Goebeler, Jylhä & Hervonen 2003, Tsoi et al. 2014). On average, the oldest old suffer from numerous chronic conditions and have a high mortality risk (Goebeler, Jylhä & Hervonen 2003, Jylhä, Enroth & Luukkaala 2013), which sets the focus of this study, obesity, to a different context than among younger seniors.

With increasing age, cognitive decline becomes more common, and a substantial percentage of the oldest old suffer from it (Goebeler, Jylhä & Hervonen 2003, Yang, Slavin & Sachdev 2013). Approximately 25−30% of those in their early 90s, 50% of those in their late 90s, and 60% of centenarians (i.e., people aged 100 years and older) suffer from some form of dementia (Yang, Slavin & Sachdev 2013). The prevalence of dementia is lower in oldest old men than in women, but at the age of 90, the incidence of dementia does not differ between the genders (Yang, Slavin & Sachdev 2013). Dementia also appears to be the most important medical reason for institutionalization in the oldest old (Goebeler, Jylhä & Hervonen 2003).

2.3 Physical functioning

Physical functioning is one of the central factors contributing to independent living and quality of life (Guralnik, Fried & Salive 1996, Villareal et al. 2004, Elkins et al. 2006, Felix 2008). The World Health Organization (WHO) defines functioning through body functions and structures, activities and participation, and environmental factors. This framework is presented in the International Classification of Functioning, Disability and Health (ICF) (WHO 2001). Derived partially from the ICF model, this study focuses on the following aspects of physical functioning: 1) physical performance (neuromusculosceletal and movement-related functions in the ICF model), 2) mobility, 3) activities of daily living (self-care and domestic life in the ICF model), and 4) physical disability. The exact definition for physical functioning used in the outcomes of this study is presented in Section 6.2 Measurements.

Physical performance, mobility and activities of daily living represent positive aspects of physical functioning, and the present Section 2.3 focuses on these factors. Physical performance (e.g., five-times sit-to-stand test) describes objectively different aspects of physical functioning, and it is measured using standardized protocols (Guralnik & Winograd 1994). Mobility (e.g the ability to walk 500 meters) is defined as moving by changing body position or location or by transferring (WHO 2001). Activities of daily living represent basic daily tasks of self-care (e.g., washing or dressing oneself) and instrumental activities of daily living (e.g., performing household duties) (WHO 2001). Mobility and activities of daily living are often self-reported measures, with individuals reporting theid own perceptions of their the ability to complete such tasks (Reuben et al. 1995). Performance-based measures and self-reported measures complement each other and provide a more comprehensive picture on the level of physical functioning when used together (Guralnik et al. 1994).

The level of physical functioning decreases with aging, and limitations in it are more common in women than in men (Hardy et al. 2008, Brown & Flood 2013). Muscle strength and, even more importantly, muscle power are among the central determinants of physical functioning (Brill et al. 2000, Aagaard et al. 2010, Reid & Fielding 2012, Schaap, Koster & Visser 2013). Increased total body fat is also an important factor causing a decline in physical functioning (Visser et al. 2005, Lebrun et al. 2006, Bouchard et al. 2007, Schaap, Koster & Visser 2013). In addition, several factors causing age-related attenuation in muscle quality, such as fat infiltration to the muscle, increase the likelihood of functional limitation (Visser et al. 2005, Delmonico et al. 2009, Fragala, Kenny & Kuchel 2015). Altogether, several factors contribute to functional decline, including diseases and chronic conditions, low level of physical activity and smoking (Stuck et al. 1999).

Age-related changes in body composition and physical functioning

Aging is accompanied by several changes in body composition, and many of these changes contribute to a decline in physical functioning. First, height declines with aging, with a faster pace in women than in men (Dey et al. 1999, Sorkin, Muller & Andres 1999, Sagiv et al. 2000, Droyvold et al. 2006). Based on a prospective population-based study, height loss per decade among people in their 70s has shown to be 2.3 cm for women and 1.9 cm for men (Droyvold et al. 2006). Height loss is primarily attribured to loss of mineral content in vertebral bodies and reduction of height in intervertebral discs, but altogether, changes in bones, muscles and joints are related to height loss (Ross 1997, Sagiv et al. 2000). Additionally, the amount of water in the body diminishes with aging (Buffa et al. 2011).

A central change in body composition is that muscle mass and muscle strength decrease with age (Gallagher et al. 1997, Janssen et al. 2000, Mitchell et al. 2012). Older adults lose approximately 1% of their lean mass (mainly muscle mass) per year, with men losing more muscle mass than women both in absolute and relative terms (Gallagher et al. 1997, Visser & Harris 2012). Although muscle mass is associated with muscle strength, strength declines even two to five times faster than muscle mass (Goodpaster et al. 2006, Mitchell et al. 2012). The decline in muscle strength contributes considerably to the decline in physical functioning. In a community-dwelling population aged 70–79 years, the decline in muscle strength has been shown to be approximately 3–4% per year, with men losing almost twice as much strength as women (Goodpaster et al. 2006). However, in all age-groups men are stronger than women (Danneskiold-Samsoe et al. 2009).

Another central age-related change in body composition is the increase and redistribution of fat mass. The amount of body fat increases on average from young adulthood until the age of approximately 80 years and appears to gradually decrease thereafter (Visser & Harris 2012). Even in older adults who have a stable weight, the percentage of body fat increases with age as muscle mass decreases (Gallagher et al. 2000). Redistribution of fat mass occurs with aging as more visceral fat accumulates in the abdominal region and less subcutaneous fat is found in other regions of the body (Kotani et al. 1994). Fat accumulation in other non-fat tissues also occurs with aging. This ectopic fat may, in addition to being visceral, be intramuscular or intermuscular, or it may accumulate in organs such as the liver, pancreas or heart (Zamboni et al. 2014).

Physical functioning of the oldest old

In a Finnish population-based sample of nonagenarians (i.e., people aged 90 years and over) 69−74% of women and 81−85% of men were shown to be independent in ADL, measured as the ability to get in and out of bed and dress and undress (Jylhä, Enroth & Luukkaala 2013). Regarding mobility, 36−39% of women and 58−62% of men were able to move indoors, walk 400 m and use stairs in this same population, measured between 2001 and 2010 (Jylhä, Enroth & Luukkaala 2013). Thus, oldest old men do better than women in both ADL and mobility. It appears that physical functioning of the oldest old has remained rather stable, and there have been no major changes in functioning in recent years (Jylhä, Enroth & Luukkaala 2013). Yet, the results of a Danish population-based study on centenarians have shown improvement in basic ADL and mobility in women, but not in men (Engberg et al. 2008).

A population-based study of people aged 80 years and older demonstrates that higher age (>85 years), female gender, continuous use of five or more medications, no visits to friends and/or relatives at least once a week, and worse perceived health relative to peers are independently associated with worse physical functioning (Nogueira et al. 2010). In addition, physical functioning is an important predictor of mortality in the oldest old (Nybo et al. 2003, Tiainen et al. 2013). It appears to be an even more important predictor than chronic conditions (Lee et al. 2008).

2.4 Disability

Disability represents the negative aspect of physical functioning and is included in the definition of physical functioning in this study. Disability is defined as difficulty doing activities in any areas of life due to a health issue or a physical problem (Verbrugge & Jette 1994). The pathway leading to disability is presented in the framework of the disablement process by Verbrugge & Jette (1994). The disablement model begins with pathology (e.g., arthritis), which imposes impairments (e.g., decrease in muscle strength) that may in turn lead to functional limitation (e.g., difficulty climbing stairs) and subsequently to disability (e.g., inability to go outdoors independently) (Verbrugge & Jette 1994). Personal and environmental factors affect the pathway to disability through physical, psychological and social components.

Disabilities increase the need for help, and at some point a person is no longer able to live independently and requires some form of assisted living or institutionalization. The oldest old populations living at home and those living in an institution are distinctively different from each other in terms of disability (Berlau et al. 2012), although the level of dependency varies a lot also among the home-dwelling oldest old (Jagger et al. 2011). In 2014, 44% of the oldest old in Finland used home care, institutional care or housing services (Väyrynen & Kuronen 2015). Thus, disability prevalence in the oldest old is high, and future projections suggest that the number of the oldest old requiring 24-hour care will substantially increase by the 2030s (Berlau, Corrada & Kawas 2009, Jagger et al. 2011, Forma et al.). Furthermore, disability incidence increases in the oldest old with advancing age, and the increase is similar in both women and men (Berlau et al. 2012). However, oldest old men with disability have a higher mortality risk than oldest old women with disability (Tiainen et al. 2013). Altogether, oldest old women are more disabled than men but men have a higher mortality risk (Nybo et al. 2001).

In all, the oldest old are the most susceptible age group to suffer from disease and disability, and developments in mortality, morbidity and disability rates have fundamental effects on the sustainability of a modern society (Christensen et al. 2009). A number of studies cover findings from older adults, including often also the oldest old participants, but their number in these studies is usually very low. Most findings that concentrate on the oldest old are based on clinical data or specific population subgroups, and studies using a representative population-based sample are rare (Jylhä, Enroth & Luukkaala 2013). Thus, more research is needed to explore the factors associated with health and functioning of the oldest old.

3 Definition and indicators of obesity

The WHO defines obesity and overweight as “abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired” (WHO 2000). Obesity and body fatness can be measured in various ways, including anthropometric measures, imaging techniques, densiometric methods, and bioelectrical impedance (Duren et al. 2008, Woodrow 2009). Imaging techniques provide the most accurate, yet expensive, method to measure for measuring body fatness. Dual-energy X-ray absorptiometry is often considered the gold standard of body composition assessment (Visser & Harris 2012). Yet more sophisticated imaging methods, such as magnetic resonance imaging and computed tomography, provide accurate results on visceral, intramuscular and intermuscular fat (Lee & Gallagher 2008, Fragala, Kenny & Kuchel 2015). Anthropometric measures, including body mass index (BMI) and waist circumference (WC), are based on the size and proportions of selected body parts and provide the easiest and the cheapest method of estimating body fatness.

Body mass index (BMI)

BMI is defined as weight in kilograms divided by the square of height in meters (kg/m^2). It is the most widely-used method for assessing body fatness (Willett, Dietz & Colditz 1999). BMI was first described by its founder Adolphe Quetelet in 1832, and it was originally known as the Quetelet Index (Eknoyan 2008). The WHO uses the BMI categorizations presented in Table 1 (WHO 2000). The categories apply to all ages for both men and women, and they are used in this study as well. Though, for underweight the cutoff point of 20.0 kg/m^2 (Sergi et al. 2005) is used in addition to the WHO cutoff point of 18.5 kg/m^2. General obesity in this study is defined as BMI $\geq$30.0 kg/m^2.

Neither the WHO nor any other international organization or party has set separate cutoff points for BMI in older adults. However, in Finland the Current Care Guidelines recommend the BMI range of 24–29 kg/m² for adults aged >60 years (Current Care Guidelines 2013). This recommendation is based on an epidemiological study by Dey and colleagues (2001) in which mortality risk was predicted by quintiles of BMI in a 70-year-old population.

Table 1. Classification for BMI according to WHO (adapted from World Health Organization 2000).

Classification	BMI, kg/m²	Risk for comorbidities
Underweight	<18.50	Low (but risk of other clinical problems increased)
Normal weight	18.50–24.99	Average
Overweight*	≥25.00	
Pre-obese	25.00–29.99	Increased
Obese	≥30.00	
Obese, class I	30.00–34.99	Moderate
Obese, class II	35.00–39.99	Severe
Obese, class III	≥40.00	Very severe

Notes: BMI = Body mass index

*The National Institute of Health in the U.S.A. (National Institutes of Health 2000) categorizes BMI range 25.0–29.9 as overweight. The same identification is used in this study.

Due to age-related changes in body composition described in Section 2.3, obesity indicators reflect the amount of body fat differently in younger and older adults. As height declines with aging, BMI is artificially increased (Silver et al. 1993, Sorkin, Muller & Andres 1999, Ding et al. 2007). It has been demonstrated that between the ages of 20 and 80, BMI increases by an average of 2.5 kg/m² in women and 1.5 kg/m² in men due to height loss (Sorkin, Muller & Andres 1999).

BMI and body weight in general usually increase until old age, reach a plateau, and then begin to decline (Visser & Harris 2012). Estimates regarding when BMI reaches its peak vary from 50 years to 80 years (Flegal et al. 1998, Dey et al. 2001, Droyvold et al. 2006, Ding et al. 2007). Evidence from case studies and clinical experience suggests that most individuals maintain their weight until a period of accelerated change in body composition, which is accompanied by deterioration of health status (Alley et al. 2008).

Waist circumference (WC) and waist-to-hip ratio (WHR)

For a given BMI the amount of body fat in the abdominal region may vary considerably. The most frequently used measure for abdominal obesity is WC. A WC ≥80 cm in women and ≥94 cm in men indicates increased health risks, whereas a WC ≥88 cm in women and ≥102 cm in men is considered to indicate seriously increased health risks when compared to normal WC values (WHO 2000). Separate categorizations for WC in older adults have also been proposed based on prediction of mobility limitation (Heim et al. 2010). Data on persons aged 70–88 years suggest that women with a WC ≥88 cm and men with a WC ≥97 cm should avoid gaining further weight, and that women with a WC ≥98 cm and men with a WC ≥110 cm should try to lose weight (Heim et al. 2010).

The definition of abdominal obesity in this study is based on WC, which is used both as a continuous measure and as a tertile-based and median-based measure. The term abdominal obesity in this study refers to a higher (continuous and median-based measure) or the highest (tertile-based measure) values of WC. The specific cutoff points used in the study for abdominal obesity are presented in Section 6.2 Measurements.

WHR is another widely used measure for abdominal obesity (WHO 2000). It is calculated as waist circumference divided by hip circumference, measured from the widest part of the pelvis (WHO 1995). In women, a WHR >0.85, and in men, a WHR >1.0 are considered to be associated with increased health risks (WHO 2000).

4 Obesity and its consequences in older adults

4.1 Trends in obesity prevalence

During the past four decades, overweight and obesity prevalence has markedly increased in both younger and older adults worldwide (Villareal et al. 2005, Ng et al. 2014, Howel 2012, NCD Risk Factor Collaboration 2016). In the general population in Finland the proportion of obese women has increased from 17% to 23% between the years 1978−1980 and 2000, being 26% in 2011 (Aromaa et al. 2004, Lundqvist et al. 2012). In men the obesity prevalence has increased from 12% in 1978−1980 to 21% in 2000, being 23% in 2011 (Aromaa et al. 2004, Lundqvist et al. 2012). Evidence from an extensive study by Ng and coworkers (2014) suggests that since 2006 the increase in adult obesity has slowed in developed countries. However, the slowing down should be interpreted with caution and for example the increase in extreme obesity has been evident (Sperrin et al. 2014, Visscher et al. 2015). Furthermore, increases in abdominal obesity, as measured by WC, have been even more pronounced than increases in general obesity, as measured by BMI (Visscher et al. 2015).

Figure 1 presents trends in obesity prevalence among older adults aged 65–74 years, 75−84 years, and ≥85 years in Finland. Throughout 1978−1980, 2000 and 2011, obesity prevalence among women increased in all three age groups. Among oldest old women, obesity increased from 12% to 26% (Aromaa et al. 2004, Lundqvist et al. 2012; personal communication with Annamari Lundqvist and Seppo Koskinen). Among men, the increase in obesity prevalence has been evident in persons aged 65−74 years, and in persons aged 75−84 years between 1978−1980 and 2000. Somewhat surprisingly among oldest old men obesity prevalence appears to have decreased from 20% to 9% (Aromaa et al. 2004, Lundqvist et al. 2012; personal communication with Annamari Lundqvist and Seppo Koskinen). Yet, low number of the oldest old persons in these surveys need to be acknowledged when interpreting the results.

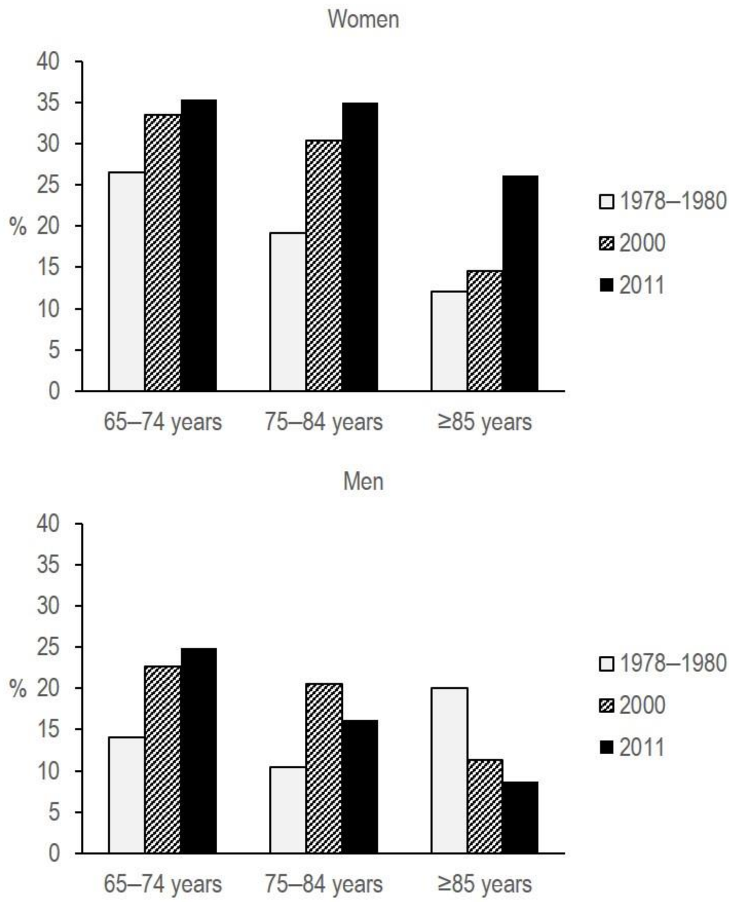

Figure 1. Obesity prevalence (%) among older women and men in Finland by age groups: years 1978–1980, 2000 and 2011 (adopted from reports by Aromaa et al. 2004 and Lundqvist et al. 2012 and by personal communication with Annamari Lundqvist and Seppo Koskinen)

4.2 High and low body weight: Associations with health risks

Evidence for the harmful effects of obesity in the general population is compelling. Obesity is associated with morbidity, poor physical functioning, and impaired quality of life, and it predisposes individuals to premature death in the general population (Visscher & Seidell 2001, Guh et al. 2009, Pi-Sunyer 2009). The effects of obesity are cumulative, and the longer one has experienced obesity, the more likely the adverse health effects (Stenholm et al. 2007a, Janssen & Bacon 2008, Hu et al. 2014). Additionally, the more severe the obesity, the more marked the adverse effects (Must et al. 1999, Al Snih et al. 2007). However, the relationship between excess body weight and health changes with aging (Canning et al. 2014) and findings from younger adults may not apply to older adults.

The majority of the studies that have reported associations between obesity and morbidity pool the results of older adults together with younger adults. However, studies on community-dwelling people and nursing home residents aged ≥65 years have shown that general obesity, and especially abdominal obesity, continues to be a risk factor for several diseases in older adults (Villareal et al. 2005, Felix 2008, Samper-Ternent & Al Snih 2012, MacDonell et al. 2015). The prevalence of many metabolic abnormalities such as metabolic syndrome, dyslipidemia, type II diabetes and hypertension is higher among obese older adults in the general population than among normal weight counterparts (Goodpaster et al. 2005, Canning et al. 2014). Moreover, visceral fat in older adults has been shown to be independently associated with the prevalence of metabolic syndrome, especially in normal weight persons (Goodpaster et al. 2005). Yet obesity is more closely associated with metabolic conditions in young and middle-aged persons when compared to older adults (Canning et al. 2014). It appears that in older adults, general obesity is not associated with the incidence or prevalence of cardiovascular disease (Canning et al. 2014, Dhana et al. 2016). Instead, those who have metabolic syndrome have an increased risk of developing cardiovascular disease regardless of weight (Dhana et al. 2016).

In older adults, obesity has been shown to be a risk factor for the development of several types of cancers (Arnold et al. 2016). Older adults with a history of obesity are also at an increased risk of developing osteoarthritis of the knees, which is a leading cause of pain and disability among older adults (Felson et al. 1988, Silverwood et al. 2015). Obesity in midlife increases the risk of cognitive impairment at the age of 65 years and beyond (Dahl et al. 2013b). However, among older adults, it appears that general obesity does not increase the risk of dementia (Dahl et al. 2008, West & Haan 2009). It seems that in older adults, only abdominal obesity increases the risk of incidenes of dementia or cognitive impairment, and, instead of general obesity or overweight, BMI <25 kg/m^2 is associated with an increased dementia risk (West & Haan 2009). Additionally, obese older adults have a high risk for multimorbidity (van den Bussche et al. 2011), whereas overweight has been shown to only be a modest risk factor for diseases (Janssen 2007).

Only limited data are available for the association between obesity and morbidity in the oldest old. In a cross-sectional population-based study by Dong et al. (2012) obese oldest old persons had more diabetes, chronic heart failure and urinary incontinence, and they also had greater comorbidity than normal weight persons. None of the studied diseases were more prevalent in normal weight when compared to overweight or obese persons (Dong et al. 2012). Bowman et al. (2016) studied general practice patients aged ≥85 years, who were considered "healthier agers". In their study, both overweight (BMI 27.0–29.9 kg/m2) and obesity (BMI 30.0–34.9 kg/m^2 and 35.0–39.9 kg/m^2) increased the risk for developing type 2 diabetes when compared to a BMI of 23.0–26.9 kg/m^2. Interestingly, obesity did not increase the risk for developing coronary heart disease, but a BMI of 27.0–29.9 kg/m^2 did when compared to a BMI of 23.0–26.9 kg/m^2.

Finally, this study approaches obesity from the perspective of Western society. In an environment in which undernutrition is common and infection risk is high, obesity in older adults is seldom a concern (Schaible & Kaufmann 2007, Gurven et al. 2009). From an evolutionary perspective, energy accumulation has been advantageous in terms of survival (Lev-Ran 2001). However, the role of obesity in evolution remains unresolved (Speakman 2013). Altogether, the obesity epidemic of today is a result of two factors: environmental change that has taken place over the course of history and genetic predisposition that originates from evolutionary history (Speakman 2013).

Importance of nutrition

Nutrition is an essential element that contributes to overall well-being (Ahmed & Haboubi 2010), and poor nutrition often leads to low body weight. Aging is accompanied by several challenges that make it difficult to meet nutritional needs (Ahmed & Haboubi 2010, Leslie & Hankey 2015). Older adults often have reduced appetites and diminished energy expenditures (Leslie & Hankey 2015). Together with a decline in biological and physiological body functions, such as reduced muscle mass, changes in hormonal levels, or changes in the regulation of electrolytes, gastric emptying is delayed, and the senses of smell and taste are diminished (Ahmed &

Haboubi 2010). Additionally, pathogenic changes that take place with aging, such as chronic diseases and psychological illness, contribute to the complex etiology associated low nutritional status in older adults (Ahmed & Haboubi 2010). Overall, nutritional intake may be impaired because of factors such as social isolation, depression and problems in swallowing, all of which cause deterioration in nutritional status (Leslie & Hankey 2015).

To detect deficiencies in nutritional status, the concept of malnutrition is often used. However, several different diagnostic criteria have been presented for malnutrition (Jensen et al. 2010, White et al. 2012, Jensen et al. 2013, Cederholm et al. 2015). According to the consensus statement of the European Society for Clinical Nutrition and Metabolism, malnutrition should be based on either low BMI (<18.5 kg/m²) or on weight loss combined with either low BMI (<20 kg/m² in persons <70 years, and <22 kg/m² for persons ≥70 years) or low fat free mass index (Cederholm et al. 2015). Also in this study, malnutrition refers to undernutrition, not to overnutrition. Malnutrition is associated with ample adverse effects: decline in physical functioning, morbidity and mortality (Morley 1997, Ahmed & Haboubi 2010, Saka et al. 2010, Lin et al. 2012, Bollwein et al. 2013).

Unintentional weight loss is an especially important sign of deteriorating health and increased mortality risk (Dey et al. 2001, Alibhai, Greenwood & Payette 2005). Malnutrition and the risk of malnutrition is common in community-dwelling older adults (Nykänen et al. 2013, Jyväkorpi et al. 2015). Even in apparently healthy older adults insufficient nutrient intake is common and is not restricted to underweight people (de Groot, van den Broek & van Staveren 1999, Alam et al. 2011). However, malnutrition is the most pronounced problem among home care clients and institutionalized persons (Suominen et al. 2005, Ahmed & Haboubi 2010, Vikstedt et al. 2011, Nykänen et al. 2013, Jyväkorpi et al. 2015, Wadas-Enright & King 2015). In a population-based study of home care clients aged 75 years and older in Finland, 86% of the study participants were at risk for malnutrition or were malnourished (Kaipainen et al. 2015). In another study of nursing home residents aged 75 years and older in Finland, 90% of women and 83% of men were at risk of malnutrition or suffered from it (Suominen et al. 2005).

In Finland, the National Nutrition Council (2010) has provided nutritional recommendations especially designed for older adults. In general, these recommendations highlight the importance of 1) Taking into account the nutritional needs of older adults at different stages of the aging process, 2) Evaluating nutritional needs regularly, 3) Using vitamin D supplementation regularly (20 μg or 800 IU per day all year around), and 4) Nutrtional care that ensures sufficient intake of energy, protein, nutrients, fiber and liquids (National Nutrition Council 2010). Relevant to these measures, there has been much discussion regarding the importance of protein intake and the optimal recommendation for daily protein intake among older adults (Wolfe, Miller & Miller 2008, Volpi et al. 2013). In Finland, a daily intake of 1.2–1.4 g/kg is recommended for older adults (National Nutrition Council 2014). However, during acute illness, the need for protein may be even greater (Wolfe, Miller & Miller 2008).

"The obesity paradox"

Many chronic conditions ultimately lead to weight loss among older adults and at that time being obesity may provide additional protection. For example, patients with chronic conditions such as cardiovascular diseases (Lavie, Milani & Ventura 2009), chronic kidney disease (Kalantar-Zadeh et al. 2005, Park et al. 2014) and rheumatoid arthritis (Escalante, Haas & del Rincon 2005), or patients recovering from surgical operations (Valentijn et al. 2013) seem to benefit in one way or another from overweight or mild obesity. The benefits are presented in terms of enhanced disease prognosis, improved recovery from surgery, or better survival compared to leaner counterparts. This phenomenon is known as "the obesity paradox". An active scientific conversation about the paradox has been ongoing in recent years, examining evidence both for and against it (Lainscak et al. 2012, Park et al. 2014, Dixon et al. 2015, Lavie, De Schutter & Milani 2015, Prado, Gonzalez & Heymsfield 2015). The most recent studies emphasize the role of muscle mass (Prado, Gonzalez & Heymsfield 2015) and cardiorespiratory fitness (McAuley et al. 2010, Goel et al. 2011) in explaining the decreased health risks associated with obesity, and the obesity paradox may not apply to physically fit persons (Barry et al. 2014, Lavie, De Schutter & Milani 2015). However, several factors continue to support the view that increased weight may have protective effects. These factors include better nutritional reserves, better hemodynamic stability and better capacity to store environmental toxins (Oreopoulos et al. 2009, Hong et al. 2011, Park et al. 2014).

4.3 Biological aspects of obesity

Body weight is regulated by metabolic factors, diet, and physical activity (Weinsier et al. 1998). Simply put, obesity results when energy intake is higher than energy expenditure over the long run (Galgani & Ravussin 2008). However, the biological origins of obesity are complex and the development of obesity may begin very early on. Childhood obesity often follows into adulthood, and several environmental and lifestyle factors, even before pregnancy, during pregnancy and during early life, are associated with weight gain (Lamb et al. 2010, Thompson 2012, Weng et al. 2012). Still, obesity is largely determined by genes (Choquet & Meyre 2011a, Choquet & Meyre 2011b). Epigenetic factors associated with the functioning of genes also play a role in developing obesity (van Dijk et al. 2015). In recent years, the role of gut microbiota in the pathogenesis of obesity has also gained interest and raised for the possibility of new therapeutics (Mishra, Dubey & Ghosh 2016).

In obesity, the body carries an excessive amount of white adipose tissue (Balistreri, Caruso & Candore 2010). For many years, it was believed that adipose tissue merely represented a relatively inactive storage of energy, but the past few decades have shown that adipose tissue is in fact very active and can be regarded as a dynamic endocrine organ (Licastro et al. 2005, Exley et al. 2014). Adipose tissue produces many bioactive molecules, called adipokines or inflammatory cytokines, which regulate systemic metabolism and have immunoregulatory properties (Fain 2010, Exley et al. 2014). Inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP) have been shown to be associated with BMI, WC or WHR (Meier et al. 2002, Park, Park & Yu 2005, Tsai & Tsai 2008). The excessive adipose tissue is immunologically active and metabolically harmful when it is located viscerally, as opposed to subcutaneously, in the abdominal region (Ibrahim 2010). It promotes a pro-inflammatory status, "low-grade inflammation", which in turn has an essential role as the origin and maintainer of various chronic diseases, such as cardiovascular disease, cancer, and Alzheimer's disease (Coussens & Werb 2002, Cesari et al. 2003, Glass et al. 2010). Low-grade inflammation also accompanies aging (Vasto et al. 2007) and is associated with increased mortality risk (Harris et al. 1999). Furthermore, inflammation is present in chronic and acute disease-related malnutrition (Jensen et al. 2013). Yet no studies have examined whether obesity indicators remain associated with inflammatory markers in the oldest old population.

4.4 Obesity and physical functioning

Obesity accelerates functional decline, based on both performance-based and self-reported measures of physical functioning, but the magnitude of the decline depends on the level of obesity and on the specific measure used (Backholer et al. 2012, Samper-Ternent & Al Snih 2012). The relationship between both BMI and WC, and physical functioning is U- or J- shaped among older adults, indicating that both low and high body weight predisposes individuals to functional decline (Al Snih et al. 2007, Backholer et al. 2012, Samper-Ternent & Al Snih 2012). However, high WC has been shown to predict a more likely decline in physical functioning than high BMI in older adults (Angleman, Harris & Melzer 2006). Studies have been controversial regarding whether overweight increases (Marsh et al. 2011) or decreases (Mendes de Leon et al. 2006) the risk of low physical performance in older adults, and whether overweight increases the risk for ADL disability (Al Snih et al. 2007) or even has potential protective effects (Rejeski et al. 2010). These controversial results may be due to variations in muscle strength or varying controlling for diseases or physical activity (Rejeski et al. 2010, Schaap, Koster & Visser 2013). However, in a meta-analysis by Backholer and coworkers (2012), overweight was associated with ADL disability in both cross-sectional and prospective settings.

Obesity and physical functioning in the oldest old

Only a limited number of studies have explored the association between body weight and physical functioning in the oldest old. In recent cross-sectional population-based studies obesity has been associated with low physical functioning in oldest old women (Dong et al. 2012, Yang et al. 2014, Hajek et al. 2015) and men (Dong et al. 2012, Yin et al. 2014, Hajek et al. 2015). Low WC and low BMI have also been associated with low physical functioning − namely disability − in the general population (Yang et al. 2014, Yin et al. 2014) and with a lower ADL score among either geriatric patients or persons receiving different levels of care (Kaiser et al. 2010, Kiesswetter et al. 2015). Kiesswetter and colleagues (2015) found that the association between BMI and physical functioning depends on health and care status. In persons receiving care, the association between low BMI and a low ADL score was lost after adjusting for cognitive status (Kiesswetter et al. 2015). Two studies have used a performance-based measure of physical functioning when investigating the association with BMI (Kaiser et al. 2010, Dong et al. 2012). Kaiser and colleagues (2010) found no association between the Timed Up and Go test and BMI among nursing home residents, whereas in the population-based study by Dong and colleagues (2012) obese participants had significantly lower performance in the Timed Up and Go test compared to both normal weight and overweight participants.

Few prospective studies have presented results on the association of body weight and physical functioning in the oldest old. Among community-dwelling oldest old persons (Reynolds & McIlvane 2009) and among persons aged ≥66 years at baseline and with a follow-up extending to 85 years of age (Rillamas-Sun et al. 2014), obesity has been associated with disability (Rillamas-Sun et al. 2014, Reynolds & McIlvane 2009). Data on nursing home residents with a mean age of 86 years have demonstrated the association between lower weight and lower physical functioning (Kaiser et al. 2010). Of these three prospective studies, none used a population-based sample, one used only self-reported measures of BMI and also included participants with disability at baseline (Reynolds & McIlvane 2009), and one studied only women (Rillamas-Sun et al. 2014). Furthermore, the results from Reynolds and McIlvane (2009) addressing active life expectancy were weighted to reflect a population aged ≥70 years. To conclude, existing studies examining the association of obesity with physical functioning in the oldest old are primarily cross-sectional and based on self-reported measures of physical functioning. No longitudinal studies have examined disability incidence exclusively in the oldest old population. In addition, previous studies have primarily used BMI as an obesity indicator and no studies have examined the association between WC and physical performance in the oldest old.

4.5 Obesity and mortality

General obesity and mortality

Many studies conducted over the past few decades have examined the relationship between general obesity and mortality in older adults (Allison et al. 1997, Heiat, Vaccarino & Krumholz 2001, Price et al. 2006, Janssen & Mark 2007, Kulminski et al. 2008, Pischon et al. 2008, Prospective Studies Collaboration et al. 2009, Berraho et al. 2010, de Hollander et al. 2012b, Dahl et al. 2013a, Flegal et al. 2013, Winter et al. 2014). In the largest and most recent meta-analysis concentrating solely on older adults including nearly 200,000 community-dwelling adults aged ≥65 years, the relationship between BMI and all-cause mortality was found to be U-shaped with the lowest mortality risk observed between 24.0 and 30.9 kg/m^2 (Winter et al. 2014). Overweight indicated a significantly lower mortality risk, while BMIs <23 kg/m^2 and >33 kg/m^2 indicated a significantly higher mortality risk when compared to the reference group of 23.0–23.9 kg/m^2. The results were adjusted for smoking but further adjustment for diseases did not markedly alter the results (Winter et al. 2014). Other studies have shown that the increased mortality risk associated with high BMI in older adults is primarily driven by cardiovascular disease mortality, although the association is not as strong as in younger adults (Stevens et al. 1998, de Hollander et al. 2012b).

Previous systematic reviews have shown varied results regarding the relationship between BMI and mortality in older adults. Studies have used different categorizations and reference groups, which renders comparison difficult. The results of Winter and coworkers (2014) are consistent with earlier systematic reviews in that overweight indicates a lower mortality risk than normal weight and the association of obesity with mortality is weakened in older adults (Heiat, Vaccarino & Krumholz 2001, Janssen & Mark 2007). Yet differing results have also been found. Prospective Studies Collaboration (2009) examined the association between BMI and mortality in nearly 900,000 adults in four separate age groups: <60 years, 60–69 years, 70–79 years and 80–89 years. They found that for a BMI range of 25–50 kg/m^2, 5 kg/m^2 higher BMI was associated with on average 30% higher overall mortality in all age groups. These more adverse consequences of extra weight in older adults compared to other reviews may be explained by the fact that all deaths occurring during the first five years of the follow-up were excluded. Additionally, in the review by Heiat and coworkers (2001), when only those studies examining older adults without severe diseases were included, both overweight and obesity increased mortality risk. These results highlight the long-known importance of diseases in explaining the effects of body weight on mortality (Willett, Dietz & Colditz 1999).

For further comparison, the results of the Prospective Studies Collaboration (2009) on low BMI and mortality are consistent with the results by Winter and colleagues (2014) as BMI <22.5 kg/m² was associated with increasing overall mortality. When the results by Winter and colleagues (2014) are compared to the results by Flegal and colleagues (2013), the findings regarding obesity contrast. In the study by Flegal et al. (2013) representing the general population, neither BMI ≥30 kg/m² nor ≥35 kg/m² increased mortality risk when compared to normal weight in persons aged ≥65 years. The results were obtained by using the most complex model available in the adjustments (Flegal et al. 2013). However, the study has raised considerable dialogue, as additionally in younger adults BMI 30–35 kg/m² did not increase mortality risk, and the results have been questioned, e.g., for its heterogeneous comparison group (Willett, Hu & Thun 2013). However, it should also be noted that the study by Flegal and colleagues (2013) represents the general population, whereas the study by Winter and colleagues (2014) represents community-dwelling participants.

The older the population, the less data that are available on the associations between BMI and mortality. With increasing age, mortality risk associated with BMI is decreasingly U-shaped (Thinggaard et al. 2010), and the BMI value for the lowest mortality seems to increase (Heiat, Vaccarino & Krumholz 2001). In older populations, the differences between community-dwelling people and nursing home residents and the relevance of recent weigh loss are also important to acknowledge. In a study by Wirth et al. (2016), the association between BMI and six-month mortality was assessed in more than 10,000 nursing home residents with a mean age of 85 years. It was found that BMI<20.0 kg/m² and weight loss <5 kg during the past year were both independent and equally relevant risk factors for mortality (Wirth et al. 2016). However, weight gain has also been shown to be predictive of mortality in both population-based and community-dwelling samples of older adults with a mean age ranging from 78 to 85 (Rajala et al. 1990, Dahl et al. 2013a). Yet, the risks associated with weight gain appear to be less severe in persons aged ≥80 years as compared to persons aged 70–79 years (Dahl et al. 2013a).

In a Japanese population aged ≥80 years, all-cause and respiratory disease mortality has been shown to be the highest in the leanest BMI group (<19.5 kg/m²), whereas the lowest mortality risk has been shown to be for a BMI range (22.5–23.7 kg/m²) (Takata et al. 2013). Yet the optimal BMI for health is lower for Asian and Pacific populations as compared to the general recommendation (WHO 2000, WHO

Expert Consultation 2004). Regarding morbidity, Nilsson and coworkers (Nilsson, Hedberg & Ohrvik 2011) reported that BMI <25 kg/m^2 was associated with an increased all-cause and cardiovascular mortality risk in persons aged ≥75 years with type II diabetes or impaired fasting glucose but not in persons without them.

Few studies have investigated the relationship between BMI and mortality separately in oldest old people (Mattila, Haavisto & Rajala 1986, Rajala et al. 1990, Nybo et al. 2003, van Vliet et al. 2010, Bowman et al. 2016). These studies, along with central studies concerning various population groups of older adults with different ages are presented in Table 2. The recent study by Bowman and colleagues (2016) contributes considerably to the literature on the association of BMI with mortality in the oldest old. Among over 96,000 general practice patients aged ≥85 years, class I obesity (BMI 30.0−34.9 kg/m^2) indicated a lower mortality risk and underweight a higher mortality risk in both "healthy" and "non-healthy" agers when compared to normal weight. However, among "healthy agers", the results for BMI ≥35.0 kg/m^2 were not statistically significant, whereas among "non-healthy agers" also BMI ≥35.0 kg/m^2 indicated a lower mortality risk (Bowman et al. 2016). In a further analysis among "healthy agers" when persons with weight loss, both ≥2.5 kg and ≥5 kg, were excluded, mortality risk among persons with a BMI 27.0−29.9 kg/m^2 and among obese persons did not differ from those with a BMI 23.0–26.9 kg/m^2. In all, the results from the oldest old indicate that low BMI is a more relevant indicator than high BMI in predicting mortality risk. However, representative population-based data stratified by gender on BMI and mortality in the oldest old are still needed.

Table 2. Central studies on the association of BMI with all-cause mortality among older adults stratified by age for all and by population group for the age group ≥65 years: Participants with mainly Western Europe or Northern American descent (women and men together unless otherwise stated)

Source	Age	Sample size	Follow-up	Adjustments (Notes)	BMI groups, kg/m²	Mortality: HR (95% CI) unless otherwise stated	BMI, S/M
Age ≥65 y, Community-dwelling participants							
Winter et al. 2014	≥65 y	197,940	12 y (mean)	None used with the present results (Self-reported anthropometric measurements, adjustment for intermediary factors, and exclusion of early deaths or preexisting disease did not markedly alter the associations)	17.0–17.9	1.48 (1.42–1.55)	S,M
					18.0–18.9	1.38 (1.33–1.43)	
					19.0–19.9	1.28 (1.24–1.32)	
					20.0–20.9	1.19 (1.17–1.22)	
					21.0–21.9	1.12 (1.10–1.13)	
					22.0–22.9	1.05 (1.05–1.06)	
					23.0–23.9	1.00 (reference)	
					24.0–24.9	0.96 (0.96–0.97)	
					25.0–25.9	0.93 (0.92–0.94)	
					26.0–26.9	0.91 (0.90–0.92)	
					27.0–27.9	0.90 (0.88–0.92)	
					28.0–28.9	0.91 (0.88–0.93)	
					29.0–29.9	0.93 (0.90–0.96)	
					30.0–30.9	0.95 (0.91–0.99)	
					31.0–31.9	0.98 (0.93–1.03)	
					32.0–32.9	1.03 (0.97–1.09)	
					33.0–33.9	1.08 (1.00–1.15)	
					34.0–34.9	1.13 (1.05–1.23)	
					35.0–35.9	1.21 (1.10–1.33)	
					36.0–36.9	1.28 (1.16–1.43)	
					37.0–37.9	1.36 (1.21–1.52)	

(Table 2 continues)

Age ≥65 y, Nursing home residents						*ORs*	
Wirth et al. 2016	≥65 y	10,298	6 mo	Age, gender, severe cognitive impairment and immobility	≥20, WL<5 kg	1.00 (reference)	S
				(Weight change during the past	≥20, WL>5 kg	1.53 (1.25–1.88)	
				year was reported;	<20, WL<5 kg	1.67 (1.43–1.95)	
				Mean age 85 years)	<20, WL>5 kg	3.51 (2.80–4.39)	
						In absolute terms mortality-% decreased from <16.0 kg/m^2 till 27–28 kg/m^2, after which it remained on a similar or a bit higher level)	
Age ≥65 y, General population							
Flegal et al. 2013	≥65 y	*No. of HRs* 33	Not reported	Most complex model available used	18.5–24.9	1.00 (reference)	S,M
				(Population-based sample;	25.0–29.9	0.90 (0.86–0.94)	
				Only studies using WHO	≥30.0	1.03 (0.94–1.12)	
				cutoff points were used)	30.0–34.9	0.87 (0.72–1.05)	
					≥35.0	1.20 (0.94–1.52)	
Age ≥70 y						*HR per 5 kg/m^2 higher BMI*	
Prospective Studies Collaboration 2009	70–79 y	21,436	Not reported	Age, sex, study, smoking	15–25	0.82 (0.77–0.87)	S,M
				(Not explicitly reported, which population groups are included;	25–50	1.27 (1.23–1.32)	
	80–89 y	4,331		Those who died during the first	15–25	0.89 (0.80–0.97)	
				5 years of the follow-up and those with baseline history of heart disease or stroke were excluded)	25–50	1.16 (1.10–1.23)	

(Table 2 continues)

Dahl et al. 2013	70–95 y	882	–18 y	None (except for Bonferroni adjustments; Analyses were centered at the age of 80 years) (Participants drawn from twin registers and from population register; Mean age 81.1 years; Weight change over a two- or a four-year period was measured)	<25	1.00 (reference)	M
					25.0–29.9	0.80 (0.67–0.95)	
					≥30.0	0.93 (0.71–1.22)	
					BMI change		
					5% loss	1.65 (1.34–2.04)	
					Stable	1.00 (reference)	
					5% gain	1.53 (1.18–1.99)	
Age ≥80 y						*Mortality-%*	
Haavisto et al. 1990	84–88	722	3 y	None (Community-dwelling sample; Mean age 85.5 y)	<22.0	32.4	M
					22.0–29.9	19.9	
					≥30.0	16.2	
						The lowest and middle BMI group differed from each other (p<0.01); When women and men analyzed separately, only the result for women was statistically significant	
Age ≥85 y							
Bowman et al. 2016	≥85 y	96,498	3.6 y (mean)	Age, gender, alcohol, smoking, calendar year, and Index Multiple of Deprivation (For the "Healthy agers" current smokers, patients with cancer (last 5 years), dementia, heart failure and multi-morbidity, and the first 3.9 years of the follow-up were excluded; The "non-healthy agers" consisted of current smokers, patients with cancer (last 5 years), dementia, heart failure, and the whole follow-up period)	*"Healthy agers"*		S,M
					14.0–18.4	1.38 (1.27–1.51)	
					18.5–24.9	1.00	
					25.0–29.9	0.85 (0.82–0.89)	
					30.0–34.9	0.89 (0.83–0.95)	
					≥35.0	0.91 (0.78–1.05)	
					"Non-healthy agers"		
					14.0–18.4	1.70 (1.63–1.77)	
					18.5–24.9	1.00	
					25.0–29.9	0.77 (0.75–0.79)	
					30.0–34.9	0.72 (0.69–0.75)	
					≥35.0	0.89 (0.82–0.96)	

(Table 2 continues)

Mattila et al. 1986	≥85 y	526	5 y	None (Population-based sample; representativeness 78%)	<20.0 20.21.9 22.0–23.9 24.0–25.9 26.0–27.9 ≥28.0 ≥30	The highest mortality (87%) with BMI<20; the lowest mortality (53%) with BMI≥30; Mortality decreased with increasing BMI; Survival curves with BMI≥22 did not significantly differ from each other	M
Nybo et al. 2003	93 y	2,249	15 mo	None used in relation to findings presented in this table (Population-based sample; representativeness 78%)	*Mortality rate per 100 person years* <22 22–27 ≥28	 W: 25.4 (22.1–29.1) M: 44.7 (35.2–56.9) W: 16.8 (14.2–19.8) M: 23.0 (14.8–35.6) W: 16.8 (11.5–24.4) BMI ≥28 associated with the lowest mortality risk, also after adjustments	S
van Vilet et al. 2010	85 y	599	10 y	None used in relation to findings presented in this table (Population-based sample; Participants were annually assessed for weight during the first five years of the follow-up)		In absolute terms BMI declined annually among all; Participants who died at the age of 90–91 (n=57) years had stronger annual declines in BMI and significantly lower BMI (p<0.001) as compared to those who survived 10 years (n=113)	M

BMI = body mass index; CI= confidence interval; HR = hazard ratio; OR = odds ratio; S = self-reported; M = measured; WL= weight loss during the past year; W = women; M = men

Abdominal obesity and mortality

Over the past decade, large studies have investigated the association between abdominal obesity and mortality in older adults (Price et al. 2006, Pischon et al. 2008, de Hollander et al. 2012a, Rillamas-Sun et al. 2014). The largest meta-analysis by de Hollander and colleagues (2012a), which concentrated exceluively on older adults aged 65–74 years, demonstrates that the association between WC and mortality risk is J-shaped, and persons with an increased WC have an increased all-cause, cardiovascular disease and cancer mortality risk. The lowest mortality risk was at 77 cm for women and at 94 cm for men. WC above the generally used cutoff points of 88 cm for women and 102 cm for men indicated an increased mortality risk (de Hollander et al. 2012a). The results differ to some extent from the meta-analysis by Pischon et al. (2008), which presented results for older adults aged ≥65 years. In both in women and men, the lowest mortality risk was identified in the lowest WC quintile (<70 cm in women and <86 cm in men). In women, the mortality risk was statistically significantly higher for a WC ≥81 cm, whereas in men the gradual increase in mortality risk was statistically significant for a WC ≥86 cm (Pischon et al. 2008). In all, many other studies on older adults have also shown increased mortality risks for high WC (Guallar-Castillon et al. 2009, Reis et al. 2009, Rillamas-Sun et al. 2014). However, in some studies, no association between WC and mortality has been found (Price et al. 2006), or in some cases only increased mortality risk on low values of WC has been statistically significant (Lee et al. 2012).

Studies on WHR and mortality in older adults are much lower in number when compared with studies on BMI or WC and mortality. Additionally, the findings on WHR and mortality are conflicting. Some results show no association between WHR and mortality (Reis et al. 2009), whereas other studies find it to be the most suitable indicator over BMI and WC in assessing the risk of death in older adults (Folsom et al. 2000, Price et al. 2006, Srikanthan, Seeman & Karlamangla 2009). In all, studies are inconsistent regardig which anthropometric measure provides the most accurate estimates in predicting adverse outcomes in older adults, although a majority of studies acknowledge that BMI is not a good reflector of body fat distribution (Chang et al. 2012).

When both general and abdominal obesity have been assessed in older adults, higher BMI values have been shown to indicate lower mortality risk when the risk associated with WC has been accounted for, and higher values in WC have indicated higher mortality risk when the risk associated with BMI has been accounted for (Janssen, Katzmarzyk & Ross 2005, Guallar-Castillon et al. 2009). Thus, BMI has an inverse association and WC has a direct association with mortality in older adults when both measures are analyzed in the same model, and the adverse effects of high WC become more evident (Beleigoli et al. 2012, de Hollander et al. 2012a). Moreover, among older adults, it appears that a normal weight person with a large WC has a higher mortality risk than an overweight person with a large WC (de Hollander et al. 2012a). Many studies recommend that in addition to BMI, a measure of abdominal obesity should be incorporated into the clinical setting (Janssen, Katzmarzyk & Ross 2005, Pischon et al. 2008, de Hollander et al. 2012a).

As far as is known, no studies have examined the association between WC and mortality specifically in the oldest old. Thus, examining the effects of abdominal obesity on mortality, separately and in combination with BMI, is needed in the oldest old population

Associations between inflammation, obesity and mortality

One factor that may affect the relationship between body fatness and mortality is inflammation (Escalante, Haas & del Rincon 2005). Pro-inflammatory status is closely associated with obesity and mortality (Park, Park & Yu 2005, Harris et al. 1999). Based on this premise alone it could be assumed that obesity is an obvious risk factor for mortality in older adults, but that is not the case (Oreopoulos et al. 2009). At the low end of the weight spectrum, disease-related malnutrition and low weight are associated with pro-inflammatory status as well as mortality (Jensen et al. 2013). Related to chronic kidney disease, research addressing these issues has been conducted (Beddhu 2004, Kalantar-Zadeh 2005, Kalantar-Zadeh et al. 2005, Beddhu et al. 2007, Park et al. 2014). In chronic kidney disease, obesity is associated with inflammation and atherosclerosis, but it has been hypothesized that the effect of malnutrition on mortality is much greater than that of atherosclerosis (Beddhu 2004). Furthermore, Beddhu (2004) hypothesized that in chronic kidney disease low BMI with malnutrition conveys the highest mortality risk and high BMI due to high muscle mass the lowest mortality risk. However, assumptions and findings on patients with chronic kidney disease may not apply to older adults in general, and other studies examining the consequences of inflammation and body fatness together are scarce.

Pérez and colleagues (2016) address the concepts of inflammation and obesity and link them with aging. They contend that "to a great extent, obese adults are prematurely aged individuals" (Pérez et al. 2016). This view is based on the fact that dysfunction in adipose tissue shares several biological similarities with the aging process, such as chronic inflammation and functional changes in multiple systems (Pérez et al. 2016). However, the interplay between adipose tissue, inflammation and health outcomes is complex. Lakoski and colleagues (2011) sought to demonstrate an increased mortality risk among obese community-dwelling older adults with higher levels of inflammation. However, their research found that inflammatory status did not distinguish those in risk of premature death in obese persons. Instead, a pro-inflammatory status was a powerful risk factor for mortality in both underweight and normal weight persons (Lakoski et al. 2011). The absolute mortality risk was the highest in those with low BMI and high inflammation, emphasizing the hazards associated with low weight. In all, the relationships between obesity, inflammatory status and mortality have been scantly studied, and related studies on the oldest old are lacking.

5 Aims of the study

The aim of this study was to investigate whether obesity and low body weight are associated with physical functioning and mortality in the oldest old.

The specific aims of the study were as follows:

1) To examine if BMI and WC are associated with physical functioning in the oldest old in a cross-sectional (Study I) or in a prospective (Study II) setting.

2) To explore whether BMI, WC and WHR predict mortality in the oldest old (Study III).

3) To investigate the associations of inflammatory markers with BMI, WC and WHR. In addition, the combined associations of BMI and WC, and inflammatory status on mortality in the oldest old were examined (Study IV).

6 Materials and methods

6.1 Design and participants

Data for the original studies are derived from the Vitality 90+ Study, a prospective, population-based study of people aged 90 years and older, living in the area of Tampere, Finland. The Vitality 90+ Study includes mailed surveys with the entire population aged 90 and older, face-to-face interviews and health examinations for the population aged 90 years, and narrative life-story interviews for selected groups. This study is based on the health examinations, but the mailed survey data is also used for prospective analyses. Both community-dwelling and institutionalized people were invited to participate in the health examinations. Data were gathered from individuals born in 1909–1910, 1911, 1912–1913, and 1920 (Figure 2). Health examinations were conducted during 2000 (cohort born in 1909–1910), 2001 (cohort born in 1911), 2003 (cohort born in 1912–1913) and 2010 (cohort born in 1920). Thus, for each of these years, the target population for the study was all inhabitants aged 90 years who were living in the city of Tampere according to the population register. For the entire population in these cohorts n=1,827. In 2000, 2001 and 2010 the study population included both community-dwelling and institutionalized persons, but in 2003 only community-dwelling persons, as anthropometric measures were not available for institutionalized participants. In 2003, altogether 94 persons (38%) who participated in the health examinations were institutionalized persons and, thus, were lacking the anthrpometric data.

Health examinations were conducted by trained study personnel at the place of residence of each participant. The study personnel consisted of medical students of the Faculty of Medicine, University of Tampere. The health examinations included 1) an interview on sociodemographic factors, lifestyle, health, illness and medication, and on cognitive and physical functioning, 2) measurement of anthropometrics, and 3) assessment of physical performance. In 2000, blood tests were also conducted. Altogether, 891 persons (666 women and 225 men) took part in the health examinations. Participants were then followed up for physical functioning and for all-cause mortality. Follow-up data for physical functioning were gathered in the years 2001, 2003, 2007, 2010 and 2014 by mailed questionnaires, which were sent to all people aged 90 years and older, who were living in the city of Tampere. The median follow-up for disability was 3.6 years (range 0.6–7.8 years). For mortality, both four-year and eight-year follow-ups were used. Dates of death were drawn from Statistics Finland and from the National Population Register, Finland. A flow chart of the participants in the study is presented in Figure 3.

The cohorts and populations included in the original studies varied (Figure 2 and Figure 3). In Study II, in which physical functioning was followed-up, only disability-free participants were included in the analyses (Figure 3). Thus, at baseline 384 (43%) of the 891 participants who had disability were excluded from the analyses. In all of the other sub-studies inclusion criteria was related to availability of the explanatory factors (anthropometric measures in Studies I−IV and inflammatory markers in Study IV) or the outcome measures (measures for physical functioning in Studies I−II; There were no missing data in the mortality follow-up (Studies II−IV)).

The study protocol was approved by the Ethics Committee of the Pirkanmaa Hospital District or the Ethics Committee of the Tampere Health Center depending on the year of data collection. All participants or their legal representatives gave their written informed consent.

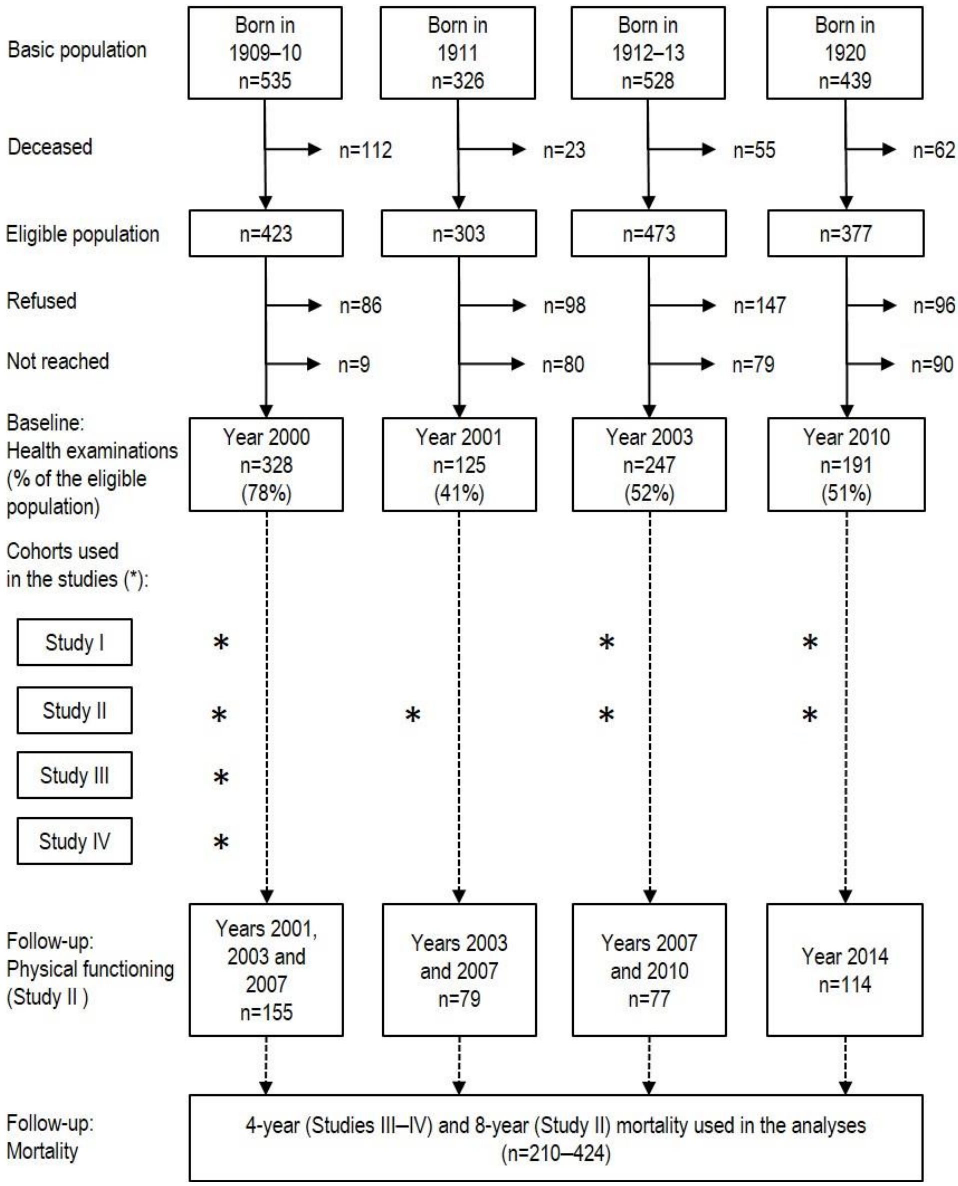

Figure 2. Design for the study: Cohorts used in the original studies and selection of the participants for the health examinations within the Vitality 90+ Study. For the follow-ups the final number of participants is presented.

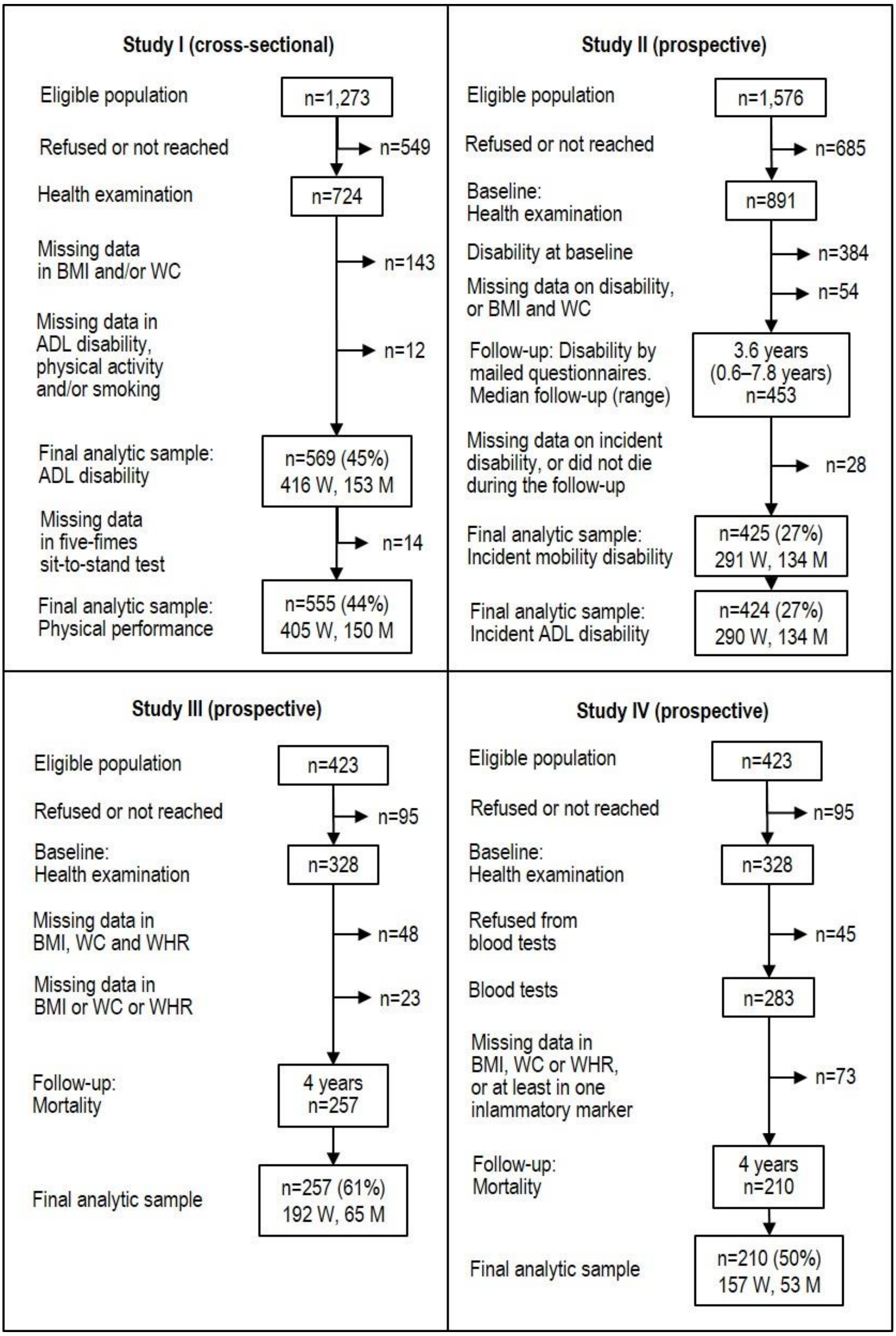

Figure 3. Flow chart of the participants. For the final analytic samples, the proportion (%) of the participants included in the study, based on the eligible population, is presented in parentheses. BMI = body mass index, WC = waist circumference, ADL = activities of daily living, WHR = waist-to-hip ratio, W = women, M = men.

6.2 Measurements

Explanatory factors

Obesity indicators (Studies I–IV)

The obesity indicators used in the study are presented in Table 3. In this study the term general obesity is defined as obese BMI, i.e., BMI ≥30 kg/m^2. The definition for abdominal obesity in this study is based on WC. Abdominal obesity refers to a higher (continuous and median-based measure) or the highest (tertile-based measure) values of WC. Depending on the original study in which WC was used as a categorized measure (Studies I, II and IV), the definition of abdominal obesity ranges from 86 to 92 cm and above for women and from 94 to 100 cm and above for men.

Table 3. Definitions and categories for body mass index, waist circumference and waist-to-hip ratio used in the study

Variable	Study	Definitions / categories
Explanatory factors		
Body mass index	I–IV	Measured height and weight
	I–II	<20.0 kg/m^2 (underweight), 20.0–24.9 kg/m^2 (normal weight), 25.0–29.9 kg/m^2 (overweight), and ≥30.0 kg/m^2 (obese) (Sergi et al. 2005)
	III	<18.5 kg/m^2 (underweight), 18.5–24.9 kg/m^2 (normal weight), 25.0–29.9 kg/m^2 (overweight), and ≥30.0 kg/m^2 (obese) (WHO 2000)
Waist circumference	I–IV	Measured between the lowest rib and the iliac crest (Studies I–IV) (WHO 2000) or at the level of the iliac crest (Studies I–II) (National Institutes of Health 2000)
	I	Tertiles: <83 cm, 83–91 cm, and ≥92 cm for women; <92 cm, 92–99 cm, and ≥100 cm for men
	II	Tertiles: <82 cm, 82–89 cm, and ≥90 cm for women; <91 cm, 91–99 cm, and ≥100 cm for men
Waist-to-hip ratio	III–IV	Waist circumference measured between the lowest rib and the iliac crest, and hip circumference from the widest part of the pelvis (WHO 1995). Used as a continuous variable.

Body mass index (BMI). BMI was computed as weight in kilograms divided by height in meters squared (kg/m^2). During the measurement of weight and height, the participant was standing while wearing light clothing. Weight was measured with a digital scale (Soehnle, Germany) and height with a wall measure. Yet, in 2010 heights and weights were self-reported in 7 cases (Studies I–II). In the years 2000–2003 weight was recorded to the nearest kilogram and height to the nearest centimeter. In 2010 weight was recorded to the nearest 0.1 kilograms and height to the nearest 0.5 centimeters. In the first conducted study, Study III, BMI was categorized according to the WHO definition (WHO 2000) (Table 3). In Studies I–II the cutoff point for the underweight category was set to 20.0 kg/m^2 (Sergi et al. 2005) instead of the 18.5 kg/m^2 recommended by WHO (WHO 2000). The reason for using a slightly higher cutoff point was to obtain more participants for the lowest category for the analyses as only 6–12 participants had a BMI below 18.5 kg/m^2. In Study IV, BMI was used as a continuous variable when the associations between BMI and the levels of inflammatory markers were assessed.

Waist circumference (WC). In the years 2000–2003 WC was measured midway between the lowest rib and the iliac crest (WHO 2000). In 2010 the measurement site was changed and WC was measured at the level of the iliac crest. The decision to change the measurement site was based on the recommendation of thee U.S. National Institute of Health (National Institutes of Health 2000). The measurement was taken next to the skin with a tape measure at the end of expiration while the participant was standing. In Studies I–II WC was categorized according to sex-specific tertiles of the final study population (Table 3). In Studies III−IV WC was used as a continuous variable.

Waist-to-hip ratio (WHR). WHR was computed as WC divided by hip circumference. WC was measured as described above and hip circumference was measured from the widest part of the pelvis (WHO 1995). The measurement was taken with a tape measure while the participant was standing wearing light clothing. WHR was used in Studies III−IV, and was treated as a continuous variable.

Combination of BMI and WC. In older people, combining the level of BMI with the level of WC has been shown to provide additional information on the association with mortality when compared to analyzing the variables separately (Janssen, Katzmarzyk & Ross 2005). In Studies I and III, a four-class variable of BMI and WC was used by combining low or high BMI (25.0 kg/m^2 as cutoff point) with low or high WC (sex-specific median as cutoff point). In Study I the cutoff point for WC was 87 cm in women and 96 cm in men. In Study III only normal weight (BMI 18.5–24.9 kg/m^2) and overweight (BMI 25.0–29.9 kg/m^2) participants were included in the analyses, and the cutoff point for WC was 86 cm in women and 94 cm in men.

<u>Inflammatory markers and their combination with obesity indicators (Study IV)</u>

Interleukin-1 receptor antagonist (IL-1RA), interleukin-6 (IL-6), tumor necrosis factor a (TNF-a) and C-reactive protein (CRP). The inflammatory markers were selected on the basis of their wide use in the literature and reported association with levels of adiposity. In the year 2000 blood samples were collected by a study nurse in the morning after an overnight fast. EDTA tubes in ice were used for the samples. Plasma was separated after centrifugation (15 minutes at 700x*g*), divided into aliquots, and stored at -80°C until analyzed. Concentrations of IL-1RA and IL-6 were analyzed using enzyme-linked immunosorbent assay (ELISA) kits (Pelikine Compact human IL-6; Quantikine, R&D Systems, Minneapolis, MN for IL-1RA). The optical density of the wells was analyzed using Multiscan Biochromatic 348 spectrophotometer (Labsystems, Helsinki, Finland). Concentration of TNF-α was analyzed with a Luminex-based multiplex analysis system (Bio-Plex 200 System, Bio-Rad Laboratories, Inc.). High-sensitivity CRP was analyzed using a Cobas Integra 700 automatic analyzer with reagents and calibrators as recommended by the manufacturer (Hoffman-La Roche Ltd., Basel, Switzerland; COBAS Integra C-reactive Protein, Latex). In CRP values below the detection level (0.10 mg/L) were coded as 0.05 mg/L.

Combination of inflammatory status with BMI and WC. A separate variable describing inflammatory burden was formed on the basis of the number of markers found in IL-1RA, IL-6, CRP, and TNF-α that had a higher level than the sex-specific median. Inflammatory status was categorized as (i) low inflammation (0–1 inflammatory markers above the sex-specific median), and (ii) high inflammation (2–4 inflammatory markers above the sex-specific median). Low or high BMI (25.0 kg/m^2 as cutoff point) and WC (sex-specific median as cutoff point; 85 cm for women and 93 cm for men) were combined with low or high inflammation to form four-class variables.

Outcomes

The outcomes for the study were physical functioning and mortality. Physical functioning was measured as physical performance, activities of daily living (ADL) disability and mobility disability (Table 4). These were drawn using: 1) the five-times sit-to-stand test (physical performance), 2) the Barthel Index (ADL disability), and 3) the mailed questionnaire (mobility and ADL disability).

Table 4. Outcome measures and their definitions used in the original studies

Variable	Study	Measurement / definitions
Physical performance	I	Measured by five times sit-to-stand test (Bohannon 2012) Categorized as (i) high performance (<16 s), (ii) low performance (≥16 s), and (iii) unable to complete the test
Acitivities of daily living disability	I	Score 0–95 in Barthel Index (Mahoney & Barthel 1965)
	II	Self-reported mobility disability (inability to walk 400 meters or climb stairs independently), and inability to get dressed and undressed, or to get in and out of bed (Stenholm et al. 2014)
Mobility disability	II	Self-reported inability to walk 400 meters or climb stairs independently (Guralnik, Fried & Salive 1996)
Mortality	II–IV	Dates of death from the National Population Register, Finland, and Statistics Finland

Physical functioning (Studies I–II)

Physical performance was measured using the five-times sit-to-stand test (Guralnik et al. 1994, Bohannon 2012). The chair for the test was chosen from the residence of each participant. First, the participant was asked to rise from a chair with arms folded across the chest. If successful, the participant was asked to perform five rises from a chair with arms folded across the chest as fast as possible. Timing with a stopwatch started with the participant in the sitting position and ended upon completion of the fifth stand. If the participant was unable to complete five rises, or decided not to take the test because of a medical condition or pain, or if the participant or the person testing felt it too risky to take the test, the performance was coded as “unable”. Participants who refused to take the test were coded as missing (n=6). The five-times sit-to-stand test was missing from eight persons with no reported reason.

Physical performance was used in a cross-sectional setting in Study I and it was defined according to the level of performance time in the five-times sit-to-stand test. Physical performance was classified according to the median time (women and men together) and was categorized as (i) high performance (<16 s), (ii) low performance (≥16 s), and (iii) unable to complete the test.

Activities of daily living (ADL) disability. The Barthel Index (Mahoney & Barthel 1965) is comprised of 10 questions that address 1) eating, 2) transferring from a bed to chair and back, 3) personal hygiene 4) toileting, 5) bathing or showering, 6) walking 50 m on level ground, 7) climbing stairs, 8) dressing, 9) controlling the bowel, and 10) controlling the bladder. Each question is scaled with a maximum score of 5−15 points, and the smallest increment in a score is 5 points.

In this study, the Barthel Index provided the data for ADL disability in the cross-sectional setting (Study I) and for the baseline status of ADL disability and mobility disability in the longitudinal setting (Study II; this is explained in more detail in the next section, *Mobility disability and ADL disability*). In Study I, ADL disability was defined by a Barthel Index score between 0–95. Those who had Barthel Index score 100 were fully independent in ADL.

Mobility disability and ADL disability. A mailed questionnaire was used to follow mobility disability and ADL disability in a disability-free population. The following questions were asked: 1) "Are you able to walk at least 400 meters?", 2) "Are you able to climb stairs?", 3) "Are you able to get in and out of bed?", and 4) "Are you able to dress and undress yourself?". In each of these questions answers "Yes, without difficulty" and "Yes, but it's difficult" were coded as independent, and answers "Only if somebody helps" and "No" were coded as dependent.

Mobility disability was used in a longitudinal setting in Study II and it was defined based on the mailed questionnaire. Specifically, mobility disability was defined as dependent in walking at least 400 meters or climbing stairs (incident mobility disability). Those, who were independent in walking at least 400 meters and climbing stairs, had no incident mobility disability. At baseline identical mobility disability measures were not available. Thus, based on the Barthel Index, at baseline all participants selected for Study II were independent in walking 50 meters on level ground, climbing stairs, dressing, and getting in and out of bed.

In Study II, ADL disability was defined based on the mailed questionnaire. Specifically, ADL disability was defined as dependent in either getting in and out of bed, or in dressing and undressing, and dependent in mobility (walking at least 400 meters or climbing stairs) (incident ADL disability). Those who were independent in getting in and out of bed, in dressing and undressing and in mobility (walking at least 400 meters and climbing stairs) had no incident ADL disability. At baseline, identical ADL disability measures were not available, and based on the Barthel Index, all participants selected for Study II were independent in walking 50 meters on level ground, climbing stairs, dressing, and getting in and out of bed.

Mortality (Studies II–IV)

All-cause mortality was followed up and dates of death were drawn from Statistics Finland (Study II) or from the National Population Register (Studies III–IV). In Studies III–IV, mortality was the main outcome, and four-year mortality risk was used. The follow-up time was calculated from February 21, 2000 to the date of death or to February 21, 2004 for survivors. In Study II, mortality risk was a secondary outcome, and it was followed in conjunction with disability. Follow-up time began on the day of baseline measurements and ended on the date of death. Participants who died during the follow-up without developing disability were categorized as deceased. Mortality was followed up using the same period as disability (maximum follow-up time 7.8 years). However, for the cohort born in 1920, the maximum follow-up time was 3.3 years for mortality and 3.7 years for disability. There were no losses to mortality follow-up.

Covariates

Altogether, separate diseases (Study IV), comorbidity (Studies I–III), physical activity (Studies I and III), physical functioning (Study III), smoking (Studies I, III and IV), alcohol intake (Study III) and living residence (Study I) were used as covariates in the study.

Diseases (Study IV) and comorbidity (Studies I–III)

In the Vitality 90+ Study, data on diseases have been gathered using both medical records data and questionnaires. In the year 2000, medical diagnoses were collected using medical records of the city of Tampere. These records included public health care physicians' reports of each patient visit in the city health centers and city hospitals (Goebeler 2009). The medical records date back to the year 1972 and also include special health care provided by the city hospitals. Altogether, the city hospitals included a general hospital and four geriatric hospitals. Diagnoses were coded according to the International Classification of Diseases, 10th Revision (ICD-10) (Goebeler, Jylhä & Hervonen 2003).

In 2001, 2003 and 2010 self-reported diagnoses from the mailed questionnaires were used. The participants were asked if a doctor had diagnosed them with high blood pressure, heart disease (coronary heart disease, arrhythmia or heart infarction), calcification of arteries, cancer, stroke, dementia (dementia, Alzheimer's disease or cognitive decline), problems with cerebral circulation, diabetes, osteoarthritis, rheumatoid arthritis, Parkinson's disease, hip fracture or depression.

Diseases were used separately only in Study IV, where record-based data on cardiovascular disease, infectious disease, cancer (all cancers except for basal cell carcinoma), respiratory disease, and diabetes were used. In Studies I−III a comorbidity variable was used and the exact diseases included varied in each study (Table 5). In Studies I−II comorbidity was based both on record-based and self-reported diagnoses. In Study I for the cohort measured in the year 2000, diseases in ICD classes A–C (for cancer other than basal cell carcinoma), D50–, E–N (in class H ear and eye diseases were treated as separate classes), and Q–Z (classes S−Y, traumas, were treated as one class) were included (Table 5). Tertiles of the number of these ICD-10 classes with at least one diagnosis were used in the analyses (Table 5). Class D0−49, benign tumors, was excluded because it represents non-cancerous tumors, which do not generally have health effects. Class O, vitamins, minerals and enteral nutrition, was excluded because it did not stand for diseases as such. Class P, pregnancy problems, was excluded because the class was not equal for women and men.

In Study III, only record-based diagnoses were used. In addition, cognitive status, as measured by the Mini-Mental State Examination (MMSE), was included for the comorbidity variable in Study III (score 0−22 indicated lower cognitive status). Comorbidity was divided into three categories (Study III) or four categories (Studies I–II) according to the tertiles of diseases, including a separate class for missing data (Table 5).

Table 5. Diseases and comorbidity as covariates used in the original studies

Variable	Study	Diagnoses / definitions
Diseases separately	IV	Diagnoses from records: cardiovascular disease, infectious disease, cancer, respiratory disease, and diabetes
Comorbidity*	I	For the cohort born in 1909–1910 record-based diagnoses: Tertiles of the number of the following ICD-10-classes with at least one diagnosis: A, bacterial infections; B, viral infections; C, cancer (other than basal cell carcinoma); D50–99, hematological diseases; E, endocrinological diseases; F, psychiatric diseases; G, neurological diseases; H0–59, eye diseases; H60–99, ear diseases; I, cardiovascular diseases; J, respiratory diseases; K, gastrointestinal diseases; L, skin diseases; M, musculoskeletal diseases; N, urinary tract diseases; Q, congenital malformations; R, symptoms (vertigo); S–Y, injuries; W, accidents; Z, other reason for using health care. Comorbidity was classified as low (0–3 diseases), middle (4–5 diseases), and high (≥6 diseases). For the other cohorts tertiles of the number of self-reported diagnoses: high blood pressure, heart disease (coronary heart disease, arrhythmia or myocardial infarction), calcification of arteries, cancer, stroke, dementia (dementia, Alzheimer's disease or cognitive decline), problems with cerebral circulation, diabetes, osteoarthritis, rheumatoid arthritis, Parkinson's disease, hip fracture or depression; low (0–1 diseases), middle (2–3 diseases), and high (≥4 diseases)
	II	Record-based diagnoses for cohort born in 1909–1910 and self-reported diagnoses for other cohorts: heart disease, cancer, dementia, stroke, diabetes, osteoarthritis or arthrosis, Parkinson's disease, hip fracture and depression; low (0 diseases), middle (1 disease), high (≥ 2 diseases)
	III	Diagnoses from records: cardiovascular disease, infectious disease, cancer (other than basal cell carcinoma, respiratory disease, and diabetes, and additionally MMSE score (0–22 vs. 23–30); low (0–2 chronic conditions), high (3–6 chronic conditions)

ICD = International classification for diseases
*Missing data in comorbidity was included as a separate variable

Other covariates (Studies I–IV)

Covariates used in the study were selected because they may confound the association of obesity with physical functioning or mortality. In addition to diseases and comorbidity, physical activity, physical functioning, smoking, alcohol intake, sample year at baseline and living residence were used as covariates in the analyses. Physical activity was based on the question: "How often do you exercise?" The participant chose from the following answers: every day, 3–4 times a week, 1–2 times a week, or not very often. In the analyses, physical activity was classified as (i) high (every day), (ii) middle (at least once a week), or (iii) low (not very often). When physical functioning was used as a covariate (Study III), it was based on Barthel Index (Mahoney & Barthel 1965) and was categorized as (i) score 0–90, or (ii) score 95–100. Smoking was categorized as (i) current or former or (ii) never smoker. Alcohol intake was based on the question "How often do you take alcohol?" and was classified as (i) at least once a week, (ii) occasionally or (iii) not at all. The sample year at baseline was either the year 2000, 2001, 2003 or 2010. In the year 2010, participants chose living residence from options 1) regular apartment, 2) sheltered housing <24h, 3) sheltered housing 24h, 4) retirement home, 5) nursing home or nursing home for dementia, or 6) health center or hospital. Options 1–2 were categorized as home and options 3–6 as institution. In the years 2000, 2001 and 2003 home and institution were the only given options in the interview, and living residence was classified for all as (i) home or (ii) institution.

6.3 Statistical methods

The study examined both cross-sectional and prospective associations between obesity indicators, physical functioning and mortality. All analyses were performed separately for men and women. The number of men in the study was low, but it was considered important to include men in the analyses as a separate group because earlier findings are scarce, and in the majority of the analyses, the results demonstrated different directions between the genders. In studies that included data for different cohorts (Studies I–II), analyses were performed for all cohorts combined. Analyses were carried out with SPSS for Windows (SPSS Inc., Chicago, IL), versions 18.0–20.0.

Study I

In Study I, the association of BMI and WC with physical performance was assessed with multinomial logistic regression models. The reference group was normal weight for BMI and the lowest tertile for WC, and the baseline category for physical performance was those with high performance (above median). The association of BMI and WC with ADL disability was analyzed using logistic regression models. In both multinomial logistic and logistic regression models BMI and WC were analyzed separately and together in the model. In addition, the associations of combined BMI and WC with physical performance, and combined BMI and WC with ADL disability, were examined. All of the models were adjusted for comorbidity, physical activity, smoking, living residence and sample year.

Study II

In Study II, multinomial regression models were used in examining whether BMI and WC were associated with incident mobility disability, or incident ADL disability. Analyses for mobility disability and ADL disability were performed separately, and in both analyses the deceased were treated as an alternative outcome. The reference group was the overweight category for BMI and the middle tertile for WC, and the baseline category for disability was those with no incident disability. The overweight category was used as a reference group instead of the normal weight category to examine possible differences between overweight and obese participants. Follow-up times were calculated separately for mobility disability and ADL disability. Follow-up began on the day of baseline measurement, and ended on the date of the latest questionnaire. All analyses were adjusted for comorbidity and sample year at baseline. Differences in follow-up times were taken into account as an offset option by using the natural logarithm of the follow-up time.

In Study II, death was assessed as an alternative outcome for disability. Follow-up time for all-cause mortality began on the day of baseline measurements and ended on the date of death. Participants who died during the follow-up without developing disability were categorized as deceased. Mortality was followed up using the same time period as disability (maximum follow-up time 7.8 years). However, for the cohort born in 1920, the maximum follow-up time was 3.3 years for mortality and 3.7 years for disability.

Study III

In Study III, Cox proportional hazards models were used to analyze associations of BMI, WC and WHR with all-cause mortality over a four-year follow-up. The associations of BMI, WC and WHR with mortality were analyzed in a univariate model, and in a model in which BMI, WC and WHR were each separately adjusted for comorbidity, physical functioning, smoking and alcohol intake. The overweight category was used as a reference group for BMI. WC and WHR were used as continuous variables with the results representing 1 cm change in WC and 0.1 unit change in WHR. The combined effects of BMI and WC on four-year mortality were also analyzed. Due to the small number of overweight men with low WC (n=3), normal weight together with lower values in WC served as a reference group. In addition, to examine the role of reverse causality, unadjusted mortality analyses concerning BMI, WC and WHR were separately performed for those subjects who were still alive after the first two years of follow-up (n=161 in women and n=41 in men).

Study IV

In Study IV, associations between BMI, WC and WHR, and inflammatory markers (IL-1RA, IL-6, CRP and TNF-α) were analyzed with linear regression models. Unadjusted and adjusted models were performed to analyze the association of each anthropometric measure with each inflammatory marker. Models were adjusted for diseases (cardiovascular disease, cancer, diabetes, respiratory disease and infectious disease), physical functioning and smoking. Cox proportional hazards models were used to analyze the combined associations of BMI and WC and inflammatory status with all-cause mortality over four years. Unadjusted and adjusted models were used, and adjustments were made for cardiovascular disease, infectious disease, cancer, respiratory disease, diabetes, functional status and smoking.

7 Results

7.1 Characteristics of the study population (Studies I–IV)

The study populations varied between the sub-studies. The proportion of obese participants ranged from 7% to 14% in women, and from 5% to 10% in men. With a cutoff point of 18.5 kg/m², 2% of women and 0% of men were underweight. With a cutoff point of 20.0 kg/m², 7% of women and 6–7% of men were underweight. Mean WC varied between 86 cm and 88 cm in women and between 94 cm and 96 cm in men. Altogether 10–18% of women and 2–11% of men lived in an institution.

7.2 Associations of BMI and WC with physical functioning (Studies I–II)

Cross-sectional associations

Table 6 presents cross-sectional associations of BMI and WC with physical performance. Women in the highest WC tertile had lower physical performance (odds ratio [OR] 3.02, 95% confidence interval [CI] 1.59–5.76) and were more likely to be unable to perform the chair stand (OR 2.09, 95% CI 1.04–4.19) than women in the lowest WC tertile when compared to high performance. BMI was not associated with physical performance in women or men. When BMI and WC were included in the same model, high WC in women remained significantly associated with an inability to perform chair stand, whereas, overweight (OR 0.35, 95% CI 0.16–0.73) and obese (OR 0.27, 95% CI 0.09–0.85) women were more often able to perform the chair stand than normal weight women, when compared to high performance. In men, no statistically significant results were found (Table 6).

Table 6. Cross-sectional associations between BMI and WC and physical performance in women and men aged 90 years: multinomial logistic regression analysis

Model 1: BMI & WC Separately*	**High Performance**	**Low Performance**	**Unable**
		OR (95% CI)	
Women (n = 405)			
BMI			
Underweight vs. normal weight	1.0	0.52 (0.16–1.66)	1.59 (0.57–4.44)
Overweight vs. normal weight	1.0	0.94 (0.54–1.62)	0.64 (0.34–1.20)
Obese vs. normal weight	1.0	1.77 (0.80–3.88)	1.14 (0.47–2.77)
WC tertiles			
II vs. I	1.0	1.41 (0.78–2.57)	0.73 (0.37–1.42)
III vs. I	1.0	**3.02 (1.59–5.76)**	**2.09 (1.04–4.19)**
Men (n = 150)			
BMI			
Underweight vs. normal weight	1.0	0.34 (0.06–2.05)	1.33 (0.17–10.4)
Overweight vs. normal weight	1.0	0.80 (0.33–1.92)	0.53 (0.15–1.91)
Obese vs. normal weight	1.0	1.02 (0.27–3.90)	0.26 (0.02–3.89)
WC tertiles			
II vs. I	1.0	1.34 (0.52–3.46)	1.32 (0.37–4.75)
III vs. I	1.0	1.03 (0.39–2.72)	0.40 (0.09–1.73)
Model 2: BMI & WC Together*	**High Performance**	**Low Performance**	**Unable**
		OR (95% CI)	
Women (n = 405)			
BMI			
Underweight vs. normal weight	1.0	0.68 (0.21–2.24)	2.04 (0.70–5.94)
Overweight vs. normal weight	1.0	0.62 (0.33–1.15)	**0.35 (0.16–0.73)**
Obese vs. normal weight	1.0	0.64 (0.23–1.78)	**0.27 (0.09–0.85)**
WC tertiles			
II vs. I	1.0	1.59 (0.83–3.04)	1.16 (0.55–2.46)
III vs. I	1.0	**3.97 (1.69–9.32)**	**5.79 (2.21–15.2)**
Men (n = 150)			
BMI			
Underweight vs. normal weight	1.0	0.34 (0.06–2.07)	1.34 (0.17–10.6)
Overweight vs. normal weight	1.0	0.80 (0.27–2.37)	0.65 (0.15–2.86)
Obese vs. normal weight	1.0	1.21 (0.21–6.85)	0.52 (0.02–12.8)
WC tertiles			
II vs. I	1.0	1.38 (0.50–3.80)	1.60 (0.41–6.20)
III vs. I	1.0	0.98 (0.25–3.77)	0.61 (0.09–4.14)

Notes: BMI = body mass index; WC = waist circumference; OR = odds ratio; CI = confidence interval
BMI categories: underweight, <20.0 kg/m^2; normal weight, 20.0–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; obese, ≥30.0 kg/m^2.
WC tertiles for women <83 cm, 83–91 cm, and ≥92 cm, and for men <92 cm, 92–99 cm, and ≥100 cm.
*Models adjusted for comorbidity, physical activity, smoking, sample year and living residence.
Statistically significant associations are bolded.

Women in the highest WC tertile were more likely to have ADL disability (OR 2.98, 95% CI 1.67–5.31) when compared to the lowest WC tertile (Table 7). Additionally, overweight (OR 2.03, 95% CI 1.21–3.40) and obese (OR 2.50, 95% CI 1.21–5.19) women were more likely to have ADL disability, when compared to normal weight. When both BMI and WC were included in the same model, only the highest WC tertile was associated with ADL disability (OR 3.17, 95% CI 1.51–6.68). In men, no statistically significant results were found (Table 7).

Table 7. Cross-sectional associations between BMI and WC and ADL disability in women and men aged 90 years: Logistic regression analysis

		ADL Disability	
		Model 1* BMI & WC Separately	**Model 2* BMI & WC Together**
	n	**OR (95% CI)**	**OR (95% CI)**
Women	416		
BMI			
Underweight	30	2.12 (0.80–5.59)	2.67 (0.97–7.33)
Normal weight	185	1.0	1.0
Overweight	141	**2.03 (1.21–3.40)**	1.46 (0.82–2.58)
Obese	60	**2.50 (1.21–5.19)**	1.07 (0.44–2.61)
WC tertiles			
I (<83 cm)	127	1.0	1.0
II (83–91 cm)	144	1.21 (0.70–2.11)	1.28 (0.69–2.34)
III (≥92 cm)	145	**2.98 (1.67–5.31)**	**3.17 (1.51–6.68)**
Men	153		
BMI			
Underweight	10	2.98 (0.64–13.8)	3.31 (0.70–15.7)
Normal weight	77	1.0	1.0
Overweight	51	0.64 (0.27–1.49)	0.45 (0.16–1.27)
Obese	15	1.10 (0.31–3.89)	0.67 (0.14–3.29)
WC tertiles			
I (<92 cm)	48	1.0	1.0
II (92–99 cm)	40	1.11 (0.45–2.73)	1.55 (0.58–4.10)
III (≥100 cm)	65	1.11 (0.45–2.78)	2.13 (0.61–7.49)

Notes: BMI = body mass index; WC = waist circumference; ADL = activities of daily living; OR = odds ratio; CI = confidence interval. BMI categories: underweight, <20.0 kg/m^2; normal weight, 20.0–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; obese, ≥30.0 kg/m^2

*Models adjusted for comorbidity, physical activity, smoking, sample year and living residence.

Statistically significant associations are bolded.

Longitudinal associations

Altogether 47% (n=136) of women and 28% (n=37) of men developed mobility disability during the follow-up. In women, 15% (n=44) had incident ADL disability as compared to 8% (n=10) in men. BMI or WC was not associated with incident mobility disability in either women or men (Table 8). In women, the lowest WC tertile was associated with an increased probability of developing ADL disability when compared to the middle WC tertile (OR 3.98, 95% CI 1.35–11.77) (Table 9).

Table 8. Associations of BMI and WC with incident mobility disability in a maximum follow-up of 7.8 years in women and men aged 90 years: Multinomial logistic regression analysis

Mobility Disability*	**No Incident Disability**	**Incident Disability**	**Deceased**
		OR (95% CI)	
Women (n = 291)			
BMI			
Underweight vs. overweight	1.0	0.50 (0.13–1.92)	0.57 (0.11–3.06)
Normal weight vs. overweight	1.0	1.24 (0.57–2.72)	1.11 (0.38–3.25)
Obese vs. overweight	1.0	1.64 (0.57–4.76)	0.47 (0.12–1.83)
WC tertiles			
I vs. II	1.0	1.66 (0.66–4.15)	2.79 (0.88–8.82)
III vs. II	1.0	1.19 (0.54–2.62)	0.96 (0.34–2.73)
Men (n = 134)			
BMI			
Underweight vs. overweight	1.0	NA	NA
Normal weight vs. overweight	1.0	0.81 (0.16–4.17)	1.31 (0.25–6.93)
Obese vs. overweight	1.0	1.45 (0.14–14.57)	0.92 (0.05–16.30)
WC tertiles			
I vs. II	1.0	0.56 (0.08–4.03)	0.50 (0.08–3.17)
III vs. II	1.0	1.21 (0.21–6.94)	0.42 (0.07–2.53)

Notes: BMI = body mass index; WC = waist circumference; OR = odds ratio; CI = confidence interval; NA = not applicable; not enough participants for the analyses

BMI categories: underweight, <20.0 kg/m^2; normal weight, 20.0–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; obese, ≥30.0 kg/m^2

WC tertiles for women <82 cm, 82–89 cm, and ≥90 cm, and for men <91 cm, 91–99 cm, and ≥100 cm.

* Adjusted for comorbidity and sample year at baseline. Differences in follow-up times were taken into account by using a natural logarithm of follow-up time.

Table 9. Associations of BMI and WC with incident ADL disability in a maximum follow-up of 7.8 years in women and men aged 90 years : Multinomial logistic regression analysis

ADL Disability*	No Incident Disability	Incident Disability	Deceased
		OR (95% CI)	
Women (n = 290)			
BMI			
Underweight vs. overweight	1.0	2.51 (0.45–13.84)	2.18 (0.65–7.37)
Normal weight vs. overweight	1.0	1.72 (0.70–4.23)	**2.15 (1.13–4.11)**
Obese vs. overweight	1.0	0.79 (0.18–3.47)	0.73 (0.29–1.87)
WC tertiles			
I vs. II	1.0	**3.98 (1.35–11.77)**	1.58 (0.75–3.30)
III vs. II	1.0	1.68 (0.60–4.76)	0.52 (0.27–1.02)
Men (n = 134)			
BMI			
Underweight vs. overweight	1.0	NA	NA
Normal weight vs. overweight	1.0	0.10 (0.004–2.47)	0.95 (0.28–3.25)
Obese vs. overweight	1.0	NA	0.31 (0.05–1.85)
WC tertiles			
I vs. II	1.0	0.54 (0.04–7.59)	0.73 (0.21–2.54)
III vs. II	1.0	0.61 (0.05–6.87)	0.49 (0.14–1.65)

Notes: BMI = body mass index; WC = waist circumference; ADL = activities of daily living; OR = odds ratio; CI = confidence interval; NA = not applicable; not enough participants for the analyses
BMI categories: underweight, <20.0 kg/m^2; normal weight, 20.0–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; obese, ≥30.0 kg/m^2
WC tertiles for women <82 cm, 82–89 cm, and ≥90 cm, and for men <91 cm, 91–99 cm, and ≥100 cm.
* Adjusted for comorbidity and sample year at baseline. Differences in follow-up times were taken into account by using a natural logarithm of the follow-up time. Statistically significant associations are bolded.

In the analyses in which death was assessed as an alternative outcome for incident mobility disability, neither BMI nor WC was associated with mortality (Table 9). However, when death was assessed as an alternative outcome for incident ADL disability, normal weight in women increased the odds of death as compared to overweight (OR 2.15, 95% CI 1.13–4.11). The results on WC and mortality in women were borderline significant in the ADL disability analyses, as the OR for the highest WC tertile was 0.52 (95% CI 0.27–1.02) when compared to the middle tertile.

7.3 BMI, WC and WHR as predictors of mortality (Study III)

No significant associations were found between BMI and mortality in women. In men, normal weight was associated with a higher mortality risk when compared to overweight after adjusting for covariates (HR 3.09, 95% CI 1.35–7.06; Table 10). Low or high WC was not associated with mortality risk in women but higher WC was associated with lower mortality in men after adjustment for covariates (HR 0.96, 95% CI 0.93–1.00). In women, higher WHR was associated with higher mortality in the unadjusted model (HR 1.43, 95% CI 1.06–1.92) but not in the adjusted model. In men, WHR was not associated with mortality (Table 10).

Table 10. Associations of BMI, WC and WHR with four-year mortality in 90-year-old women and men: Cox proportional hazards models

Mortality risk		Unadjusted	Adjusted*
	n	HR (95% CI)	
Women	192		
BMI			
Underweight	3	NA	NA
Normal weight	113	1.42 (0.88–2.30)	1.29 (0.79–2.08)
Overweight	62	1.00	1.00
Obese	14	1.59 (0.69–3.69)	1.07 (0.45–2.52)
WC	192	1.01 (0.99–1.03)	1.00 (0.98–1.02)
WHR	192	**1.43 (1.06–1.92)**	1.30 (0.94–1.80)
Men	65		
BMI			
Underweight	0	NA	NA
Normal weight	42	1.92 (0.94–3.91)	**3.09 (1.35–7.06)**
Overweight	20	1.00	1.00
Obese	3	NA	NA
WC	65	0.97 (0.94–1.00)	**0.96 (0.93–1.00)**
WHR	65	0.81 (0.50–1.31)	0.75 (0.45–1.24)

Notes: BMI = body mass index; WC = waist circumference; WHR = waist-to-hip ratio; HR = hazard ratio; CI = confidence interval; NA = not applicable

BMI classifications: underweight, <18.5 kg/m^2; normal weight, 18.5–24.9 kg/m^2; overweight, 25.0–29.9 kg/m^2; obese, ≥30.0 kg/m^2. WC and WHR were continuous variables, hazard ratios were computed for each 1 cm change in WC and for each 0.1 unit change in WHR.

*BMI, WC and WHR were each separately adjusted for comorbidity, physical functioning, smoking and alcohol intake. Statistically significant associations are bolded.

Reverse causality was accounted for by excluding persons who died during the first two years of the follow-up. The directions of the associations were otherwise the same but the (nonsignificant) coefficients for WC and WHR in men suggested different directions in associations as compared to the main analyses

7.4 Combined associations of BMI and WC with physical functioning and mortality (Studies I, III)

Low or high BMI was combined with low or high WC, and the associations with physical functioning and mortality were examined in separate analyses. Women with high BMI and low WC tended to have better physical performance, as they were less likely to have low physical performance in the five-times sit-to-stand test (marginally significant; OR 0.49, 95% CI 0.22–1.08) and less likely to be unable to complete the test (marginally significant; OR 0.39, 95% CI 0.15–1.07) than women with low BMI and low WC (Table 11). Men with high BMI and low WC were less likely to have ADL disability (OR 0.14, 95% CI 0.02–0.93) than men with low BMI and low WC (Table 12).

Table 11. Cross-sectional associations between combined BMI and WC with physical performance in women and men aged 90 years: Multinomial logistic regression analysis

Physical Performance	n	High Performance	Low Performance	Unable
			OR (95% CI)	
Women	405			
Low BMI & low WC†	157			
Low BMI & high WC	54	1.0	2.16 (0.88–5.32)	**4.40 (1.77–11.0)**
High BMI & low WC	48	1.0	0.49 (0.22–1.08)	0.39 (0.15–1.07)
High BMI & high WC	146	1.0	**2.09 (1.17–3.74)**	1.45 (0.75–2.80)
Men	150			
Low BMI & low WC†	62			
Low BMI & high WC	24	1.0	1.98 (0.64–6.10)	1.24 (0.25–6.23)
High BMI & low WC	12	1.0	1.20 (0.26–5.65)	0.77 (0.10–5.87)
High BMI & high WC	52	1.0	1.13 (0.46–2.79)	0.43 (0.11–1.73)

Notes: BMI = body mass index; WC = waist circumference; OR = odds ratio; CI = confidence interval
Low BMI <25 kg/m²; High BMI ≥25 kg/m²; Low WC <87 cm in women and <96 cm in men; High WC ≥87 cm in women and ≥96 cm in men
*Models adjusted for comorbidity, physical activity, smoking, sample year and living residence. Statistically significant associations are bolded.
†Reference group

Table 12. Cross-sectional associations between combined BMI and WC with ADL disability in women and men aged 90 years: Logistic regression analysis

ADL Disability	n	OR (95% CI)
Women	416	
Low BMI & low WC	160	1.0
Low BMI & high WC	55	**3.18 (1.50–6.71)**
High BMI & low WC	48	1.47 (0.70–3.10)
High BMI & high WC	153	**3.21 (1.86–5.53)**
Men	153	
Low BMI & low WC	62	1.0
Low BMI & high WC	25	0.71 (0.25–2.06)
High BMI & low WC	12	**0.14 (0.02–0.93)**
High BMI & high WC	54	0.77 (0.33–1.80)

Notes: BMI = body mass index; WC = waist circumference; OR = odds ratio; CI = confidence interval
Low BMI <25 kg/m^2; High BMI ≥25 kg/m^2; Low WC <87 cm in women and <96 cm in men; High WC ≥87 cm in women and ≥96 cm in men
*Models adjusted for comorbidity, physical activity, smoking, sample year and living residence.
Statistically significant associations are bolded.

Women with high BMI and low WC had significantly lower mortality risk when compared to women with low BMI and low WC (HR 0.34, 95% CI 0.12–0.97) (Table 12). In men, no statistically significant associations were found.

Table 13. Combined effects of BMI and WC on four-year mortality in 90-year-old women and men: Cox proportional hazards model

Combination of BMI and WC	n	Deceased (%)	HR (95% CI)
Women			
Low BMI and low WC	72	48.6	1.00
Low BMI and high WC	41	53.7	1.17 (0.69–1.99)
High BMI and low WC	20	20.0	**0.34 (0.12–0.97)**
High BMI and high WC	42	47.6	0.97 (0.56–1.68)
Men			
Low BMI and low WC	29	82.8	1.00
Low BMI and high WC	13	61.5	0.58 (0.26–1.30)
High BMI and low WC	3	0.0	NA
High BMI and high WC	17	58.8	0.57 (0.27–1.19)

Notes: BMI = body mass index; WC = waist circumference; HR = hazard ratio; CI = confidence interval; NA = not applicable
Low BMI: 18.5–24.9 kg/m^2; High BMI: 25.0–29.9 kg/m^2; Low WC: <86 cm in women and <94 cm in men; High WC: ≥86 cm in women and ≥94 cm in men
Statistically significant associations are bolded.

7.5 BMI, WC and WHR: Associations with inflammation and mortality (Study IV)

Higher BMI was associated with higher levels of IL-1RA and CRP in women ($p < 0.05$), and lower levels of CRP (borderline significant; $p=0.06$) in men. Higher WC was associated with higher levels of IL-1RA and CRP in women ($p < 0.05$), whereas no significant associations were found in men. WHR was not associated with any inflammatory marker in any analyses.

When BMI and WC were combined with the level of inflammatory status, no significant results were found for BMI in women (Table 14). In men, both high BMI and low inflammation (HR 0.13, 95% CI 0.03–0.59) and high BMI and high inflammation (HR 0.25, 95% CI 0.09–0.76) were associated with a lower mortality risk when compared to men with low BMI and low inflammation. Regarding WC, in women mortality risk was significantly higher in all the other groups when compared to low WC and low inflammation. The highest mortality risk in women was observed with high WC and low inflammation (HR 7.23, 95 % CI 2.70–19.39). On the contrary, in men mortality risk was significantly lower with high WC and low inflammation (HR 0.13, 95% CI 0.03–0.59) and with high WC and high inflammation (HR 0.25, 95% CI 0.09–0.76) compared to low WC and low inflammation.

Table 14. BMI and WC combined with inflammatory status: Associations on four-year mortality in 90-year-old women and men

Women (n = 157)	**N**	**Deceased n (%)**	**Mortality risk HR (95% CI)***
BMI and inflammatory status			
Low BMI and low inflammation	47	16 (34.0)	1.00
Low BMI and high inflammation	48	33 (68.8)	1.77 (0.93–3.38)
High BMI and low inflammation	16	7 (43.8)	1.81 (0.72–4.57)
High BMI and high inflammation	46	20 (43.5)	1.14 (0.58–2.24)
WC and inflammatory status			
Low WC and low inflammation	35	6 (17.1)	1.00
Low WC and high inflammation	38	25 (65.8)	**5.63 (2.18–14.55)**
High WC and low inflammation	28	17 (60.7)	**7.23 (2.70–19.39)**
High WC and high inflammation	56	28 (50.0)	**2.73 (1.10–6.76)**
Men (n = 53)	**N**	**Deceased n (%)**	**Mortality risk HR (95% CI)***
BMI and inflammatory status			
Low BMI and low inflammation	13	11 (84.6)	1.00
Low BMI and high inflammation	21	17 (81.0)	0.59 (0.22–1.54)
High BMI and low inflammation	6	2 (33.3)	**0.07 (0.01–0.51)**
High BMI and high inflammation	13	8 (61.5)	**0.31 (0.10–0.94)**
WC and inflammatory status			
Low WC and low inflammation	10	9 (90.0)	1.00
Low WC and high inflammation	14	11 (78.6)	0.62 (0.19–1.95)
High WC and low inflammation	9	4 (44.4)	**0.13 (0.03–0.59)**
High WC and high inflammation	20	14 (70.0)	**0.25 (0.09–0.76)**

Notes: BMI = body mass index; WC = waist circumference; HR = hazard ratio; CI = confidence interval
Inflammatory status: C-reactive protein, interleukin-6, interleukin-1 receptor antagonist and tumor necrosis factor-α : Low inflammation : 0–1 inflammatory markers above the sex-specific median; High inflammation: 2–4 inflammatory markers above the sex-specific median
Low BMI: <25 kg/m^2.; High BMI: ≥25 kg/m^2; Low WC: <85 cm in women and <93 cm in men; High WC: ≥85 cm in women and ≥93 cm in men
*Cox proportional hazards models. Each univariate model adjusted for comorbidity, physical functioning and smoking. Statistically significant associations are bolded.

8 Discussion

8.1 Interpretation of the main findings

This study is among the first to explore the associations of obesity indicators with physical functioning and mortality among oldest old people. In women, low WC proved to be beneficial in terms of physical functioning when studied cross-sectionally and in terms of mortality when combined with overweight BMI or with low inflammatory status. However, in a longitudinal setting, women with low WC were more likely to develop ADL disability than women with moderate WC. In men, low WC combined with high BMI was beneficial in terms of physical functioning, but low WC and low BMI increased mortality risk regardless of inflammatory status. From the perspective of obesity, abdominal obesity in women was associated with poor physical functioning but general or abdominal obesity was not associated with an increased mortality risk in women or men.

BMI and WC in relation to physical functioning

Previous studies have demonstrated associations of both general and abdominal obesity with limited physical functioning among oldest old women (Reynolds & McIlvane 2009, Dong et al. 2012, Yang et al. 2014, Hajek et al. 2015). However, non-associations have also been reported (Kaiser et al. 2010, Yin et al. 2014). In nursing home populations or in persons receiving help aged ≥80 years, low BMI appears to be specifically associated with low physical functioning (Kaiser et al. 2010, Kiesswetter et al. 2015). Cross-sectional analyses in this study demonstrate that in women, high WC was associated with lower physical functioning based on both physical performance and ADL disability. However, the results for BMI differed depending on whether WC was accounted for in the analyses. Overweight and obese women were more likely to have lower physical functioning, but when WC was accounted for in the analysis, overweight and obese women had even better physical performance than normal weight women. The finding suggests that WC may be a more relevant measure for obesity than BMI in this age group. This view is supported by earlier findings in persons aged 55–74 years, which demonstrate that high WC is more closely associated with disability outcomes than high BMI (Angleman, Harris & Melzer 2006).

None of the results for men on the associations of BMI or WC alone with physical functioning were statistically significant. This may be due at least in part to a small sample size, as in a study by Yin et al. (2014), both high BMI and high WC were associated with ADL disability among oldest old men. However, the results of the present study are consistent with earlier findings showing that the associations between body fatness and physical functioning are more evident in women than in men (Friedmann, Elasy & Jensen 2001, Stenholm et al. 2007b, Jensen & Hsiao 2010).

This study is the first to examine the associations of BMI and WC with incident disability in the oldest old. In the longitudinal setting, abdominal obesity or general obesity did not predict incidence of mobility or ADL disability in women or in men. Instead, low WC in women predicted incident ADL disability. The discrepancy in the results based on cross-sectional and longitudinal associations may be partly explained by changing health status, which is common with advancing age and has an influence on weight and functioning. Changes in health status may be rapid, and it is not known if changes in weight have occurred. Overall, the results of this study suggest that at the age of 90 years, general or abdominal obesity no longer predisposes individuals to the development of physical disability.

Obesity prevalence in the present study population was low ranging from 5% to 14%. In Finland, obesity prevalence in the oldest old has ranged from 9% to 26% during the years 2000 and 2011 (Aromaa et al. 2004, Lundqvist et al. 2012), and in this study it is difficult to estimate whether the obesity prevalence identified is representative of the entire 90-year-old population in Finland. On one hand, obesity prevalence in this study might be underestimated, as high WC was associated with poor physical functioning in women, and low physical functioning was most likely more common among those persons who did not participate in the study when compared to those who did. On the other hand, it may be that in persons needing a lot of help and nursing home residents in general, low weight particularly is associated with poor physical functioning (Kaiser et al. 2010, Bahat et al. 2012, Kiesswetter et al. 2015), and quality of life is higher with higher weight (Beck & Damkjaer 2008). In fact, Kiesswetter and colleagues (2015) have shown that the association of BMI with physical functioning is dependent on both health and care status. Furthermore, among persons receiving care, it was found that the association between low BMI and low ADL score was lost after adjusting for cognitive status (Kiesswetter et al. 2015). It may well be that biological age matters more than chronological age in the dynamics between body weight and physical functioning

(Alley et al. 2008). It can be hypothesized that high body weight is associated with low physical functioning until severe chronic conditions, weight loss and closeness of death, after which low weight is more closely associated with low physical functioning than high weight (Kiesswetter et al. 2015). Further research addressing this hypothesis is warranted.

BMI and WC in relation to mortality

This study demonstrated that general obesity is not associated with increased mortality risk in the oldest old. The result confirms earlier findings which indicate that high BMI does not increase mortality risk among the oldest old (Mattila, Haavisto & Rajala 1986, Rajala et al. 1990, Nybo et al. 2003). Regarding abdominal obesity, the study provided novel results demonstrating that high WC does not increase mortality risk either in the oldest old. On the other hand, the results lend further credence regarding the adverse effects of low weight in the oldest old (Mattila, Haavisto & Rajala 1986, Rajala et al. 1990, Nybo et al. 2003, van Vliet et al. 2010). Especially in men, low BMI and low WC independently increased mortality risk. In women, low or high BMI or WC was not associated with mortality risk in the main analyses. However, when death was assessed as an alternative for ADL disability, well-functioning women who were normal weight were more likely to die than overweight women.

The underlying factors of why low WC or low BMI predicted both an increased mortality risk and limitations in physical functioning are the same. Low WC and low BMI may reflect malnutrition, which relates to diseases, such as cancer, as well as to disability and death (Van Cutsem & Arends 2005, Ferrer et al. 2008, Morley 1997, Hiesmayr et al. 2009, Ahmed & Haboubi 2010). Malnutrition can be both the cause and the consequence of diseases (Alberda, Graf & McCargar 2006, Saunders & Smith 2010). Nutritional needs are dramatically increased during illness, which often leads to malnutrition (Alberda, Graf & McCargar 2006). However, malnutrition also affects the functioning and recovery of the organ systems, which in turn may lead to illness (Alberda, Graf & McCargar 2006, Saunders & Smith 2010). It is noteworthy that a person with a high weight may also suffer from malnutrition. Nowadays, the term protein-energy malnutrition is often used to describe individuals with protein and/or energy malnutrition (Alberda, Graf & McCargar 2006, Batool et al. 2015). In particular, individuals with protein malnutrition may have a relatively high weight.

Weight loss is an especially strong indicator of deteriorating health and increased mortality risk (Dey et al. 2001, Alibhai, Greenwood & Payette 2005). Weight loss in prolonged malnutrition is due to the loss of both fat and muscle mass (Saunders & Smith 2010). Accounting for weight loss also appears to be a central factor that contributes to whether or not obesity is associated with increased mortality risk in older adults. In a recent study by Bowman and colleagues (2016), when older adults without conditions associated with weight loss were examined, obesity was associated with a shorter survival rate when compared to a BMI of 23.0–26.9 kg/m^2. However, in the oldest old, the effect was not significant (Bowman et al. 2016).

Among a wide array of conventional risk factors and genetic factors identified in the Vitality 90+ Study, Jylhävä and colleagues (2014) investigated which factors best predicted mortality in the oldest old. Inflammatory signaling was one of the genetic factors that arose from the data but among the conventional risk factors low BMI and frailty suited the models the best (Jylhävä et al. 2014). This puts the results on BMI and mortality into a perspective and highlights the importance of low BMI as a predictor of mortality in the oldest old.

BMI and WC combined: Associations with physical functioning and mortality

In the analyses for both mortality and physical functioning, low or high WC was combined with low or high BMI. Previous studies have shown that in older adults higher BMI indicates lower mortality risk when the risk for WC has been accounted for and higher WC indicates higher mortality risk when the risk for BMI has been accounted for (Janssen, Katzmarzyk & Ross 2005). In this study low WC combined with high BMI was associated with beneficial effects both in women and in men in terms of both mortality and physical functioning. However, in the analyses of physical functioning, only the result demonstrating that men with low WC and high BMI had less ADL disability was statistically significant. Additionally, the protective effect of low WC and high BMI against poor physical performance in women was borderline significant. As for mortality, the number of men with low WC and high BMI was very low.

It has been proposed that when BMI and WC are analyzed simultaneously, BMI reflects greater muscle mass and WC greater fat mass (Janssen, Katzmarzyk & Ross 2005). Muscle mass correlates strongly with muscle strength (Landers et al. 2001), which is closely associated with better physical functioning (Schaap, Koster & Visser 2013). Large muscle mass is also beneficial in terms of metabolic health, as it is associated with better insulin sensitivity and lower risk of type II diabetes (Srikanthan, Hevener & Karlamangla 2010, Srikanthan & Karlamangla 2011). During illness, greater muscle mass provides more amino acids for the immune system and for energy purposes when compared with smaller muscle mass (Attaix et al. 2005, Bonaldo & Sandri 2013). Thus, it appears that when both BMI and WC are included in the analyses, the beneficial effects associated with high muscle mass, as indicated by high BMI, and the adverse effects associated with high body fatness, as indicated by high WC, are highlighted.

BMI and WC: Associations with inflammatory status and mortality

Previous studies have shown that BMI and WC are associated with inflammatory markers in younger and older adults (Meier et al. 2002, Park, Park & Yu 2005, Tsai & Tsai 2008, Assoumou et al. 2011). Study IV also demonstrated that in the oldest old, some inflammatory markers are associated with BMI or WC but the results are different between women and men. The positive association of BMI and WC with IL-1RA was the most consistent finding. Jylhä and colleagues (Jylhä et al. 2007) previously demonstrated in the Vitality 90+ Study that IL-1RA has a strong positive association with mortality risk. The finding appears to be independent from BMI and WC, as it was not reflected in the findings related to mortality in Study III. Beddhu and colleagues (2007) have also shown in dialysis patients that BMI and inflammatory status are independently associated with mortality. However, in Study IV, which combined low or high BMI and WC with low or high inflammatory status, concomitant adverse effects of high IL-1RA and high WC were partly reflected. In women, who had low WC and low inflammatory status, mortality risk was particularly low, and all of the other combinations of WC and inflammatory status were associated with increased mortality risk.

In men, the association between high CRP and low BMI was borderline significant. The result may partly explain the association between low BMI and high mortality risk found in Study III. The finding suggests that high CRP among the oldest old men is more closely associated with low BMI and malnutrition (Kalantar-Zadeh et al. 2003, Kalantar-Zadeh 2005) than with high BMI. As opposed to the findings in women, in men low BMI and low WC were associated with increased mortality risk regardless of inflammation. However, the number of men in the analyses was very low. It may well be that with a larger sample size, the adverse effects associated with high inflammatory status would have been evident, as previously found among younger older adults (Harris et al. 1999). Yet it has been suggested that in certain conditions, a pro-inflammatory response may also be beneficial (Lecour & James 2011). Experimental findings in heart failure patients and also in the oldest old have shown that the capacity to generate a pro-inflammatory immune response may be protective and may also predict survival (Lecour & James 2011, Wijsman et al. 2011).

Low BMI and low WC were more strongly associated with mortality in men than in women. This may partly be explained by differences in disease status. CRP was positively associated with BMI in women but was negatively associated with BMI in men, although the result for men was borderline significant. An elevation in CRP is associated with diseases and mortality (Kushner, Rzewnicki & Samols 2006), and based on the level of CRP, it appears that men with low BMI had a higher disease burden than women in this study. Naturally, women with low WC and low inflammatory status reduced the adverse effects associated with low WC alone. Differences in body composition may also partly explain differences in mortality related to gender. Women have more adipose tissue than men (Gallagher et al. 1996) and thus have more energy reserves when needed. Based on another study derived from the Vitality 90+ Study and using the same sample as Studies III and IV, women had higher levels of leptin, a surrogate marker for adipose tissue, than men, but no gender differences for BMI were found (Lisko et al. 2013). These findings suggest that in the oldest old of this study, women also have more adipose tissue than men.

The present study adds to the conversation regarding the obesity paradox (Oreopoulos et al. 2009). However, it is questionable as to whether obesity paradox is the right term to use in the oldest old because of the highly selected population and the obvious associations between diseases and low weight. Overall, in men the results provide further support for the benefits that are derived from high weight, as low BMI and low WC were associated with increased mortality risk regardless of inflammation. Conversely, the results on women related to inflammation did not support the protective role of obesity and offered a sound public health message: relatively healthy oldest old women with low WC have the lowest mortality risk.

8.2 Methodological considerations

Study sample and design

The study was based on the Vitality 90+ Study, which gave the opportunity to study the rather unexplored field of obesity in the oldest old. The strengths of the study include the following: 1) the high age of the participants, 2) both community-dwelling and institutionalized participants were included, 3) measured height, weight, WC and physical performance, 4) follow-up data on physical functioning, 5) follow-up data on mortality, and 6) blood samples from a sub-sample.

The basic population of the Vitality 90+ Study is likely to represent nonagenarians well throughout Finland. During the study period, the proportion of people aged 90 years and older in Tampere was the same as that throughout Finland, beginning at 0.4% in 2000 and reaching 0.8% in 2014 (Statistics Finland, 2015b). However, non-response bias needs to be addressed herein (Kelfve, Thorslund & Lennartson 2013). The participation rate for the health examinations of the Vitality 90+ Study was 57% across the cohorts but there was a large variability between cohorts. In 2000, 78% of the eligible population (basic population after excluding the deceased) participated in the health examination, but in 2001 only 41% were included. Among cohorts measured in 2001, 2003 and 2010 altogether 22% of the eligible population was not reached, whereas for the cohort measured in 2000 only 2% of the eligible population was not reached. It is difficult to estimate if the unreached persons differed from those, who were reached, since studies examining possible differences between the study sample in the Vitality 90+ Study and the basic population have not been conducted. With all cohorts combined, 27% of the eligible population refused the health examination. The main reason for refusing was poor physical or mental condition. In addition, on average 14% of the participants in the health examinations across the sub-studies had missing data in anthropometrics. After excluding persons with missing data in anthropometrics, 44–45% of the eligible population was included in the analyses in Study I, 27% in Study II, 61% in Study III and 50% in Study IV, respectively. Low participation rates in Studies I and IV limit the generalizability of the findings, because participants included in the sub-studies are likely to represent a healthier part of the population. On the other hand, the low percentage (27%) in Study II is explained by the study design since, only disability-free participants were included.

Another limitation is that the analyses were not stratified according to the place of residence; the low number of institutionalized persons did not allow separate analyses for them. Yet place of residence or physical functioning was adjusted in the majority of the analyses. On the other hand, among the oldest old, it is very difficult to reach a representative sample. Given the very high age of the participants in the study, a satisfactory or, in the case of Study III (61%), a relatively high proportion of the eligible population was included in the analyses.

Obesity indicators

Objectively measured height and weight, and thus BMI, are strengths of the study. However, BMI does not discriminate between fat mass and muscle mass and is often questioned for its validity to measure obesity. BMI is also problematic at lower values, because especially in older adults, persons with normal weight BMI are a mixture of those who are physically fit, those who have lost weight because of diseases and those who smoke (Han, Tajar & Lean 2011). It may be viewed that with all of the methodology that the modern technology may provide, BMI is too simple a method on which to exclusively focus. Additionally, the importance of muscle strength in relation to physical functioning (Barbat-Artigas et al. 2013) cannot be overemphasized. On the other hand, the whole point of this study was to explore whether or not BMI itself serves as an indicator of physical functioning or mortality in the oldest old population. Thus, even though it is a limitation of the study that more specific data on body composition were not available or that muscle strength was not included, BMI as such offers valuable new information.

For the cohort measured in 2010 a question on recent weight loss was included in the health examination. However, for the other cohorts, no data on weight loss were gathered, which is a limitation of this study. Data on recent weight loss for the entire population would have been valuable in providing a possible explanation as to why, especially in men, high BMI was associated with lower mortality (Bowman et al. 2016). In addition, no data on nutrient intake was gathered, which is also a limitation of this study. Sufficient intake of macro- and micronutrients is essential to a healthy life throughout the lifespan, and the importance of it is emphasized in older populations (Peter et al. 2015). Furthermore, in the oldest old, measurement of height is not simple. Due to kyphosis, a slouching posture, height may be underestimated, which in turn results in overestimates of BMI (Nishiwaki et al. 2011).

It is clearly a strength of this study that WC was included in the anthropometric measurements. WC is often considered a measure of visceral adipose tissue, but actually it correlates better with total body fat and subcutaneous adipose tissue than with visceral adipose tissue (Harris et al. 2000, Despres 2012). However, with any given BMI, a person with a larger WC has more abdominal fat than a person with a lower WC (Despres 2012). Both WC and BMI may be inaccurate measures of body fat for an individual, but at the population level, they correspond reasonably well with the percentage of body fat within the same sex and age groups, including persons aged ≥80 years (Flegal et al. 2009). In terms of comparability of the results of the different sub-studies, the different cutoff points used for BMI, WC, and the combined BMI and WC complicate comparison of the results to some extent. However, basically all of the results show the main directions for low and high values, and the results with slightly differing cutoff points can be compared.

Certain aspects in the measurement of WC need to be addressed. First, the measurement site for WC was different in the cohort measured in 2010 as compared to the other cohorts, and WC has been shown to differ according to the measurement site (Wang et al. 2003, Ross et al. 2008). However, it has been shown that the association between WC and mortality or morbidity does not substantially depend on the measurement site for WC (Ross et al. 2008). We also adjusted the analyses for the cohort and it is reasonable to assume that low, middle and high WCs were adequately separated. Second, measuring WC in the oldest old is challenging. Aging is accompanied with an increased kyphosis angle and with a reduced lumbar lordosis (Katzman et al. 2010) and standing in an upright posture during the WC measurement may be challenging for many oldest old persons. A possible slouching posture limits the accuracy of the WC measurement. Third, certain health conditions, including heart failure, cause edema (Watson, Gibbs & Lip 2000), which may also limit the accuracy of the WC measurement. Possible edema limits the accuracy of BMI as well.

In Studies III and IV, measurement of WHR was also included. However, unlike BMI and WC, WHR was not associated with any of the inflammatory markers, which indicated that WHR may not be closely associated with body fatness in the oldest old. This hypothesis was addressed in another study related to the Vitality 90+ Study, which demonstrated that WHR in women was poorly associated with plasma leptin, a surrogate marker for body fatness (Lisko et al. 2013). In some analyses of this study, an increase in WHR in women was associated with a decrease in mortality risk, but it has been suggested that WHR reflects mostly gluteal muscle mass and therefore may be negatively associated with mortality (Srikanthan, Seeman & Karlamangla 2009). However, in Studies I and II it was decided to concentrate on BMI and WC, both of which appear to reflect body fatness among oldest old women and men (Lisko et al. 2013).

In all, several other methodological factors related to obesity indicators may have influenced the results of this study. According to Willett et al. (1999) reverse causality is the most serious problem when the association of body weight with total mortality is being studied. It means that people with severe illnesses tend to weigh less than healthy individuals, which makes obesity appear beneficial (Willett, Dietz & Colditz 1999). In Study III, investigating mortality as the sole outcome, reverse causality was accounted for by excluding deaths that occurred during the first two years of the follow-up. This did not markedly alter the results, but it is noteworthy that in men the HR related to WC switched from below 1 to slightly above 1. Thus, the role of reverse causality should be examined more thoroughly in a larger population sample of the oldest old. It could also be argued that the number of years discarded is not sufficient (Willett, Dietz & Colditz 1999), but given both the advanced age of the study population and the follow-up time used, it is impossible to fully account for reverse causality. However, if reverse causality is not accounted for, BMI may be regarded as an indicator of underlying health status (Alley et al. 2008), and the results on BMI and mortality reflect the view that the weight associated with the lowest mortality is influenced by aging and chronic disease (Dixon et al. 2015).

Partly related to reverse causality, the concept of competing risks is also important to recognize when discussing the results of this study (Heiat, Vaccarino & Krumholz 2001). In older people many risk factors lead to morbidity and mortality, and the significance of each individual factor becomes smaller (Heiat, Vaccarino & Krumholz 2001). The oldest old in particular have multiple diseases (Goebeler 2009) and are susceptible to rapid changes in health and physical functioning. With all their burden and competing risk factors, general obesity did not emerge as a significant factor predicting mortality or the development of functional limitations in this study. Smoking is also considered an important factor that distorts the association between body weight and mortality, as smoking is associated with lower weight (Manson et al. 1987, Willett, Dietz & Colditz 1999, Tobias & Hu 2013). However, in this study a smoking history, particularly in women, was not common, and smoking was also accounted for in the analyses for mortality. Thus, the results of the study do not arise from the consequences of smoking. Finally, an important factor when interpreting the results of this study is selective survival. Persons who are prone to the adverse effects of obesity may have already died, which leaves behind those who may be more resistant to the effects of obesity (Elia 2001).

Physical functioning

The measures used in the study for physical functioning, namely five-times sit-to-stand test and the Barthel Index, are well-validated, have been shown to be reliable and are widely used (Kasner 2006, Bohannon 2011, Bohannon 2012). This is naturally a strength of the study. However, with a larger data set, it would have been possible to use more categories in the performance of the five-times sit-to-stand test and to explore the effects on the results. Because a third of the women and one in five men were not able to complete the five-times sit-to-stand test, it was more appropriate to use a categorized rather than a continuous variable. With some other measure for physical performance, such as walking speed, it would have been useful to employ also the continuous variable.

Disability

The validity of the measure used for mobility disability needs to be addressed. When the association between obesity and incident disability was assessed in Study II, at baseline mobility disability concerned walking 50 meters independently, whereas at follow-up it concerned walking 400 meters independently. Because incident mobility disability was included in the definition of incident ADL disability, ADL disability was also affected. Yet both at baseline and at follow-up, the question indicated that walking was to occur outside, and the effect of a possible bias was equal for each BMI and WC group.

In Study II, data on incident mobility and ADL disability were gathered by mailed questionnaires. The time interval between the baseline and the first possible questionnaire ranged from one year to four years depending on the cohort. Thus, some of the incident disabilities were certainly lost to mortality. The long intervals between data collection might also partly explain the differing results found for men and women on incident disability. Women with low WC were prone to develop ADL disability but in men the effect could not be seen. Tiainen and colleagues (2013) have demonstrated a gender difference in terms of survival with disability in the oldest old. It can be speculated that as disability increases mortality risk more in the oldest old men than in women (Tiainen et al. 2013), men with incident disability died before they got the chance to answer to the mailed questionnaire. This possible effect might also have led to some bias as low WC and BMI in men in the main analyses of Study III increased mortality risk and, thus, in particular, men with low weight might have experienced disability prior to death.

Comorbidity and medications

Inflammatory status is likely to better represent better the prevailing disease status than the number of chronic conditions, and the blood levels of inflammatory markers are a strength of this study. However, some aspects related to inflammatory status need to be addressed. First, it is possible that some participants had an acute inflammatory condition, which would present as high values for the inflammatory markers. Second, nonsteroidal anti-inflammatory drugs and some other drugs, such as statins, are known to reduce inflammation (Kushner, Rzewnicki & Samols 2006, Corsonello et al. 2010). However, these medications were looked into, and their number in the year 2000, when the blood samples were taken, was very low. Hence, there was no need to include medications for the analyses. Thus, it is a strength of this study that medications did not affect inflammatory status. In all, medications may have had some impact on the results of the study, as several different drugs or their combined effects have been shown to be associated with a decline in physical functioning or increased mortality risk (Fox et al. 2014, Sköldunger et al. 2015).

In Studies I and II, self-reported diagnoses and diagnoses from health center records were combined, which might lead to describing chronic conditions differently in different cohorts. However, earlier analyses of the Vitality 90+ Study demonstrate that there is sufficient congruence between these two sources of information (Goebeler, Jylha & Hervonen 2007). Assessing comorbidity and its impacts in older adults is not simple. People may have undiagnosed conditions, and the severity of a given disease often varies (Guralnik 1996). Here, comorbidity was based on the number of chronic conditions but even if the severity of the diseases had been taken into account, it would have carried limitations as well (Guralnik 1996).

8.3 Future directions

It has long been recognized that the current guidelines for BMI on healthy weight are not appropriate for older adults (Heiat, Vaccarino & Krumholz 2001, Price et al. 2006). According to the guidelines (WHO 2000), a BMI of 18.5–24.9 kg/m² is considered to represent a healthy weight for all, but there is strong evidence that in older adults, a BMI <23 kg/m² is associated with increased mortality risk (Prospective Studies Collaboration et al. 2009, Winter et al. 2014, Bowman et al. 2016). The findings from this study lend further credence regarding the need to provide separate, generally accepted guidelines for BMI in older adults. However, the fact that no consensus on appropriate cutoff points has yet been reached indicates that the matter is complicated. Especially with respect to obesity, the scientific literature does not provide clear answers. It also complicates things that in older adults, obesity appears to be more closely associated with disability than with mortality (Al Snih et al. 2007). With increasing age, populations become increasingly heterogeneous, BMI becomes less associated with body fatness, and the dynamics in weight history becomes more relevant as compared to younger adults (Ferrucci & Alley 2007, Han, Tajar & Lean 2011, Lowsky et al. 2014). It may also be that it is more the biological than the chronological age that makes the difference in the association between BMI and health risks. As Dixon and colleagues (2015) propose, ideal body weight varies at different stages of life and depends on disease status.

But at which stage of the aging process does general obesity begins to reflect more longevity than high mortality? Instead of concentrating on BMI and WC, future studies should explore the associations of body composition and physical fitness with mortality, and also with physical functioning, at different stages of the aging process. The effects of weight history and nutritional intake should also be incorporated. Concurrently, how these results are reflected in BMI and WC, should be investigated. Because of the strong heterogeneity involved in the pace of the aging process (Lowsky et al. 2014), instead of grouping individuals according to age, individuals could be stratified according to the level of physical functioning, or based on diseases. Closeness of death (Forma et al. 2009) might also offer an interesting viewpoint regarding the association of BMI and WC with mortality. It could be investigated how older adults with differing distances to death vary according to BMI and WC. This same approach could also be used to further elucidate the relationship of BMI and WC with physical functioning.

Despite the complexity associated with BMI in old age, BMI is a helpful tool in detecting low weight also in the oldest old. To ensure that old people, and especially the oldest old, meet their nutritional needs, nutritional screening incorporating, for example, the mini-nutritional assessment (MNA) (Vellas et al. 2006) and intervening when required (Guigoz 2006) would most likely carry health benefits. In the oldest old, it may be especially important for those with a BMI below 25 kg/m^2. However, it should be noted that nutritional care cannot always reverse malnutrition. With severe protein-energy wasting found often for example in cancer patients or in chronic kidney disease, nutritional care is not sufficient enough to reverse the catabolic state (Palesty & Dudrick 2011, Park et al. 2014). It should also be noted that the MNA may not identify all persons with poor energy and protein intakes (Jyväkorpi et al. 2016).

The finding that abdominal obesity in women in particular was associated with poor physical functioning but did not increase mortality risk carries an important message. Obesity prevalence has increased over the past few decades (Ng et al. 2014), and more and more people are living for longer periods with excess weight. When generations with long obesity duration become old and very old, the demand for care will most likely increase. Thus, effective obesity prevention is required. To date, obesity prevention has not been very successful, and conversations regarding the most efficient actions are discussed (Ezzati & Riboli 2012, Kleinert & Horton 2015, Roberto et al. 2015). Three main domains in which policy action for prevention should be taken have been identified (Roberto et al. 2015): 1) the food environment (e.g., nutrition labeling, food taxes and restriction of food advertising) 2) food systems promoting the consumption of energy-dense and nutrient-poor foods and beverages (encouragement of healthy behavior through health-related and non-health-related policies), and 3) behavior-change communication (e.g., visits to health care, public awareness campaigns and nutrition-counseling interventions). Obesity prevention targeted at children is especially important (Birch & Ventura 2009, Saraf et al. 2012), but obviously prevention targeted at other age groups is of great importance as well.

9 Main findings and conclusions

The main findings and conclusions of the present study are summarized as follows:

1. Abdominal obesity was associated with poor physical functioning in women, but general or abdominal obesity was not associated with increased mortality risk in women or in men.

2. Women with low WC had relatively good physical functioning in the cross-sectional setting. They also had low mortality risk when low WC was combined with overweight or with low inflammation. However, women with low WC had an increased likelihood of developing ADL disability.

3. High or low BMI did not predict increased mortality in women in the main analyses. However, well-functioning normal weight women were more likely to die when compared to overweight women when death was an alternative for developing ADL disability.

4. Men with low BMI or low WC had an increased mortality risk regardless of inflammatory status. However, current physical functioning or development of disability did not differ according to BMI or WC in men.

5. Combining low WC with high BMI yielded beneficial health outcomes in both men and women in terms of both physical functioning and mortality.

In conclusion, low body weight is a greater concern in terms of mortality than general obesity in the oldest old. However, findings especially in women emphasize the adverse effects associated with abdominal obesity in terms of both mortality and physical functioning. The results also indicate that WC and BMI are more informative together rather than separately. It should be better recognized in the health care and health services that low weight is an important indicator of declining health in old age. Malnutrition and low protein intake should be screened more and nutritional care should be provided when needed. Future studies should explore the associations of body composition and physical fitness with physical functioning and mortality at different stages of the aging process. Additionally, the effects of weight history and nutritional intake should be incorporated in future studies.

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Original publications

Association of Body Mass Index and Waist Circumference with Physical Functioning: The Vitality 90+ Study

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Running head: ADIPOSITY, FUNCTIONAL STATUS AND OLDEST OLD

ABSTRACT

Background. Both obesity and underweight are associated with impaired physical functioning but related information on the oldest old population is scarce. Our purpose was to examine whether body mass index (BMI), waist circumference (WC) and their combination are associated with physical performance and activities of daily living (ADL) disability in 90-year-old women and men.

Methods. Data are from the Vitality 90+ Study, which is a population-based study of persons 90 years and older living in the area of Tampere, Finland. Altogether 416 women and 153 men, aged 90–91 years, provided data on BMI, WC, chair stand and Barthel Index. Comorbidity, physical exercise, smoking history, living residence and sample year were used as covariates in multinomial logistic and logistic regression models.

Results. Women in the highest WC tertile had lower physical performance and were more likely unable to perform the chair stand than women in the lowest WC tertile. Women in the highest WC tertile were also more likely to have ADL disability, compared to the lowest WC tertile. In women, overweight and obesity were associated with ADL disability but not when WC was included in the model. Men with BMI $\geq$ 25 kg/m^2 and WC < sex-specific median were less likely to have ADL disability. Similarly classified women were less likely to have low performance or unable to perform chair stand (marginally significant).

Conclusions. High WC in the oldest old women but not in men is associated with both poor physical performance and ADL disability.

Key words: body composition, abdominal obesity, functional status, nonagenarians

INTRODUCTION

The harmful effects of obesity on functional status are well-established. Functional status may be defined in various ways, such as limitation or disability in physical functioning, mobility, or activities of daily living (ADL). Obesity has shown to be associated with all these measures in both cross-sectional and longitudinal studies (1-4). However, the strength of the association differs with level of obesity and with different outcomes. Women are more prone to the effects of obesity on physical functioning than men (3,5).

In studies assessing the effects of adiposity on functional status, the most widely used measure for adiposity is body mass index (BMI). However, as people get older, body composition changes (6), and the prognostic value of BMI changes (7). BMI is criticized for its impaired validity to describe the amount of adipose tissue, especially in the abdominal region, in older adults (8). Waist circumference (WC) is an easily accessible measure and widely used in studies assessing the effects of central adiposity on health and functional status (9-12). Measured either with BMI or WC, the association with physical functioning is U- or J-shaped (4,9,13). The more severe the obesity, the higher is the risk for disability, but also underweight increases the risk for poor functional outcomes. Nevertheless, there is paucity of studies confirming these findings in the oldest old, i.e. in people aged 85 years and older. To the best of our knowledge, there is only one cross-sectional and one longitudinal population-based study showing that obesity is still associated with disability in the oldest old (14,15). In a recently published study based on a large follow-up data, Rillamas-Sun (15) showed that overweight and obesity as well as waist circumference greater than 88 cm predicted higher risk of incident mobility disability in US women aged 85 years and older. Their study, however, focused only on women and the disability outcome was based on self-reported information. Thus, further studies including both genders and objective functional measurements are warranted.

Examining the effects of adiposity on physical functioning in the oldest old is relevant because excess weight seems to give survival benefit in older adults (16) and it is not clear what the public health message on ideal body weight in the oldest old should be. The purpose of this study is to examine whether BMI, WC and their combination are associated with objectively measured physical performance and self-reported ADL disability in a population-based sample of women and men aged 90–91 years.

METHODS

Participants

We use cross-sectional data from the Vitality 90+ Study which is based on repeated mailed surveys with all inhabitants aged 90 or older of the city of Tampere, Finland, conducted eight times since 1995. In addition, health examinations are conducted and blood drawn with sub samples aged 90–91 in three study years. More detailed description of the study is described elsewhere (17). Participants in this study come from cohorts born in 1909–1910, 1912–1913 and 1920 (Figure 1). Measurements for all cohorts were done at the ages of 90–91 years, i.e. in the years 2000, 2003 and 2010. Each year the basic population consisted of persons who, according to the local population register, were living in the city of Tampere at the time the register was obtained (n=535 in 2000; n=528 in 2003; and n=439 in 2010).

The final sample of 569 subjects consisted of 416 women and 153 men whose height, weight and WC had been measured (except for 7 cases in which weight was self-reported), and who had data on Barthel Index, physical exercise and smoking status (Figure 1). Altogether 381 participants were excluded because of missing data (primarily on BMI or WC). The participants represented 60% (n=255) of the eligible population in 2000, 30% (n=143) in 2003 and 45% (n=171) in 2010, respectively. In 2000 and 2010 the study group included both community-dwelling and institutionalized people, but in 2003 only community-dwelling.

The study protocol was approved by the Ethics Committee of the Pirkanmaa Hospital District and the Ethics Committee of the Tampere Health Center. All participants or their legal representatives gave their written informed consent.

Anthropometric Measurements

Anthropometric measurements included body height, weight and WC. BMI was computed as weight in kilograms divided by height in meters squared (kg/m^2) and classified as: underweight (<20 kg/m^2), normal weight (20–24.99 kg/m^2), overweight (25–29.99 kg/m^2) and obese (≥30 kg/m^2), respectively. For the underweight, we opted for slightly higher cutpoint, 20 kg/m^2, instead of the standard cutpoint 18.5 kg/m^2 recommended by WHO (18), because only 12 persons (2.1%) were below 18.5 kg/m^2. In 2000 and 2003 WC was measured midway between the level of the iliac crest and the lowest rib (19), and in 2010 at the level of the iliac crest (20). The decision to change the measurement site was based on the recommendation of US National Institute of Health (20). Earlier research shows that the measurement site for WC has no substantial influence on the association between WC and mortality or morbidity (21). Here WC was categorized according to sex-specific tertiles and because the cut-points were very similar for all the cohorts, we decided to use shared cut-points for all. In women the WC tertiles were <83 cm, 83–91 cm and ≥92 cm, and in men <92 cm, 92–99 cm and ≥100 cm.

Physical Performance and ADL Disability

Lower extremity physical performance was assessed with chair stand. Subjects were asked to perform five rises from a chair as fast as possible with arms folded across the chest. Timing started with the participant in the sitting position and ended at the end of the fifth stand. If the participant was unable to complete five rises, or decided not to do the test because of a medical condition or pain, or if the participant or the tester felt too risky to try the test, the performance was coded as “Unable”. Participants who refused from the test were coded missing (n=6). The test was missing from 8 persons with no reported reason. The performance was classified according to the median time (women and men together) and categorized as (i) Time <16 s (high performance), (ii), Time ≥16 s (low performance) and (iii) Unable. ADL disability was assessed by Barthel Index (22), a measure for basic ADL, and categorized as (i) 0–95 (ADL disability) and (ii) 100 (independent in ADL).

Comorbidity

In 2000 comorbidity was based on medical diagnoses collected from health center records. The diagnoses were coded according to the *International Classification of Diseases, 10^{th} Revision* (ICD-10) (23). Comorbidity was classified according to the number of ICD classes (classes A–C; in cancer other than basal cell carcinoma; D50–, E–H, K–N, and Q–Z) with at least one diagnose as (i) 0–3 diseases (low), (ii) 4–5 diseases (middle), (iii) ≥6 diseases (high), or (iv) data missing.

In 2003 and 2010, comorbidity was based on self-reported diseases received by a mailed questionnaire. The participants were asked if a doctor had diagnosed them with high blood pressure, heart disease, calcification of arteries, cancer, dementia, stroke, problems in cerebral circulation, diabetes, arthritis (arthrosis), rheumatoid arthritis, Parkinson’s disease, hip fracture or depression. The number of conditions were summed and categorized as (i) 0–1 diseases (low), (ii) 2–3 diseases (middle), (iii) and ≥4 diseases (high), or (iv) data missing.

Other Variables

Smoking status was categorized as (i) current or former or (ii) never smoker. Physical exercise was classified as (i) every day, (ii) at least once a week, or (iii) not very often. Living residence was classified as (i) home or (ii) institution. Sample year was classified as (i) year 2000, (ii) year 2003, or (iii) year 2010.

Statistical Analyses

Multinomial logistic regression analyses were used in assessing the association of BMI and WC with chair stand. The baseline group was those with high performance. Logistic regression models were used in examining the association of BMI and WC with Barthel Index. In both multinomial logistic and logistic analyses BMI and WC were analyzed (i) separately in the model, and (ii) together in the model. All models were adjusted for comorbidity, physical exercise, smoking history, living residence and sample year.

We also analyzed the association of combined BMI and WC (BMI <25 kg/m^2 or ≥25 kg/m^2; WC under or ≥sex-specific median; cutoff point in women 87 cm and in men 96 cm) with chair stand and Barthel Index. Multinomial logistic regression analyses were used for chair stand, and logistic regression analyses for Barthel Index. These models were also adjusted for comorbidity, physical exercise, smoking history, living residence and sample year.

All cohorts were analyzed together and all analyses were performed separately for men and women. Analyses were carried out with SPSS for Windows (SPSS Inc., Chicago, USA) version 18.0. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

For the chair stand assessment 30% of women and 19% of men were unable to perform the test (Table 1). In women, 58% and in men 47% needed help in ADL. Women in the highest WC tertile had lower performance (odds ratio [OR] 3.02, 95% confidence interval [CI] 1.59–5.76) and were more likely unable to perform the chair stand (OR 2.09, 95% CI 1.04–4.19) than women in the lowest WC tertile, when referred to high performance (Table 2). Statistically significant associations between BMI and chair stand were not found in women or men. When BMI and WC were included in the same model, high WC in women remained significantly associated with inability to perform chair stand. For BMI, however, overweight (OR 0.35, 95%

CI 0.16–0.73) and obese (OR 0.27, 95% CI 0.09–0.85) women were more often able to perform the chair stand than normal weight women, compared to high performance. In men, no statistically significant results were found (Table 2).

Women in the highest WC tertile were more likely to have ADL disability (OR 2.98, 95% CI 1.67–5.31), when compared to the lowest WC tertile (Table 3). Also overweight (OR 2.03, 95% CI 1.21–3.40) and obese (OR 2.50, 95% CI 1.21–5.19) women were more likely to have ADL disability, when compared to normal weight. But when both BMI and WC were included in the model, only the highest WC tertile remained statistically significant (OR 3.17, 95% CI 1.51–6.68). In men, no statistically significant results were found (Table 3).

Men with BMI ≥25 kg/m^2 and WC < sex-specific median were less likely to have ADL disability (OR 0.14, 95% CI 0.02–0.93), and similarly classified women were less likely to have low performance (marginally significant; OR 0.49, 95% CI 0.22–1.08) and to be unable to perform chair stand (marginally significant; OR 0.39, 95% CI 0.15–1.07) (Table 4).

DISCUSSION

Among the first in the field, we examined cross-sectional associations of BMI and WC, and their combination, with objectively measured physical performance and ADL disability in the oldest old women and men. In women but not in men, high WC was associated with a higher probability of having poor physical performance and ADL disability. Overweight and obesity measured with BMI were also associated with a higher probability of having ADL disability in women but not in men.

The results of our study confirm previous findings about the associations of overweight and obesity and high WC with limited physical functioning in the oldest old women (15). High WC showed consistency throughout the analyses, whereas high BMI was inconsistent. When WC was taken into account, overweight and obese women had even better physical performance compared to normal weight, and no associations between BMI and ADL disability were found. This suggests that in the oldest old women WC may be a more relevant measure of obesity than BMI, indicating a risk for poor functional outcomes. This is in accordance with previous research showing that WC predicts disability outcomes more closely than BMI (10), and that fat mass particularly is associated with disability (24,25). With regards to BMI, previous studies are controversial on whether overweight increases (13) or decreases (26) the risk for lower body performance. Similarly, previous studies are controversial on whether overweight increases the risk for ADL disability (27) or has even protective effects (28). However, in a recent meta-analysis by Backholer et al. (1) overweight was associated with ADL disability both in cross-sectional and longitudinal studies.

The combination of higher levels of BMI and lower levels of WC has been found to protect from mortality in older adults (29), and also in our study on the oldest old overweight combined with lower WC protected from mortality (30). Here, overweight men with low WC had a decreased likelihood of having ADL disability. Similarly classified women were less likely to have low performance or unable to perform chair stand but these results were only marginally significant. In all, the results on the associations between physical functioning and combination of BMI and WC were not systematic, and more research with a larger sample size are warranted to make conclusions on these associations.

Our results support earlier findings that also in the oldest old population the effects of adiposity on physical functioning are more evident in women than in men (3,5,31). There are several potential explanations for gender difference such as differences in disabling conditions (31,32) and in reporting physical discomfort (5,33). An additional explanation may relate to body composition. Women have more fat as well as lower absolute and relative muscle strength than men (34,35), and thus they may have more difficulties in carrying their excess weight and in moving efficiently.

The study has both strengths and limitations. The overall participation was rather low, but given the very high age of our participants it can be considered satisfactory. In two cohorts, also institutionalized persons were included and similar datasets on the oldest old are scarce. Still, the population studied is likely to represent a healthier part of the population. Objective measures on WC, BMI and physical performance can be regarded as benefits of the study. However, we had limited number of functional and disability measures available. With more detailed physical performance measures, such as walking speed, we would have had more power to detect differences across groups. The measurement site for WC was not the same for all the cohorts, but we believe that we identified well those with low, middle and high WC regardless of the exact measurement site. Finally, our setting was cross-sectional which prevents making any conclusions on causality.

In conclusion, in the oldest old women but not in men high WC is associated with both poor physical performance and ADL disability. Lifelong maintenance of healthy body weight may be useful in preventing and delaying physical functioning decline in older obese adults.

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FIGURE LABELS

Figure 1.

Flow chart of the Vitality 90+ Study: Health examinations in 2000, 2003 and 2010.

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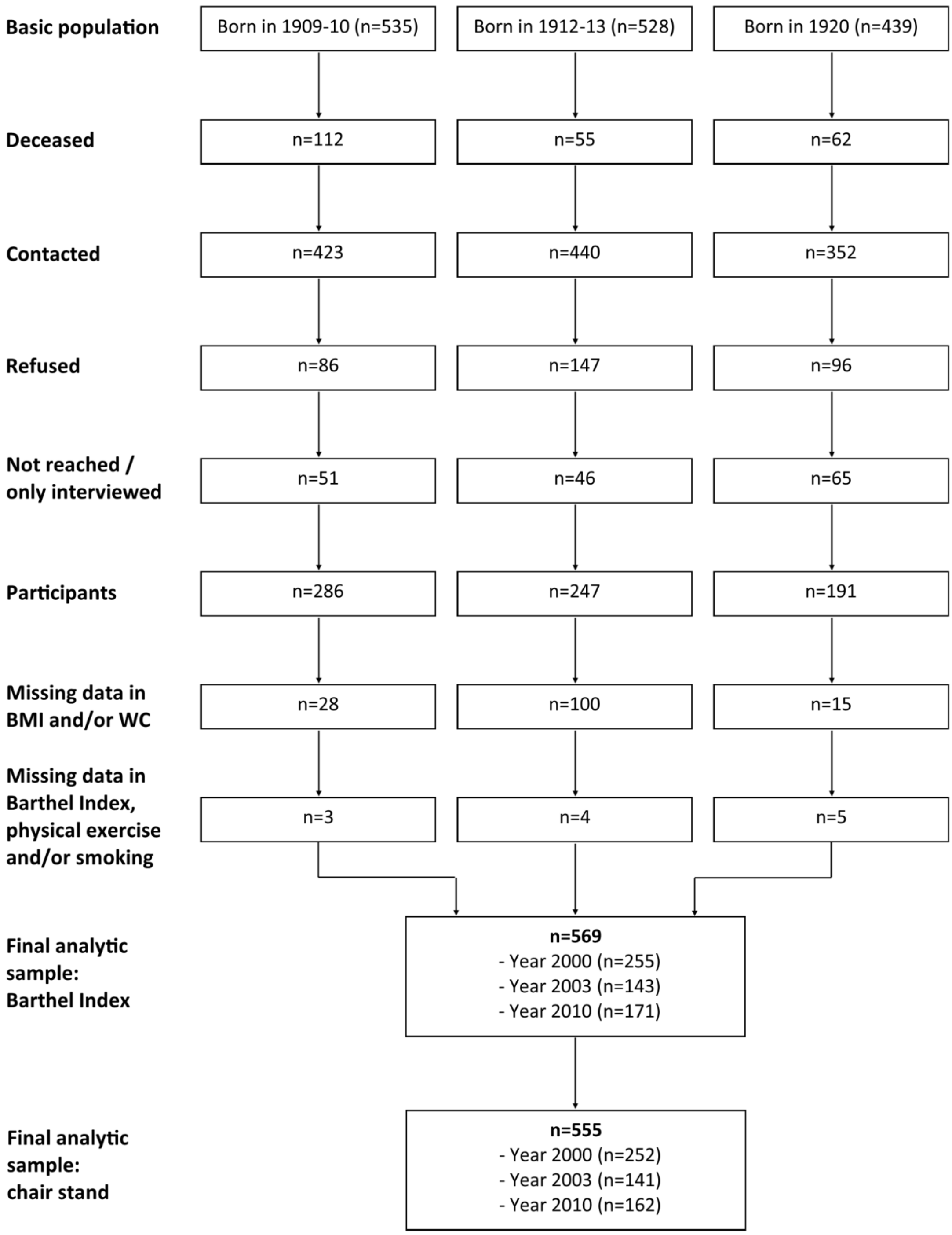
Basic population
Born in 1909-10 (n=535)
Born in 1912-13 (n=528)
Born in 1920 (n=439)
Deceased
n=112
n=55
n=62
Contacted
n=423
n=440
n=352
Refused
n=86
n=147
n=96
Not reached / only interviewed
n=51
n=46
n=65
Participants
n=286
n=247
n=191
Missing data in BMI and/or WC
n=28
n=100
n=15
Missing data in Barthel Index, physical exercise and/or smoking
n=3
n=4
n=5
Final analytic sample: Barthel Index
n=569
- Year 2000 (n=255)
- Year 2003 (n=143)
- Year 2010 (n=171)
Final analytic sample: chair stand
n=555
- Year 2000 (n=252)
- Year 2003 (n=141)
- Year 2010 (n=162)

Table 1. Characteristics of the Study Population Aged 90–91: The Vitality 90+ Study

	Women	Men
N	416	153
BMI, kg/m^2, Mean (SD)	25.5 (4.3)	25.0 (3.5)
BMI categories, kg/m^2, n (%)		
Underweight, <20	30 (7.2)	10 (6.5)
Normal weight, 20–24.9	185 (44.5)	77 (50.3)
Overweight, 25–29.9	141 (33.9)	51 (33.3)
Obese, ≥30	60 (14.4)	15 (9.8)
WC, cm, Mean (SD)	88.1 (11.2)	96.2 (0.8)
WC tertiles, cm, n (%)		
I (<83 for women, <92 for men)	129 (31.0)	50 (32.7)
II (83–91 for women, 92–99 for men)	142 (34.1)	52 (34.0)
III (≥92 for women, ≥100 for men)	145 (34.9)	51 (33.3)
Barthel Index, n (%)		
0–95	240 (57.7)	72 (47.1)
100	176 (42.3)	81 (52.9)
Chair stand (n = 555)*		
Time, s, Median (IQR)	16 (13–24)	15 (11–20)
High performance	133 (32.8)	68 (45.3)
Low performance	149 (36.8)	53 (35.3)
Unable, n (%)	123 (30.4)	29 (19.3)
Physical exercise, n (%)		
Every day	192 (46.2)	87 (56.9)
At least once a week	127 (30.5)	47 (30.7)
Not very often	97 (23.3)	19 (12.4)
Comorbidity, n (%)		
Low	101 (24.3)	40 (26.1)
Middle	157 (37.7)	69 (45.1)
High	135 (32.5)	36 (23.5)
Data missing	23 (5.5)	8 (5.2)
Smoking history, n (%)		
Current or previous	35 (8.4)	71 (46.4)
Never	381 (91.6)	82 (53.6)
Living residence, n (%)		
Home	371 (89.2)	145 (94.8)
Institution	45 (10.8)	8 (5.2)

Notes: BMI = body mass index; WC = waist circumference; IQR = interquartile range
*In women n = 405, and in men n = 150

Table 2. The Association between BMI and WC and Physical Performance (Chair Stand) in Women and Men Aged 90–91 Years: Multinomial Regression Analyses

	Chair Stand					
	Model 1* BMI & WC Separately			Model 2* BMI & WC Together		
	High Performance†	Low Performance†	Unable	High Performance†	Low Performance†	Unable
	OR (95 % Cl)					
Women (n = 405)						
BMI						
Underweight vs normal weight	1.0	0.52 (0.16–1.66)	1.59 (0.57–4.44)	1.0	0.68 (0.21–2.24)	2.04 (0.70–5.94)
Overweight vs normal weight	1.0	0.94 (0.54–1.62)	0.64 (0.34–1.20)	1.0	0.62 (0.33–1.15)	**0.35 (0.16–0.73)**
Obese vs normal weight	1.0	1.77 (0.80–3.88)	1.14 (0.47–2.77)	1.0	0.64 (0.23–1.78)	**0.27 (0.09–0.85)**
WC tertiles‡						
II vs I	1.0	1.41 (0.78–2.57)	0.73 (0.37–1.42)	1.0	1.59 (0.83–3.04)	1.16 (0.55–2.46)
III vs I	1.0	**3.02 (1.59–5.76)**	**2.09 (1.04–4.19)**	1.0	**3.97 (1.69–9.32)**	**5.79 (2.21–15.2)**
Men (n = 150)						
BMI						
Underweight vs normal weight	1.0	0.34 (0.06–2.05)	1.33 (0.17–10.4)	1.0	0.34 (0.06–2.07)	1.34 (0.17–10.6)
Overweight vs normal weight	1.0	0.80 (0.33–1.92)	0.53 (0.15–1.91)	1.0	0.80 (0.27–2.37)	0.65 (0.15–2.86)
Obese vs normal weight	1.0	1.02 (0.27–3.90)	0.26 (0.02–3.89)	1.0	1.21 (0.21–6.85)	0.52 (0.02–12.8)
WC tertiles‡						
II vs I	1.0	1.34 (0.52–3.46)	1.32 (0.37–4.75)	1.0	1.38 (0.50–3.80)	1.60 (0.41–6.20)
III vs I	1.0	1.03 (0.39–2.72)	0.40 (0.09–1.73)	1.0	0.98 (0.25–3.77)	0.61 (0.09–4.14)

Notes: BMI = body mass index; WC = waist circumference; OR = odds ratio; CI = confidence interval

*Model 1: Models analyzed separately for BMI and WC. Adjusted for comorbidity, physical exercise, smoking history, sample year and living residence.

*Model 2: Both BMI and WC in the model. Adjusted for comorbidity, physical activity, smoking history, sample year and living residence.

†High performance: Time <Median (16 s); Low performance: Time ≥Median (16 s).

‡WC tertiles for women <83 cm, 83–91 cm, and ≥92 cm, and for men <92 cm, 92–99 cm, and ≥100 cm.

Table 3. The Association between BMI and WC and ADL Disability (Barthel Index 0–95 vs 100) in Women and Men Aged 90–91 Years: Logistic Regression Analyses

		Barthel Index 0–95 vs 100	
		Model 1* BMI & WC Separately	Model 2† BMI & WC Together
	n	OR (95 % CI)	
Women	416		
BMI			
Underweight	30	2.12 (0.80–5.59)	2.67 (0.97–7.33)
Normal weight	185	1.0	1.0
Overweight	141	**2.03 (1.21–3.40)**	1.46 (0.82–2.58)
Obese	60	**2.50 (1.21–5.19)**	1.07 (0.44–2.61)
WC tertiles‡			
I	127	1.0	1.0
II	144	1.21 (0.70–2.11)	1.28 (0.69–2.34)
III	145	**2.98 (1.67–5.31)**	**3.17 (1.51–6.68)**
Men	153		
BMI			
Underweight	10	2.98 (0.64–13.8)	3.31 (0.70–15.7)
Normal weight	77	1.0	1.0
Overweight	51	0.64 (0.27–1.49)	0.45 (0.16–1.27)
Obese	15	1.10 (0.31–3.89)	0.67 (0.14–3.29)
WC tertiles‡			
I	48	1.0	1.0
II	40	1.11 (0.45–2.73)	1.55 (0.58–4.10)
III	65	1.11 (0.45–2.78)	2.13 (0.61–7.49)

Notes: BMI = body mass index; WC = waist circumference; ADL = activities of daily living; OR = odds ratio; CI = confidence interval

*Model 1: Models analyzed separately for BMI and WC. Adjusted for comorbidity, physical activity, smoking history, sample year and living residence.

†Model 2: Both BMI and WC in the model. Adjusted for comorbidity, physical exercise, smoking history, sample year and living residence.

‡WC tertiles for women <83 cm, 83–91 cm, and ≥92 cm, and for men <92 cm, 92–99 cm, and ≥100 cm.

Table 4. Association between combined BMI* and WC* with Chair Stand (Multinomial Logistic Regression) and with Barthel Index (Logistic Regression) in Women and Men Aged 90–91 Years

		Chair Stand†				Barthel Index†
		High Performance	Low Performance	Unable		0–95 vs 100
	n		OR (95 % CI)		n	OR (95 % CI)
Women	405				416	
Low BMI & Low WC‡	157				160	1.0
Low BMI & High WC	54	1.0	2.16 (0.88–5.32)	**4.40 (1.77–11.0)**	55	**3.18 (1.50–6.71)**
High BMI & Low WC	48	1.0	0.49 (0.22–1.08)	0.39 (0.15–1.07)	48	1.47 (0.70–3.10)
High BMI & High WC	146	1.0	**2.09 (1.17–3.74)**	1.45 (0.75–2.80)	153	**3.21 (1.86–5.53)**
Men	150				153	
Low BMI & Low WC‡	62				62	1.0
Low BMI & High WC	24	1.0	1.98 (0.64–6.10)	1.24 (0.25–6.23)	25	0.71 (0.25–2.06)
High BMI & Low WC	12	1.0	1.20 (0.26–5.65)	0.77 (0.10–5.87)	12	**0.14 (0.02–0.93)**
High BMI & High WC	52	1.0	1.13 (0.46–2.79)	0.43 (0.11–1.73)	54	0.77 (0.33–1.80)

Notes: BMI = body mass index; WC = waist circumference; OR = odds ratio; CI = confidence interval

*Cut-point for BMI 25 kg/m^2, and for WC sex-specific median (87 cm in women and 96 cm in men).

†Adjusted for comorbidity, physical exercise, smoking history, sample year and living residence.

High performance: Time <Median (16 s); Low performance: Time ≥Median (16 s).

‡Reference in multinomial logistic regression.

Body Mass Index, Waist Circumference and Waist-to-Hip Ratio as Predictors of Mortality in Nonagenarians: The Vitality 90+ Study

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ABSTRACT

Background. The associations of body mass index (BMI) and abdominal obesity with mortality among very old people are poorly known. The purpose of this study was to investigate the association of BMI, waist circumference (WC) and waist-to-hip ratio (WHR) with mortality in nonagenarians.

Methods. This study is part of a prospective population-based study, Vitality 90+, including both community-dwelling and institutionalized persons from Tampere, Finland. Altogether 192 women and 65 men aged 90 years were subjected to anthropometric measurements, a baseline interview and a 4-year mortality follow-up. Cox proportional hazards models were used in the statistical analyses.

Results. In men, normal weight indicated a 3 times higher mortality risk (Hazard Ratio [HR] 3.09, 95% confidence interval [CI] 1.35–7.06) compared to overweight and WC was inversely associated with mortality (HR 0.96, 95% CI 0.93–1.00) after adjustment for covariates. In women, the univariate WHR (HR 1.43, 95% CI 1.06–1.92) and BMI adjusted WHR (HR 1.45, 95% CI 1.07–1.97) were positively associated with mortality. Also overweight women whose WC was <86 cm had lower mortality than normal weight women with similar WC (HR 0.34, 95% CI 0.12–0.97).

Conclusions. In nonagenarian men low BMI and low WC predict increased mortality. In nonagenarian women WHR alone and adjusted for BMI is positively associated with mortality. The potential positive effects of overweight combined with WC warrant more detailed analyses in larger data. In all, future studies are needed to better understand the health and functional consequences of body composition among the oldest old.

Key Words: Body weight–Abdominal obesity–Mortality–Aging–Oldest old

INTRODUCTION

Overweight and obesity increase the risk of death in middle-aged and younger people. In older adults, however, overweight no longer increases the risk of death and obesity seems to produce only a modest increase in mortality (1–2). It seems that for middle-aged people the body mass index (BMI) together with waist circumference (WC) or waist-to-hip ratio (WHR) form the most applicable tool for assessing risk of death (3–4). BMI together with WC predicts mortality more accurately than either of the two alone in older adults (5).

The oldest old have been included in many studies on BMI, WC parameters and mortality (1,4–7) but only a few studies have especially focused on people aged 85 years and older (8–12). It appears that low BMI rather than high BMI predicts death and that mortality is decreasingly U-shaped (11) among the oldest old. In all, the data on the oldest old is scarce, and to our knowledge no previous studies have examined the association of WC or WHR separately, or together with BMI, with mortality in nonagenarians.

The purpose of this study was to investigate the association of BMI, WC and WHR with mortality in 90-year-old people, as well as factors that may modify the predictive value of BMI. In addition, the combined effects of BMI and abdominal girth, measured as WC and WHR, on mortality were examined.

METHODS

Participants

Our data come from the Vitality 90+ Study, which is a prospective multidisciplinary population-based study of people aged 90 or older living in the area of Tampere, Finland. The basic population for the present study consisted of all people born in 1909–1910 who, according to the local population register, were living in the city of Tampere (n=535) as of January 2000. Thus, the age of the individuals in the sample was 90 ± 1 year. Both community-dwelling and institutionalized persons were invited to participate. According to the National Population Register Center, 66 persons died before the beginning of data collection leaving 469 persons eligible for the study. An additional 42 persons died during the study but before being examined, 86 persons refused to participate, mostly due to poor physical or mental condition, and 7 persons could not be reached. Another 48 persons participated in the Vitality 90+ Study but no anthropometric measurements were performed for them, primarily due to their poor health status. In addition, 29 persons were lacking some anthropometrical data and they were excluded from the data. The final sample of 257 subjects consisted of 192 women and 65 men (60 % of the eligible population) whose height, weight (BMI), WC and hip circumference had been measured.

Interviews and anthropometric measurements were carried out in the year 2000 at homes for community-dwelling participants and in institutions for institutionalized participants. The study protocol was approved by the Ethics Committee of the Pirkanmaa Hospital District and the Ethics Committee of the Tampere Health Center. All participants or their legal representatives gave their written informed consent.

Anthropometric measurements

The anthropometric measurements included body height, weight, waist circumference and hip circumference. Height was measured to the nearest 1 cm and weight to the nearest 1 kg. BMI was computed as weight in kilograms divided by height in meters squared (kg/m^2) and classified according to the WHO definitions (13). The applied classifications were underweight (BMI<18.50 kg/m^2), normal weight (BMI 18.50–24.99 kg/m^2), overweight (BMI 25.00–29.99 kg/m^2) and obese (BMI≥30.00 kg/m^2), respectively. Waist circumference was measured midway between the level of the iliac crest and the lowest rib (13), and categorized using a sex-specific median (cutoff point for men 94 cm and for women 86 cm). Hip circumference was measured from the widest part of pelvis (14). WHR was computed as the ratio of WC to hip circumference, and categorized using a sex-specific median (cutoff point for men 0.91 and for women 0.85). WC and WHR were used both as continuous and categorical variables in the analyses.

Mortality

Dates of death were drawn from the National Population Register Center. Follow-up time was calculated from February 21, 2000 to the date of death or to February 21, 2004 for survivors. There were no losses to mortality follow-up.

Covariates

Medical diagnoses were collected from health center records maintained by public health care physicians, including diagnoses made in hospitals. The diagnoses were coded according to the *International Classification of Diseases, 10th Revision* (ICD-10) (15). We included cardiovascular disease, infectious disease, cancer (all cancers except for basal cell carcinoma), respiratory disease and diabetes. Cognitive status was assessed by the Mini-Mental State Examination (MMSE). The MMSE score was categorized as (i) 0–22 points (lower cognitive status) or (ii) 23–30 points (higher cognitive status). Co-morbidity was defined as the number of chronic conditions, including the five diagnostic categories and MMSE score of 0–22 points, and was dichotomized as (i) 0–2 chronic conditions or (ii) 3–6 chronic conditions. In the multivariate analyses, missing data in chronic conditions was included as a separate category.

Functional status at baseline, assessed by the Barthel index, was categorized as (i) 0–50 points (poor), (ii) 55–90 points (moderate) or (iii) 95–100 points (good) (16) and in the Cox proportional hazards model as (i) 0–90 points or (ii) 95–100 points. Smoking status was categorized as (i) current or former or (ii) never smoker. Alcohol intake was classified as (i) at least once a week, (ii) occasionally or (iii) not at all.

Statistical analysis

The Cox proportional hazards models were used to analyze associations of BMI, WC and WHR with all-cause mortality over a 4-year follow-up. The associations of BMI, WC and WHR with mortality were analyzed in (i) an unadjusted univariate model, (ii) a model in which BMI, WC and WHR were each separately adjusted for covariates including chronic conditions, functional status, smoking and alcohol intake, (iii) a model including BMI and WC only, and (iv) a model including BMI and WHR only. BMI was categorized and overweight group was used as a reference group. WC and WHR were used as continuous variables (the results represent 1 cm change in WC and 0.1 unit change in WHR).

Relative mortality risk according to BMI is known to differ in varied subgroups (3). Thus, we also examined the effect of BMI (normal weight and overweight) on 4-year mortality in subgroups of (i) Barthel Index, (ii) smoking, (iii) alcohol intake (iv) MMSE score, (v) cardiovascular disease, (vi) cancer, (vii) respiratory disease, (viii) infectious disease, and (ix) number of chronic conditions. Diabetes was excluded from the analyses due to the low prevalence. In each subgroup analysis overweight group was the reference group. The interactions between BMI and the subgroup variables were also analyzed.

The combined effects of BMI (normal weight and overweight) and WC (<86 cm and ≥86 cm for women and <94 cm and ≥94 cm for men) and BMI and WHR (<0.85 and ≥0.85 for women and <0.91 and ≥0.91 for men) on 4-year mortality were also analyzed. Due to the small number of overweight men with low WC (n=3), normal weight together with lower values in WC and WHR served as a reference group. Also the interactions between BMI (normal weight and overweight) and categorical WC and WHR, respectively, were analyzed. In addition, to examine the role of reverse causality, i.e. the possibility that an individual is lean because of a fatal illness, unadjusted mortality analyses concerning BMI, WC and WHR were performed for those subjects who were still alive after the first two years of follow-up (n=161 in women and n=41 in men).

All analyses were performed separately for men and women. Underweight and obese persons were excluded from the subgroup analyses (Table 3) and from the analyses of combined effects of BMI and WC, and BMI and WHR (Table 4) because of their low number. Analyses were carried out with SPSS for Windows (SPSS Inc., Chicago, USA) version 18.0. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the study population are presented in Table 1. In women, 1.6% of the population was underweight, 58.9% normal weight, 32.3% overweight and 7.3% obese. In men, 64.6% were normal weight, 30.8% overweight and 4.6% obese. In women, 33.3% of the underweight, 50.4% of the normal weight, 38.7% of the overweight and 50.0% of the obese subjects deceased during the 4-year follow-up (Figure 1). In men, 76.2% of the normal weight, 50.0% of the overweight and 66.7% of the obese subjects deceased, respectively. No significant associations were found between BMI and mortality in women (Table 2). Normal weight men had significantly higher mortality after adjusting for covariates (HR 3.09, 95% CI 1.35–7.06) compared to overweight men. When BMI was adjusted for WC or WHR, BMI was no longer associated with mortality in men or women.

WC was not associated with mortality risk in women (Table 2). In men, WC was inversely associated with mortality after adjustment for covariates (HR 0.96, 95% CI 0.93–1.00). WC adjusted for BMI was not associated with mortality in men or women. In women, WHR was positively associated with mortality in the univariate (HR 1.43, 95% CI 1.06–1.92) and BMI adjusted (HR 1.45, % CI 1.07–1.96) models but not in the model adjusted for covariates. In men, WHR was not associated with mortality in any of the models.

In the subgroup analysis, no significant effects of BMI on mortality were found in women (Table 3). In the related interaction analyses no significant interactions were found either (data not shown). In men, mortality was significantly higher in normal weight men who were current or former smokers, did not use alcohol, did not have history of cancer, respiratory disease or infectious disease, and who had less than three chronic conditions, compared to overweight men (Table 3) but the only statistically significant interaction was in the alcohol intake (data not shown).

In overweight women whose WC was below 86 cm mortality was significantly lower compared to normal weight women with the same WC (HR 0.34, 95% CI 0.12–0.97) (Table 4) but the related interaction was not statistically significant. In men, no statistically significant effects were found. Combined effects of BMI and WHR or the related interactions showed no statistically significant results in men or women.

When persons who died during the first two years of follow-up were excluded from the unadjusted mortality analyses, HR for normal weight women was 1.08 (95% CI 0.62–1.90) and for obese women 1.56 (95% CI 0.58–4.17) compared to overweight women. HR for normal weight men was 2.40 (95% CI 0.79–7.30) and for obese men 2.25 (95% CI 0.41–12.30) compared to overweight men. Regarding WC, HR in women was 1.02 (95% CI 0.99–1.04) and in men 1.01 (95% CI 0.96–1.05). Regarding WHR, HR in women was 1.40 (95% CI 0.96–2.05) and in men 1.99 (95% CI 0.92–4.30). To summarize, reverse causality did not have large effects on our results although the (non-significant) coefficients for WC and WHR in men suggested different directions in associations than in the main analyses. (Data not shown.)

DISCUSSION

In this study we investigated the association of BMI, WC and WHR with mortality in 90-year-old men and women. To our knowledge, this is the first study to assess the association of abdominal obesity with mortality in nonagenarians. Our results showed that in men, BMI in the normal range and low WC are associated with increased mortality risk, compared to men who are overweight or have high WC, respectively. In women, WHR alone and adjusted for BMI was positively associated with mortality. A further analysis implied that BMI in the overweight range combined with low WC is associated with decreased mortality risk in women.

The finding that men with low BMI have high mortality is consistent with previous studies where exceptionally high mortality has been reported in underweight older men and increased mortality in normal weight older men (17–19). Reverse causality is considered to be the most serious challenge when examining the association between BMI and all-cause mortality (20). People often lose weight as a result of an illness that is ultimately fatal and as a consequence mortality appears to be higher among people with low weight. Here, the subgroup analysis suggested that overweight may be advantageous for men who in general are healthier. Also the fact that mortality in normal weight men remained 2-fold compared to overweight men even after discarding the first two years of the follow-up, though not statistically significant, suggests that high mortality in normal weight men is not completely explained by reverse causality. Furthermore, the subgroup analysis suggested that normal weight may be associated with death especially in men who were current and previous smokers. Nevertheless, due to the small sample size and lack of statistically significant interactions the results of the subgroup analyses are merely preliminary findings and require further study with a larger sample.

There are several potential explanations for the increased mortality among normal weight persons (21). First, decreased food intake and undernutrition are known to increase mortality (22–23). Hence, it is possible that the increased mortality in normal weight men is associated with poor nutritional status. Unfortunately, we did not have information concerning the overall nutritional status of the participants. Second, substantial evidence suggests that higher BMI provides survival benefits in chronic wasting diseases (21). This may be explained, in part, by a greater amount of energy being stored as fat and by larger muscle mass, as well as by the influence of body fat on fuel selection during negative energy balance (24). Third, it is possible that overweight and obese persons who have survived to old age may have characteristics that protect them from the adverse effects of increased adiposity (21).

In addition to general obesity, fat accumulated in the abdominal area can cause additional health risks. It has been speculated that BMI partly reflects the amount of lean mass for individuals with the same WC, whereas WC reflects total and abdominal fat content for individuals with the same BMI (25). In older people higher BMI values have shown to be associated with lower mortality risk when WC has been accounted for and higher WC values have indicated higher mortality risk when BMI has been accounted for (5). Also our results suggest that high BMI combined with low WC may be beneficial at the age of 90 years at least in women. In men only three persons were categorized as overweight with WC below the median of 94 cm but they all survived the 4-year mortality follow-up. These tentative findings, likewise those from the subgroup analyses, warrant further study in more extensive data sets.

In men, the borderline negative association of WC with mortality after adjustment for covariates may well emphasize the risks related to low weight. Yet, WC was no longer associated with mortality after accounting for potential reverse causality. Moreover, it has been suggested that having either too little or too much central fat would increase mortality risk in older men (26). Although no significant association between the covariate adjusted WHR and mortality were found in women, we consider the WHR to be a relevant measure of body composition in the oldest old as it is in older adults (27). The finding that WHR, but not WC, was associated with mortality in women may be due to the ability of WHR to reflect the gluteal muscle mass (27).

The limitations of the study need to be addressed. First, the overall study population and particularly the male group was quite small. Second, the number of obese people was too low to allow a proper analysis of the effect of obesity on mortality. Third, we did not have information about recent weight loss of the participants. Fourth, as one third of the population was not included, mostly due to poor health status, the results do not apply to persons with very poor health status. On the other hand, given the very high age of our participants we had a high participation rate and similar population-based data are scarce. Objective anthropometric measurements, reliable data about mortality, medical history, functional status and cognitive status are clearly strengths of the study.

In conclusion, BMI and abdominal obesity continue to be associated with mortality at the age of 90 but the association is different in men and women. While the results of this study lend further credence to the protective role of overweight in old people and especially in very old people, the findings should be confirmed in a larger setting. Further studies are also needed to unravel the association of body composition to functional and cognitive status among the oldest old.

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Figure legends:

Figure 1. Mortality in 90-Year-Old Women and Men during 4 Years According to Body Mass Index (BMI) Categories (%)

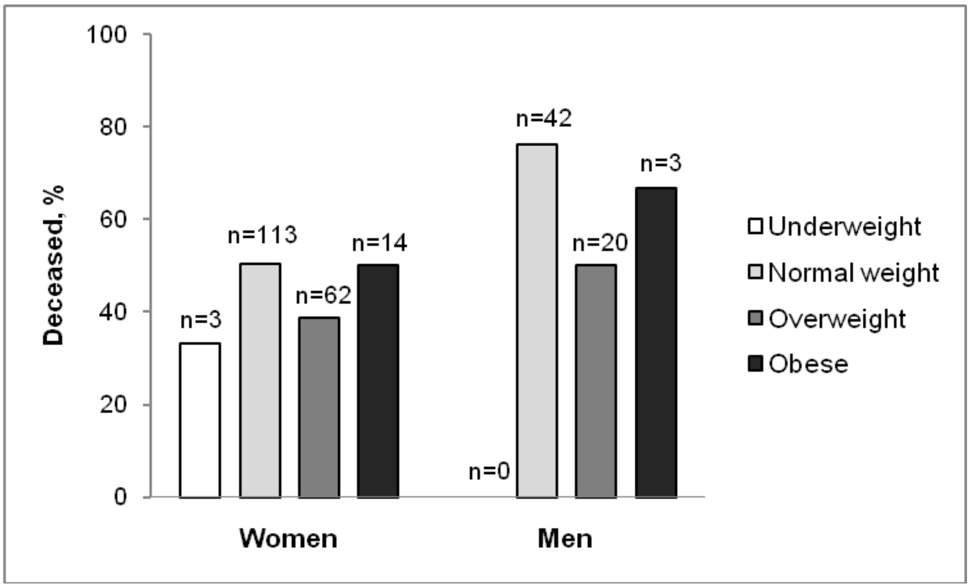

Table 1. Baseline Characteristics of the 90-Year-Old Study Population

Characteristics	Women *n*=192	Men *n*=65
Height, cm, Mean (Sd)	157.5 (6.0)	171.2 (6.8)
Weight, kg, Mean (Sd)	61.1 (10.0)	71.2 (9.8)
Body Mass Index (BMI), kg/m^2, Mean (Sd)	24.6 (3.4)	24.4 (3.2)
BMI categories, n (%)		
Underweight (<18.50)	3 (1.6)	0 (0.0)
Normal weigth (18.50–24.99)	113 (58.9)	42 (64.6)
Overweight (25.00–29.99)	62 (32.3)	20 (30.8)
Obese (≥30.00)	14 (7.3)	3 (4.6)
Waist Circumference (WC), cm, Mean (Sd)	86.1 (10.0)	94.2 (10.3)
Hip circumference, cm, Mean (Sd)	100.2 (8.4)	101.5 (7.5)
Waist-to-Hip Ratio (WHR), Mean (Sd)	0.86 (0.07)	0.93 (0.07)
Barthel Index, n (%)		
0–55	21 (10.9)	8 (12.3)
60–90	57 (29.7)	19 (29.2)
95–100	114 (59.4)	38 (58.5)
Smoking status, n (%)		
Current or former smoker	6 (3.1)	22 (33.8)
Never smoker	186 (96.9)	43 (66.2)
Alcohol intake, n (%)		
at least once a week	15 (7.8)	22 (33.8)
occasionally	53 (27.6)	17 (26.2)
not at all	124 (64.6)	26 (40)
Mini-Mental State Examination (MMSE) score 0–22, n (%)	54 (28.1)	22 (33.8)
Diseases, n (%)		
Cardiovascular disease	124 (64.6)	40 (61.5)
Diabetes	15 (7.8)	5 (7.7)
Cancer	13 (6.8)	10 (15.4)
Respiratory disease	35 (18.2)	18 (27.7)
Infectious disease	68 (35.4)	31 (47.7)
Data missing	29 (15.1)	9 (13.8)
Number of chronic conditions*, n (%)		
0–2	115 (59.9)	32 (49.2)
3–6	48 (25.0)	24 (36.9)
Data missing	29 (15.1)	9 (13.8)
Living residence, n (%)		
home	158 (82.3)	58 (89.2)
institution	34 (17.7)	7 (10.8)

*Chronic conditions are cardiovascular disease, diabetes, cancer, respiratory disease, infectious disease, and MMSE score of 0–22.

Table 2. Associations of Body Mass Index (BMI), Waist Circumference (WC)* and Waist-to-Hip Ratio (WHR)* with 4-Year Mortality in 90-Year-Old Women and Men: Cox Proportional Hazards Model with 95% Confidence Interval (95% CI)

		Unadjusted	Covariates†	BMI and WC‡	BMI and WHR‡
	n	Hazard Ratio (95% CI)			
Women	192				
BMI					
Underweight	3	1.03 (0.14–7.60)	1.09 (0.14–8.79)	1.34 (0.17–10.29)	1.04 (0.14–7.66)
Normal weight	113	1.42 (0.88–2.30)	1.29 (0.79–2.08)	1.59 (0.96–2.64)	1.47 (0.91–2.37)
Overweight	62	1.00	1.00	1.00	1.00
Obese	14	1.59 (0.69–3.69)	1.07 (0.45–2.52)	1.27 (0.51–3.16)	1.34 (0.57–3.14)
WC	192	1.01 (0.99–1.03)	1.00 (0.98–1.02)	1.02 (0.99–1.04)	
WHR	192	1.43 (1.06–1.92)	1.30 (0.94–1.80)		1.45 (1.07–1.96)
Men	65				
BMI					
Normal weight	42	1.92 (0.94–3.91)	3.09 (1.35–7.06)	1.63 (0.69–3.86)	1.87 (0.90–3.90)
Overweight	20	1.00	1.00	1.00	1.00
Obese	3	1.01 (0.22–4.62)	1.63 (0.31–8.62)	1.20 (0.24–6.00)	1.02 (0.22–4.67)
WC	65	0.97 (0.94–1.00)	0.96 (0.93–1.00)	0.99 (0.95–1.03)	
WHR	65	0.81 (0.50–1.31)	0.75 (0.45–1.24)		0.93 (0.57–1.52)

*Continuous variable, hazard ratios were computed for each 1 cm change in WC and for each 0.1 unit change in WHR.

†BMI, WC and WHR each separately adjusted for the following covariates: chronic conditions (cardiovascular disease, cancer, diabetes, respiratory disease, infectious disease and MMSE), functional status, smoking and alcohol intake.

‡Unadjusted analyses.

Table 3. Subgroup Analysis of the Association of Body Mass Index (BMI) with 4-Year Mortality in 90-Year-Old Women and Men: Univariate Cox Proportional Hazards Model with 95% Confidence Interval (95% CI)

		Women BMI			Men BMI	
		Normal weight	Overweight		Normal weight	Overweight
Subgroup	n	Hazard Ratio (95% CI)		n	Hazard Ratio (95% CI)	
Barthel index						
0–90	67	1.63 (0.82–3.28)	1.00	27	1.15 (0.44–2.99)	1.00
95–100	108	1.16 (0.59–2.27)	1.00	35	2.87 (0.97–8.51)	1.00
Smoking						
current or former	5	30.08 (0.00–4.48·10^7)	1.00	21	3.15 (1.10–8.99)	1.00
never	170	1.39 (0.86–2.24)	1.00	41	1.83 (0.63–5.30)	1.00
Alcohol intake						
at least once a week	14	1.00 (0.09–11.02)	1.00	20	0.61 (0.17–2.25)	1.00
occasionally	50	1.26 (0.46–3.47)	1.00	16	2.14 (0.56–8.14)	1.00
not at all	111	1.49 (0.85–2.60)	1.00	26	3.67 (1.19–11.25)	1.00
Mini-Mental State Examination (MMSE) score						
0–22	47	1.60 (0.68–3.90)	1.00	22	1.69 (0.54–5.24)	1.00
23–30	128	1.36 (0.77–2.40)	1.00	40	2.04 (0.82–5.10)	1.00
Cardiovascular disease						
yes	124	1.26 (0.72–2.21)	1.00	40	1.78 (0.76–4.18)	1.00
no	39	2.23 (0.60–8.27)	1.00	16	2.01 (0.50–8.11)	1.00
Cancer						
yes	13	0.75 (0.15–3.78)	1.00	10	1.50 (0.40–5.63)	1.00
no	138	1.50 (0.87–2.60)	1.00	43	2.47 (1.00–6.08)	1.00
Respiratory disease						
yes	33	1.84 (0.53–6.41)	1.00	15	0.94 (0.28–3.08)	1.00
no	118	1.37 (0.77–2.43)	1.00	38	3.00 (1.13–7.97)	1.00
Infectious disease						
yes	68	1.39 (0.71–2.75)	1.00	31	1.34 (0.58–3.11)	1.00
no	95	1.63 (0.73–3.63)	1.00	25	8.52 (1.11–65.35)	1.00
Number of chronic conditions*						
0–2	107	1.58 (0.81–3.09)	1.00	32	3.04 (1.02–9.06)	1.00
3–6	44	1.06 (0.47–2.39)	1.00	21	1.19 (0.43–3.28)	1.00

*Chronic conditions are cardiovascular disease, cancer, diabetes, respiratory disease, infectious disease and MMSE.

Table 4. The Combined Effects of Body Mass Index (BMI) and Waist Circumference (WC), and BMI and Waist-to-Hip Ratio (WHR) on 4-Year Mortality in 90-Year-Old Women and Men: Cox Proportional Hazards Model with 95% Confidence Interval (95% CI)

Women	*n*	Deceased (%)	Hazard Ratio (95% CI)
Combination of BMI and WC			
Normal weight and WC <86 cm	72	48.6	1.00
Normal weight and WC ≥86 cm	41	53.7	1.17 (0.69–1.99)
Overweight and WC <86 cm	20	20.0	0.34 (0.12–0.97)
Overweight and WC ≥86 cm	42	47.6	0.97 (0.56–1.68)
Combination of BMI and WHR			
Normal weight and WHR <0.85	53	47.2	1.00
Normal weight and WHR ≥0.85	43	51.2	1.16 (0.66–2.06)
Overweight and WHR <0.85	27	33.3	0.66 (0.31–1.41)
Overweight and WHR ≥0.85	35	42.9	0.89 (0.47–1.69)
Men			
Combination of BMI and WC			
Normal weight and WC <94 cm	29	82.8	1.00
Normal weight and WC ≥94 cm	13	61.5	0.58 (0.26–1.30)
Overweight and WC <94 cm	3	0.0	–
Overweight and WC ≥94 cm	17	58.8	0.57 (0.27–1.19)
Combination of BMI and WHR			
Normal weight and WHR <0.91	20	75.0	1.00
Normal weight and WHR ≥0.91	22	77.3	1.07 (0.54–2.15)
Overweight and WHR <0.91	6	50.0	0.65 (0.19–2.23)
Overweight and WHR ≥0.91	14	50.0	0.51 (0.21–1.26)

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Original Articles

Inflammation, Adiposity, and Mortality in the Oldest Old

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Abstract

Background: Increased proinflammatory status is associated with both increased adiposity and higher mortality risk. Thus, it is paradoxical that mild obesity does not predict increased mortality in older adults. We investigated the association of inflammatory markers with body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR) in nonagenarians, and the combined effects of BMI, WC, WHR, and inflammatory status on mortality.
Methods: This study was based on a prospective population-based study, Vitality 90+, carried out in Tampere, Finland. Altogether, 157 women and 53 men aged 90 years were subjected to anthropometric measurements, blood samples, and a 4-year mortality follow-up. Inflammatory status was based on sex-specific median levels of interleukin-1 receptor antagonist (IL-1RA), interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α).
Results: In the unadjusted linear regression analyses, IL-1RA, CRP, and TNF-α were positively associated with BMI and WC in women, whereas in men IL-1RA was positively associated with BMI and IL-6 positively with WC. In the models adjusted for diseases, functional status, and smoking, IL-1RA and CRP were positively associated with BMI and WC in women. Low WC and WHR combined with low inflammation protected from mortality in women and high BMI and WC regardless of inflammation protected from mortality in men in the adjusted Cox regression analysis.
Conclusions: In the oldest old, the effect of adiposity in combination with inflammatory status on mortality differs between men and women. More research is needed to disentangle the role of adiposity among the oldest old.

Introduction

It has become evident that white adipose tissue represents a dynamic endocrine organ that secretes several hormones and other proteins, including many inflammatory markers.[1] Circulating levels of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1RA), and tumor necrosis factor-α (TNF-α) have been reported in younger to older adults to be positively associated with increased adiposity, measured as body mass index (BMI), waist circumference (WC), or waist-to-hip ratio (WHR).[2–4] A wealth of data supports the view that the low-grade proinflammatory state has an essential role as the origin and maintainer of many chronic diseases, such as cardiovascular disease, cancer, or Alzheimer disease.[5–7] In addition, increased inflammatory status is associated with the process of aging[8] and with increased mortality risk.[9]

Inflammatory status is strongly associated with adiposity and with mortality, thus it is paradoxical that overweight and mild obesity do not predict increased mortality in older adults.[10] The relationships between adiposity, inflammation, and mortality have been previously discussed concerning chronic kidney disease.[11] Recently, Lakoski et al.[12] directly addressed the interactions between adiposity, inflammation, and mortality in middle-aged to older adults, showing that elevated CRP was a more powerful risk factor for mortality in underweight and normal weight compared to overweight or obese persons, and also that racial differences existed. However, the area is still scantily studied, and data especially on very old people are lacking. In general, there is also a paucity of data concerning the associations between inflammatory markers and adiposity in the oldest old.

Previously, we have examined the associations of inflammatory markers[13] and adiposity (BMI, WC, and WHR)[14]

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with mortality in nonagenarians. Regarding inflammation, IL-RA was a particularly powerful prognostic marker for mortality.[13] Regarding adiposity, low BMI increased mortality risk, especially in men, but the combination of high BMI and low WC seemed to be protective for both women and men.[14]

The purpose of this study was, first, to investigate cross-sectional associations between BMI, WC, and WHR and inflammatory markers (IL-1RA, IL-6, CRP, and TNF-α), and, second, to examine the combined effects of inflammatory markers and adiposity on mortality in 90-year-old people.

Methods

Participants and study design

The data are from the Vitality 90+ Study, which is a prospective, multidisciplinarym population-based study of people aged 90 or older living in the area of Tampere, Finland. The study population in this study consisted of all people born in 1909–1910, who, according to the local population register, were living in the city of Tampere ($n=535$) as of January, 2000. Both community-dwelling and institutionalized persons were invited to participate in home interviews, anthropometric measurements, and blood sampling. According to the National Population Register Center, 66 persons died before the beginning of data collection. Another 42 persons died during the study but before being examined, leaving 427 persons eligible for the study. An additional 86 persons refused to participate, mostly due to poor physical or mental condition, and 7 persons could not be reached. Another 45 persons participated, but refused the blood tests, and 79 persons were lacking at least one of the anthropometric measures or a result in at least one of the inflammatory markers. The final study population of 210 persons (49% of the eligible population) consisted of persons who had results in all of the anthropometric and inflammatory measures (157 women and 53 men).

Interviews, anthropometric measurements, and blood sampling were carried out in the year 2000 at homes for community-dwelling participants and in institutions for institutionalized participants. Medical diagnoses were collected from health center records. The study protocol was approved by the Ethics Committee of the Pirkanmaa Hospital District and the Ethics Committee of Tampere Health Center. All participants or their legal representatives gave their written informed consent.

Anthropometric measurements

The anthropometric measurements included height, weight, WC, and hip circumference. Height was measured to the nearest 1 cm and weight to the nearest 1 kg. BMI was calculated as weight in kilograms divided by height in meters squared. Due to the small number of underweight (BMI < 18.50 kg/m^2; in women $n=2$ and in men $n=0$) and obese (BMI ≥ 30.00 kg/m^2; in women $n=12$ and in men $n=2$) subjects, BMI was classified as (1) < 25.00 kg/m^2 (low BMI) and (2) > 25.00 kg/m^2 (high BMI). WC was measured midway between the level of the iliac crest and the lowest rib and classified according to the sex-specific median (cutoff point for men 93 cm and for women 85 cm). Hip circumference was measured from the widest part of pelvis.[15] WHR was computed as the ratio of WC-to-hip circumference and classified according to the sex-specific median (cutoff point for men 0.91 and for women 0.85).

Biochemical measurements

Blood samples were collected in the morning after an overnight fast using EDTA tubes in ice. Plasma was separated after centrifugation (15 min at $700\times g$), divided into aliquots, and stored at −80°C until analyzed. Concentrations of IL-6 and IL-1RA were analyzed using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Pelikine Compact human IL-6 ELISA kit, CLB, Amsterdam, The Netherlands for IL-6; Quantikine, R&D Systems, Minneapolis, MN for IL-1RA; The optical density of the wells was analyzed with a Multiscan Biochromatic 348 (Labsystems, Helsinki, Finland) spectrophotometer. Concentration of TNF-α was analyzed with a Luminex-based multiplex analysis system (Bio-Plex 200 System, BioRad Laboratories, Inc.) using a commercially available kit, (Human Serum Adipokine (Panel B) kit, catalog HADK-2-61K-B, LINKOplex). High-sensitivity CRP was analyzed using a Cobas Integra 700 automatic analyzer with reagents and calibrators as recommended by the manufacturer (Hoffman-La Roche Ltd., Basel, Switzerland; COBAS Integra C-reactive Protein, Latex). For CRP, some of the results were below the detection level of 0.10 mg/L. All values below the detection level were coded as 0.05 mg/L. The given inflammatory markers were selected on the basis of their availability, wide use in the literature, and reported association with levels of adiposity.

A separate variable to describe inflammatory burden was defined on the basis of how many markers out of IL-1RA, IL-6, CRP, and TNF-α had a higher level than the sex-specific median. Inflammatory status was categorized as: (1) 0–1 inflammatory markers above the sex-specific median (low inflammation) and (2) 2–4 inflammatory markers above the sex-specific median (high inflammation).

Mortality

Mortality follow-up was based on dates of death drawn from the Population Register Center. Follow-up time was calculated from February 21, 2000, to the date of death or to February 21, 2004, for survivors. There were no losses to mortality follow-up.

Other variables

Medical diagnoses were available for 187 participants. The diagnoses were collected from records maintained by public health care physicians including diagnoses made in hospitals, and coded according to the *International Classification of Diseases, 10th Revision* (ICD-10). History in cardiovascular disease, infectious disease, cancer (all cancers except for basal carcinoma), respiratory disease, and diabetes were chosen to describe the disease status of the participants. Functional status, assessed by Barthel index, was categorized into two groups: (1) 0–90 points (poor to moderate) or (2) 95–100 points (good). Smoking status was categorized as: (1) current or former or (2) never smoker.

Statistical analyses

Associations between BMI, WC, and WHR and inflammatory markers (IL-1RA, IL-6, CRP, and TNF-α) were analyzed by linear regression analysis. An unadjusted and an adjusted model were performed to analyze the association of

Table 1. Baseline Characteristics of the 90-Year-Old Study Population

Characteristics	*Women* n=*157*	*Men* n=*53*
Height, cm, mean (SD)	157.4 (6.1)	170.9 (7.2)
Weight, kg, mean (SD)	60.8 (10.1)	71.1 (9.9)
Body mass index (BMI), kg/m^2, mean (SD)	24.5 (3.5)	24.4 (3.3)
BMI categories, n (%)		
<25.00 kg/m^2	95 (60.5)	34 (64.2)
≥25.00 kg/m^2	62 (39.5)	19 (35.8)
Waist circumference, cm, mean (SD)	85.8 (10.2)	94.4 (10.4)
Hip circumference, cm, mean (SD)	99.7 (8.6)	101.8 (7.7)
Waist-to-hip ratio, mean (SD)	0.86 (0.07)	0.93 (0.06)
IL-1RA, pg/mL, median (IQR)	364 (276–482)	360 (261–458)
IL-6, pg/mL, median (IQR)	2.40 (1.53–3.98)	2.90 (1.89–6.67)
CRP, mg/L, median (IQR)	1.20 (0.40–4.05)	1.90 (0.75–4.15)
TNF-α, pg/mL, median (IQR)	4.14 (2.99–5.46)	4.13 (2.99–5.28)
Inflammatory markers above the median[a], *n* (%)		
0 markers	18 (11.5)	5 (9.4)
1 marker	45 (28.7)	14 (26.4)
2 markers	29 (18.5)	17 (32.1)
3 markers	45 (28.7)	8 (15.1)
4 markers	20 (12.7)	9 (17.0)
Barthel index, *n* (%)		
0–90	54 (34.4)	18 (34.0)
95–100	103 (65.6)	35 (66.0)
Smoking status, *n* (%)		
Current or former smoker	6 (3.8)	19 (35.8)
Never smoker	151 (96.2)	34 (64.2)
History of diseases, *n* (%)		
Cardiovascular disease	108 (68.8)	35 (66.0)
Diabetes	11 (7.0)	4 (7.5)
Cancer	12 (7.6)	8 (15.1)
Respiratory disease	28 (17.8)	17 (32.1)
Infectious disease	58 (36.9)	27 (50.9)
Data missing	17 (10.8)	6 (11.3)
Living residence, *n* (%)		
Home	141 (89.8)	52 (98.1)
Institution	16 (10.2)	1 (1.9)

[a]Sex-specific median of plasma levels of CRP, IL-6, IL-1RA, and TNF-α.
SD, Standard deviation; BMI, body mass index; IL-1RA, interleukin-1 receptor antagonist; IQR, interquartile range; IL-6, interleukin-6; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α.

each anthropometric measure with each inflammatory marker. Adjustments were made for history of diseases (cardiovascular disease, cancer, diabetes, respiratory disease, and infectious disease), functional status, and smoking. Because of missing data in history of diseases, both the unadjusted and adjusted analyses were performed only for those participants who did not have any missing data.

Cox proportional hazards models were used to analyze the combined effects of BMI, WC, and WHR and inflammatory status with all-cause mortality over 4 years. BMI, WC, and WHR were each combined with inflammatory status, and in each of the 4-class variables, the lower value in anthropometric measure and low inflammation was the reference group. Adjustments were made for history of diseases (cardiovascular disease, cancer, diabetes, respiratory disease, and infectious disease), functional status, and smoking. Missing data in diseases was categorized as its own group. In addition, the adjusted 4-year mortality analyses were conducted only for those participants who survived the first 2 years of the follow-up ($n=129$ in women and $n=32$ in men). This was done to examine the role of reverse causality, that is, people may have low body weight because of fatal illness. Also the interactions in the mortality analyses between BMI, WC, and WHR and inflammatory status were analyzed for all. Statistical power was analyzed for the univariate Cox proportional hazards models.

The levels of inflammatory variables were not normally distributed. For normalizing the values, all inflammatory variables were $\log_{10}$ transformed. All of the analyses were performed separately for men and women. Analyses were carried out with SPSS for Windows (SPSS Inc., Chicago, IL) version 18.0. A significance level of $p<0.05$ was considered statistically significant.

Results

Baseline characteristics of the subjects are shown in Table 1. In the unadjusted analyses, BMI was positively associated with IL-1RA, CRP, and TNF-α in women (for each $p<0.05$), and with IL-1RA ($p=0.031$) in men (Table 2). After adjustment, BMI remained positively associated with IL-1RA and

Table 2. Linear Regression Analysis of the Associations of Body Mass Index, Waist Circumference, and Waist-to Hip Ratio with Inflammatory Markers[a] in 90-Year-Old Women and Men

	BMI		*WC*		*WHR*	
	Unadjusted	*Adjusted*	*Unadjusted*	*Adjusted*	*Unadjusted*	*Adjusted*
	β (p value)		*β (p value)*		*β (p value)*	
Women ($n = 140$)						
IL-1RA	**0.401 (<0.001)**	**0.404 (<0.001)**	**0.349 (<0.001)**	**0.353 (<0.001)**	0.121 (0.155)	0.095 (0.270)
IL-6	0.035 (0.682)	0.008 (0.931)	0.029 (0.738)	−0.010 (0.910)	0.001 (0.989)	−0.047 (0.587)
CRP	**0.209 (0.013)**	**0.238 (0.008)**	**0.176 (0.038)**	**0.202 (0.022)**	−0.040 (0.638)	−0.047 (0.597)
TNF-α	**0.194 (0.021)**	0.165 (0.070)	**0.178 (0.035)**	0.131 (0.143)	0.030 (0.726)	−0.022 (0.801)
Men ($n = 47$)						
IL-1RA	**0.314 (0.031)**	0.228 (0.143)	0.241 (0.103)	0.199 (0.192)	0.107 (0.475)	0.165 (0.301)
IL-6	0.210 (0.156)	0.149 (0.346)	**0.320 (0.028)**	0.264 (0.082)	0.173 (0.246)	0.194 (0.225)
CRP	−0.233 (0.115)	−0.299 (0.062)	−0.060 (0.687)	−0.225 (0.154)	0.103 (0.489)	−0.012 (0.942)
TNF-α	0.134 (0.370)	0.129 (0.451)	0.173 (0.246)	0.145 (0.385)	0.105 (0.483)	0.134 (0.440)

The results are shown by standardized betas with *p* values. Models were performed separately for each BMI, WC, and WHR.
Unadjusted analysis: Models were performed separately for each inflammatory marker (IL-1RA, IL-6, CRP, and TNF-α).
Adjusted analysis: Adjusted for history of diseases (cardiovascular disease, cancer, diabetes, respiratory disease, and infectious disease), functional status, and smoking. Models were performed separately for each inflammatory marker (IL-1RA, IL-6, CRP, and TNF-α).
[a]Values are transfered to $\log_{10}$
BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; IL-1RA, interleukin-1 receptor antagonist; IL-6, interleukin-6; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α.

CRP in women ($p < 0.05$). In men, the negative association between BMI and CRP was borderline significant ($p = 0.062$) after adjustment. In the unadjusted analyses, WC was positively associated with IL-1RA, CRP, and TNF-α in women ($p < 0.05$) and with IL-6 ($p = 0.028$) in men. After adjustment, WC remained positively associated with IL-1RA and CRP in women ($p < 0.05$), whereas no significant associations were found in men. WHR was not associated with any inflammatory marker in any analyses.

In women, no significant results were found regarding BMI in the adjusted mortality analyses (Table 3). In men, the adjusted mortality risk was significantly lower with high BMI and low inflammation (hazard ratio [HR] 0.13, 95% confidence interval [CI] 0.03–0.59) and with high BMI and high inflammation (HR 0.25, 95% CI 0.09–0.76) compared to low BMI and low inflammation. Regarding WC and WHR, in women the adjusted mortality risk was significantly higher in all the other groups when low WC or WHR and low inflammation was the reference group. For WC, the highest mortality risk was with high WC and low inflammation (HR 7.23, 95% CI 2.70–19.39), and for WHR the highest mortality risk was with low WHR and high inflammation (HR 4.69, 95% CI 1.64–13.46), respectively. On the contrary, in men mortality risk was significantly lower with high WC and low inflammation (HR 0.13, 95% CI 0.03–0.59) and with high WC and high inflammation (HR 0.25, 95% CI 0.09–0.76) compared to low WC and inflammation in the adjusted analyses.

When people who died during the first 2 years of the follow-up were excluded from the adjusted analyses, in women only the results regarding WC and inflammatory status remained statistically significant, similarly to the main analyses. In men, the results for BMI and WC did not show any marked change, but due to the very low number of observations the results cannot be considered reliable (data not shown.)

In the mortality analyses, in women the interactions between WC and inflammatory status ($p < 0.001$) and WHR and inflammatory status ($p = 0.002$), respectively, were statistically significant (data not shown). There was also a tendency for a significant interaction between BMI and inflammatory status in women ($p = 0.07$). In men, no interactions were found.

The statistical power in women in the mortality analyses concerning WC and WHR was at a good level (range 95.9%–99.7%), but concerning BMI the values (range 10.7%–75.7 %) did not reach a level considered sufficient. In men, the statistical power in all the mortality analyses was low (range 5.4%–27.0 %), which was also expected on the basis of the low number of subjects and wide CIs.

Discussion

We investigated whether inflammatory markers are associated with levels of adiposity and whether inflammatory status and adiposity have combined effects on mortality in 90-year-old people. Our findings showed that in nonagenarians BMI and WC, but not WHR, were associated with levels of certain inflammatory markers, but the associations were different in men and women. Regarding the combined effects of adiposity and inflammatory status, the lowest mortality risk in women was in those participants who had low levels of WC or WHR combined with low inflammatory status. In men, the lowest mortality risk was in those participants who had high levels of BMI or WC combined with low inflammatory status.

On the basis of the cross-sectional analysis, IL-1RA was the most consistent marker associated with BMI and WC across genders. These positive associations are in line with the known positive association between IL-1RA and level of adiposity.[16] The fact that WHR was not associated with IL-1RA, or with any other inflammatory marker, suggests that

Table 3. Body Mass Index, Waist Circumference, and Waist-to-Hip Ratio Combined with Inflammatory Status: Effects on 4-Year Mortality in 90-Year-Old Women and Men

	Women (n = *157*)				*Men* (n = *53*)			
			Unadjusted[a]	*Adjusted*[b]			*Unadjusted*[a]	*Adjusted*[b]
	N	*N (%) of subjects who died*	*HR (95% CI)*	*HR (95% CI)*	N	*N (%) of subjects who died*	*HR (95% CI)*	*HR (95% CI)*
BMI and inflammatory status								
Low BMI and low inflammation	47	16 (34.0)	1.00	1.00	13	11 (84.6)	1.00	1.00
Low BMI and high inflammaton	48	33 (68.8)	**2.47 (1.36–4.49)**	1.77 (0.93–3.38)	21	17 (81.0)	0.91 (0.43–1.96)	0.59 (0.22–1.54)
High BMI and low inflammation	16	7 (43.8)	1.43 (0.59–3.48)	1.81 (0.72–4.57)	6	2 (33.3)	0.25 (0.06–1.14)	**0.07 (0.01–0.51)**
High BMI and high inflammation	46	20 (43.5)	1.34 (0.69–2.58)	1.14 (0.58–2.24)	13	8 (61.5)	0.52 (0.21–1.29)	**0.31 (0.10–0.94)**
WC and inflammatory status								
Low WC and low inflammation	35	6 (17.1)	1.00	1.00	10	9 (90.0)	1.00	1.00
Low WC and high inflammaton	38	25 (65.8)	**5.60 (2.30–13.68)**	**5.63 (2.18–14.55)**	14	11 (78.6)	0.86 (0.36–2.10)	0.62 (0.19–1.95)
High WC and low inflammation	28	17 (60.7)	**5.56 (2.19–14.11)**	**7.23 (2.70–19.39)**	9	4 (44.4)	0.34 (0.10–1.11)	**0.13 (0.03–0.59)**
High WC and high inflammation	56	28 (50.0)	**3.58 (1.48–8.66)**	**2.73 (1.10–6.76)**	20	14 (70.0)	0.57 (0.24–1.32)	**0.25 (0.09–0.76)**
WHR and inflammatory status								
Low WHR and low inflammation	30	5 (16.7)	1.00	1.00	7	4 (57.1)	1.00	1.00
Low WHR and high inflammaton	35	21 (60.0)	**5.06 (1.91–13.44)**	**4.69 (1.64–13.46)**	15	11 (73.3)	1.82 (0.58–5.74)	1.24 (0.32–4.79)
High WHR and low inflammation	33	18 (54.5)	**4.95 (1.83–13.33)**	**4.57 (1.57–13.34)**	12	9 (75.0)	1.88 (0.58–6.14)	0.58 (0.14–2.42)
High WHR and high inflammation	59	32 (54.2)	**4.23 (1.65–10.86)**	**2.90 (1.08–7.73)**	19	14 (73.7)	1.44 (0.47–4.38)	0.48 (0.12–1.89)

Models represent Cox proportional hazards models with hazard ratios (HR) and 95% confidence intervals (95% CI).
Inflammatory status: C-reactive protein, interleukin-6, interleukin-1 receptor antagonist, and tumor necrosis factor-α taken into account.
Low inflammation: 0–1 inflammatory markers above the sex-specific median.
High inflammation: 2–4 inflammatory markers above the sex-specific median.
Cutpoint for BMI 25.00 kg/m^2. Sex-specific median cut point for WC (85 cm in women and 93 cm in men) and WHR (0.85 in women and 0.91 in men).
[a]Unadjusted univariate analyses.
[b]Each univariate model adjusted for history of diseases (cardiovascular disease, cancer, diabetes, respiratory disease, and infectious disease), functional status, and smoking.
CI, Confidence interval; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio.

in the oldest old population BMI and WC are more closely associated with level of adiposity than WHR. This finding is logical because high WHR may represent a relative lack of gluteal muscle mass in addition to a relative abundance of abdominal fat.[17]

BMI and WC were positively associated with CRP in women, whereas in men these associations were negative although nonsignificant. However, in men, the borderline significant association between CRP and BMI may partly explain our recent finding that mortality in normal-weight oldest old men is higher compared to overweight men.[14] It is possible that high CRP in oldest old men is more strongly associated with low BMI and malnutrition–inflammation–cachexia syndrome[18] than with high BMI. In general, levels of inflammatory factors are partly regulated by genes,[19,20] and they also are influenced by factors such as gender[21,22] and dietary patterns.[23,24] It is also important whether the adipose tissue is located viscerally or subcutaneously, because visceral adipose tissue is more metabolically active.[25] However, there is an ongoing debate regarding whether CRP is an actual risk factor for diseases or merely a marker of inflammation[26,27]; *i.e.*, whether CRP has a causal link to diseases.

In the longitudinal analyses, high inflammation was associated with higher mortality risk in women who had low WC or WHR, as could be expected. On the contrary, in men who had low level of adiposity, inflammatory status made no difference in mortality, and death rate was highest for men with low BMI or WC and low inflammation. In both low- and high-inflammation groups, women with high WC or WHR had significantly higher mortality risk, whereas men with high WC or BMI had significantly lower mortality risk compared to the reference group, respectively. These gender differences might be related to the fact that women have a higher fat percentage than men in general.[28] Regarding inflammation, experimental data has also demonstrated that under certain conditions, production of proinflammatory cytokines can initiate activation of a prosurvival cardioprotective pathway.[29] The fact that the results both in men and women remained similar after excluding the first 2 years of the follow-up suggests that reverse causality, *i.e.*, illnesses causing mortality early in the follow-up, is not causing the results. However, in women, reverse causality may well explain the results concerning WHR.

A wealth of data has demonstrated a phenomenon known as the obesity paradox, meaning that obesity has protective effects on mortality.[30–32] However, recent studies have shown that the obesity paradox, at least in part, can be explained by factors such as cardiorespiratory fitness,[33,34] adipocyte and adipose tissue abnormalities,[35] or persistent organic pollutants.[36] The findings of this study also shed light for the paradox in very old women, because low WC and WHR, when combined with low inflammatory status, were associated with particularly low mortality. The same direction of association was also seen in BMI, although to a lesser extent. In contrast, in men the results give further support for the obesity paradox, because higher values in BMI and WC had a protective effect on mortality regardless of the inflammatory status. Also, in a recent study by Clark et al., both high WC and high BMI were independently associated with better survival in a cohort of heart failure patients.[37] Similarly, in a recent systematic review of the literature, BMI was inversely associated with mortality risk, but, conversely, central obesity was directly associated with mortality risk.[38]

Interestingly women with high WC and low inflammation had roughly three times higher mortality risk than women with both high WC and inflammation. It could be speculated that as WC correlates positively with inflammatory markers, a high level of adiposity combined with low inflammatory status relates to ill health in women. The result might also reflect an *ex vivo* finding that the capacity to generate a proinflammatory immune response is predictive of long-term survival in the oldest old.[39]

The study has some major limitations. First, this very old cohort has obviously experienced a high selective mortality, and the results may not apply to younger age groups. Also, only half of the basic population was included, and the study sample is likely to be healthier than the whole age group. Second, the sample size was quite small, and particularly the number of men was low. Consequently the statistical power in men in the mortality analyses was very low. However, we considered it important to include men in the analyses as a separate group because earlier findings are scarce and the results clearly differed between the genders. In addition, the participants were mostly normal weight and overweight, thus the effects of obesity or very low weight combined with inflammation could not be examined. Finally, the mortality risks are likely to vary depending on how many inflammatory markers have an elevated level and where the cut-point for low and high inflammation is set. Due to small sample size, we could not explore these effects more closely. In all, our findings need to be confirmed with a larger study sample.

In conclusion, BMI and WC, but not WHR, are associated with some inflammatory markers in the oldest old, but the results differ in men and women. The findings give novel insight on the combined effects of adiposity and inflammatory status on mortality in the oldest old. In women, low WC or WHR combined with low inflammatory status gives clear survival benefit, whereas in men the survival benefit seems to be greatest in those with high WC or BMI combined with low inflammatory status. The gender differences and the interaction between inflammatory status and adiposity should be noted in future studies.

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