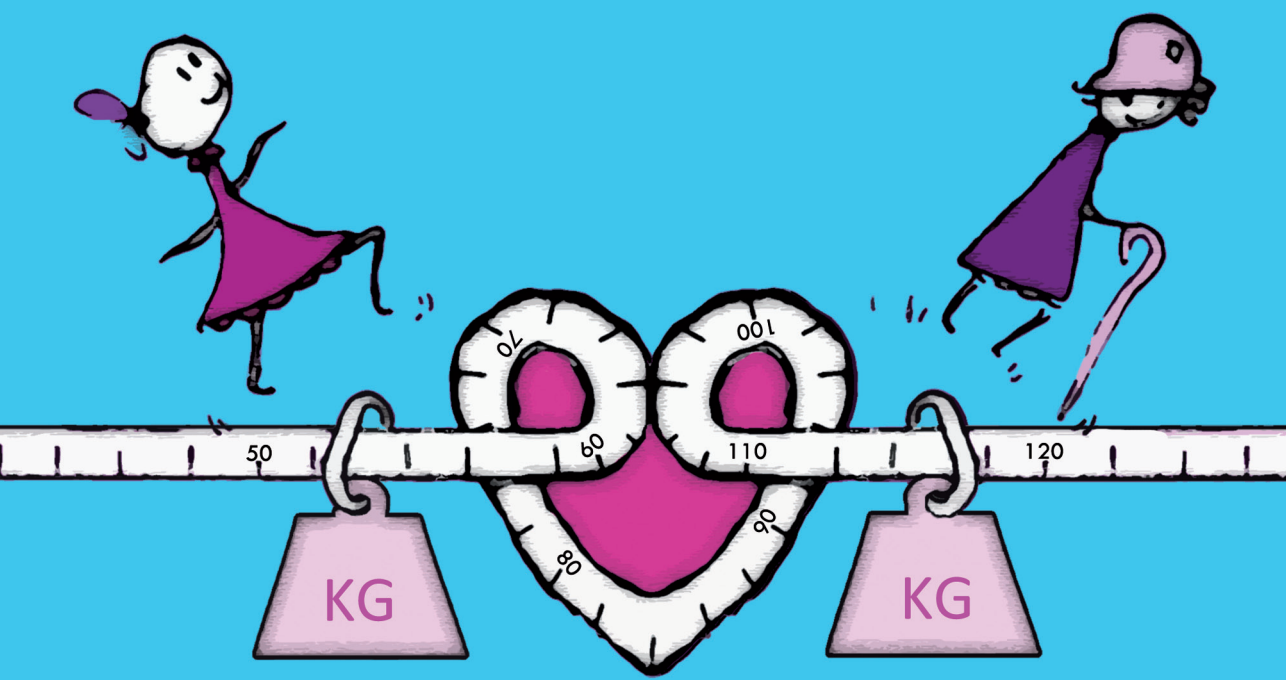
Anthropometrics and ageing
Impact of weight status on health

Ellen L. de Hollander



ANTHROPOMETRICS AND AGEING

Impact of weight status on health

Ellen Lisette de Hollander

Thesis committee

Promotor

Prof. Dr C.P.G.M. de Groot
Personal chair at the Division of Human Nutrition
Wageningen University

Co-promotor

Dr W.J.E. Bemelmans
Project leader
National Institute for Public Health and the Environment, Bilthoven

Other members

Dr P. Deurenberg, Kedah, Malaysia
Prof. Dr D. Kromhout, Wageningen University
Prof. Dr A.J. Schuit, VU University, Amsterdam
Prof. Dr M. Visser, VU University, Amsterdam

This research was conducted under the auspices of the Graduate School VLAG (Advanced studies in Food Technology, Agrobiotechnology, Nutrition and Health Sciences).

ANTHROPOMETRICS AND AGEING

Impact of weight status on health

Ellen Lisette de Hollander

Thesis

submitted in fulfilment of the requirements for the degree of doctor
at Wageningen University
by the authority of the Rector Magnificus
Prof. Dr M.J. Kropff,
in the presence of the
Thesis Committee appointed by the Academic Board
to be defended in public
on Wednesday 9 October 2013
at 1.30 p.m. in the Aula.

Ellen Lisette de Hollander
Anthropometrics and ageing - Impact of weight status on health
176 pages

PhD thesis, Wageningen University, Wageningen, NL (2013)
With references, abstract in English and summary in Dutch
ISBN: 978-94-6173-688-8

ABSTRACT

Background: Weight status is one of the factors that influence healthy ageing. It is often assessed with anthropometric measures such as body mass index (BMI) and waist circumference (WC), which indicate underweight or excess fat. Both are associated with adverse health outcomes in adults. The first paper of this thesis investigates whether this association is consistent over calendar time, to check for possible influences of improved healthcare procedures over time. In old age, this association is unclear. Using several anthropometric measures, the subsequent five papers examine the impact of weight status and development of weight status on coronary heart disease (CHD), mortality, and quality of life (QoL) among the elderly and during ageing.

Methods: A meta-regression analysis of 31 international cohort studies (n=389,212) was used to estimate the multivariable adjusted relative risk (RR) of CHD for an increased BMI and whether the RR was different between calendar periods (i.e. studies that started before 1985 and studies that started after 1985) taking account of the age of the population. Associations of BMI and changes in eight anthropometric measures with all-cause and cause-specific mortality in old age were studied by means of multivariable Cox regression analyses using data from the *Survey in Europe on Nutrition and the Elderly: a concerted action* study including 70–77-year-olds (n=1,061–1,970). Moreover, the association of WC with all-cause and cause-specific mortality was studied by means of a meta-analysis of 29 international cohort studies including 65–74-year-olds (n=58,609). For an ageing population, we used the *Doetinchem Cohort Study* including 20–70-year-olds (n=3,408–4,135) and three to four repeated measures of weight and height over a period of 10 to 15 years. In this study population, we used a multivariable regression analysis to examine the association of changes in weight and long-term BMI patterns with QoL (measured by the SF-36 questionnaire).

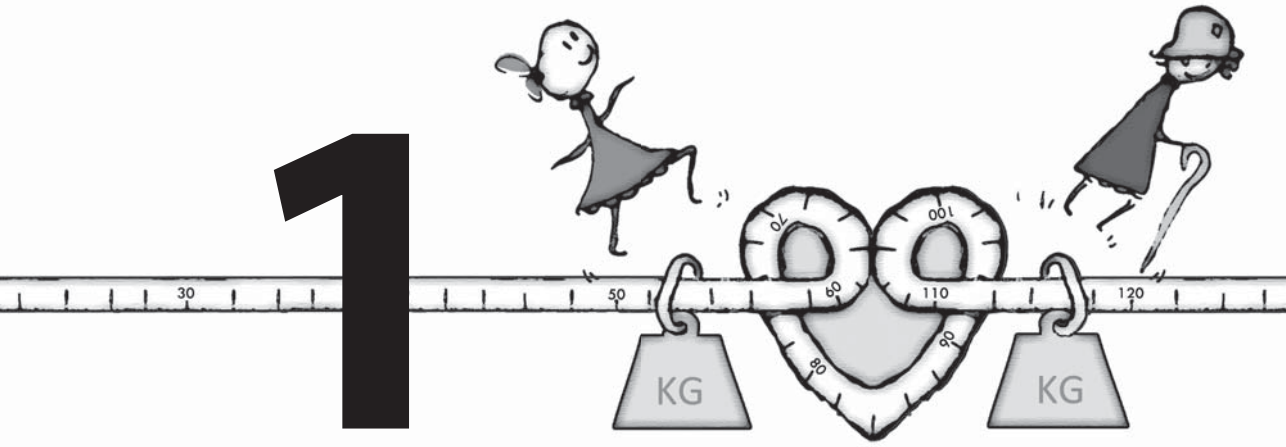
Results: After simultaneous inclusion of calendar period and age of the population in the model, the meta-regression analysis showed no difference in the RR of CHD in the association with a high BMI between calendar periods. However, a 10-year increment in population age lowered the 1.28 [95%confidence interval (CI): 1.22–1.34] RR of CHD for a five-BMI-unit increment by 29% (95%CI: -55 to -5). Among the elderly, BMI was associated with all-cause mortality, cardiovascular disease (CVD) mortality, and mortality due to causes other than CVD, cancer, and respiratory diseases ($p<0.05$). A BMI below 24 kg/m^2 and above 30 kg/m^2 were the thresholds at which risks of cause-specific mortality were increased by 10%. WC was associated with all-cause, CVD, cancer, and respiratory disease mortality ($p<0.05$). At the levels for abdominal obesity (102 cm, men; 88 cm, women), the risk of all-cause and CVD mortality

was not significantly increased, or only modestly. A risk of 2.0 (clinically relevant) for all-cause and CVD mortality was associated with a WC of 132 and 123 cm in men, and 116 and 105 cm in women, respectively. By using a combination of WC and BMI categories with the combination of a small WC (94 cm, men; 80 cm, women) and a healthy weight (20.0–24.9 kg/m^2) as the reference, we observed the highest all-cause and CVD mortality risk of approximately 2.0 for underweight (<20.0 kg/m^2; in combination with a small WC), and abdominal obesity within healthy ranges of BMI. Changes in BMI and WC were not associated with all-cause and CVD mortality, except for a decrease in WC ≥3.1 cm in the association with all-cause mortality (1.52, 95%CI: 1.01–2.31). Similarly, a decrease in weight ≥3.2 kg was associated with a 1.48 (95%CI: 0.99–2.20) increased all-cause mortality risk. Moreover, both a decrease and an increase in mid-upper arm circumference (MUAC) were associated with all-cause mortality and CVD mortality. A decrease of ≥1.6 cm and 0.6–1.6 cm in MUAC was associated with a 1.81 (95%CI: 1.17–2.79) and a 1.66 (95%CI: 1.10–2.49) all-cause mortality risk. An increase of ≥1.3 cm in MUAC was associated with a 1.52 (95%CI: 1.00–2.31) all-cause mortality risk and a 1.94 (95%CI: 1.00–3.75) CVD mortality risk. In an ageing population, we found that weight gain, especially weight gain of >6 kg, resulted in a decline in QoL. Weight loss (>2 kg) did not result in large changes in QoL. However, both weight gain and weight loss were adversely associated with changes in QoL as compared to a stable weight (changes ≤2 kg). From examination of long-term BMI patterns, the lowest QoL was observed for the 'persistent obesity (≥30 kg/m^2)' pattern. The BMI patterns, 'persistent obesity', 'developing overweight (25.0–29.9 kg/m^2)', 'developing obesity', and 'switching between BMI categories' scored 1.8–11.6 points ($p<0.05$) lower on QoL than the 'persistent healthy weight (18.5–24.9 kg/m^2)' pattern. The BMI pattern 'persistent overweight' generally did not differ from the 'persistent healthy weight' pattern. These findings were consistent among age groups.

Conclusions: Although the risk of CHD in the association with BMI attenuated with increasing age, we found associations of BMI and WC with all-cause and cause-specific mortality among the elderly. These anthropometric measures can be used as single predictors of mortality for the elderly, but higher cut-off points for BMI and WC to indicate underweight and excess fat should be considered. Moreover, a combination of these two anthropometric measures can be recommended, as that would provide more information of the body composition than one anthropometric alone. With regard to assessing changes in body composition, MUAC might be recommended for the elderly. Furthermore, a stable weight is best for health maintenance among all ages, provided this stable weight does not fall within the extreme values of weight, i.e. too light or too heavy. In all, our results underscore the value of anthropometric measures in the management of weight and the importance of the maintenance of a stable weight during ageing.

CONTENTS

1



General introduction

Ageing

Along with the decrease in mortality rates, the life expectancy in developed countries has steadily increased over the past two centuries.[1] Over the last decades in particular, the cardiovascular disease (CVD) mortality rates strongly decreased,[2-4] possibly because of early diagnosis, more effective (surgical) treatment, improved risk reduction by pharmaceutical treatment, and preventive measures with regard to lifestyle.[2,5,6] This development, together with low fertility, has resulted in ageing of the population[1] as illustrated by the 4% increase in the proportion of persons aged 65 years and older in Europe between 1999 and 2009.[7]

Although in the elderly population the prevalence of CVD, cancer, diabetes, and osteoporosis has increased over time, the life expectancy of the elderly with morbidity and comorbidity has concurrently increased because of improved healthcare and early diagnosis.[1,8] These processes, i.e. the ageing of the population and the increase in the prevalence of chronic diseases, are expected to proceed even further.[2,8,9] Therefore, it is important to examine factors that may facilitate healthy ageing. Weight status is one of those factors, as both overweight and underweight are associated with adverse health outcomes.[10-13]

Anthropometric measures

Anthropometric measures, such as body weight, body mass index (BMI, kg/m^2), and waist circumference (WC, cm) are used to assess weight status in order to predict health risks. BMI is often used in clinical practice and reflects total body weight in relation to height. Individuals can be classified according to their weight and height into underweight, normal (or 'healthy') weight, overweight, and obese (Table 1.1). This classification has been adopted in the World Health Organization (WHO) guidelines since 1995 and is based on the association of BMI with mortality.[14] WC classifications have been proposed by Lean and colleagues.[15] including two action levels: 1) prevent further weight gain and 2) lose weight (also known as 'abdominal obesity') (Table 1.1). The WHO has adopted both classifications of BMI and WC in their guidelines.[16,17]

Table 1.1 Classification of BMI and WC according to the WHO guidelines

BMI	Men and women	WC	Men	Women
Underweight	<18.5 kg/m^2			
Normal weight	18.5–24.9 kg/m^2	Small waist	<94 cm	<80 cm
Overweight	25.0–29.9 kg/m^2	Action level 1	94–101 cm	80–87 cm
Obesity	≥30.0 kg/m^2	Action level 2	≥102 cm	≥88 cm

WC reflects abdominal fat mass, which has a high correlation with visceral fat,[18] and is less influenced by muscle and bone mass. Other measures of abdominal fat are waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR), of which the cut-off points to indicate an increased health risk are a WHR of ≥0.90 in men and ≥0.85 in women[17] and a WHtR of >0.5 for both sexes.[19]

Other anthropometric measures are the triceps skinfold thickness (TSF, mm), mid-upper arm circumference (MUAC, cm), and corrected arm muscle area (CAMA, cm^2). These are generally used to assess nutritional status, mainly with regard to under-nutrition and thus underweight. TSF reflects the subcutaneous fat mass, and MUAC reflects bone, muscle, and subcutaneous fat mass. With these measures, the muscle mass of the arm, CAMA, can be calculated; this is important as a loss of muscle mass is a strong indicator of prevalent diseases. For these measures, the cut-off points that indicate increased risks are below 1–2 mm for TSF, 24 cm for MUAC, and 10 cm^2 for CAMA.[14]

Impact of weight status on health

The prevalence of overweight and (abdominal) obesity has increased worldwide since 1980 across all ages.[10,20-22] Overweight and (abdominal) obesity are associated with cardiovascular diseases, an increased mortality risk, and lower quality of life (QoL).[10,17,20-25] The prevalence of underweight in adults 20 years and older is low in the Netherlands, as well as in many other developed countries, and seems to be stable around 2–3% since 1980.[26,27] However, the prevalence of underweight is higher in Dutch elderly individuals in e.g. hospitals (10%) and nursing homes (15%) and in elderly individuals living at home (8%).[28] Underweight (measured by BMI), a low MUAC, TSF, and CAMA are associated with a lower QoL, more pain, and increased mortality risks, especially in older ages.[29-35] Thus, both overweight and underweight are associated with adverse health outcomes, including mortality.

In adults, the association between BMI and (cause-specific) mortality and between WC and (cause-specific) mortality is clear, i.e. high levels of BMI (>25 kg/m^2) and high levels of WC (>102 cm, men; >88 cm, women) are associated with increased (cause-specific) mortality risks.[11,36-42] However, in elderly individuals, the impact of a high BMI and a high WC on the risk of mortality is not consistent.[11,41,43-46] With regard to BMI, several studies concluded that overweight (25–29.9 kg/m^2) among the elderly (≥65 years) was not associated with (cause-specific) mortality and that obesity (≥30 kg/m^2) only modestly increased the risk of mortality, or that the risk started to increase significantly from 31–32 kg/m^2 and over.[43,44] However, a pooled analysis of 57 prospective studies did find an increased (cause-specific)

mortality risk in persons above the age of 70 years with a BMI of 25–50 kg/m^2.[11] With regard to WC, a few studies showed no association or even an inverse association with either all-cause or CVD mortality,[45,46] whereas another study showed a positive association with CVD mortality.[41] Thus, the associations between BMI and mortality and WC and mortality in elderly individuals seem unclear.

There might be different reasons for this. Firstly, the body composition changes with ageing: i.e. elderly individuals have a higher total fat mass (because of an age-dependent loss of lean body mass) than young adults; elderly individuals have more visceral fat than young adults for a given WC, as fat redistributes to the more central region; subcutaneous fat on the extremities transforms to visceral and ectopic fat; and elderly individuals shrink in height, causing an increase in their BMI, while body weight stays the same.[18,47-49] Therefore, the weight status of elderly individuals might relate differently to health than the weight status of young adults. Secondly, during the life course, individuals who are susceptible to the adverse effects of obesity have probably died before reaching old age. This is the so-called survival effect.[47] Thirdly, if obesity is developed at an old age, the remaining life span is relatively short to expose its adverse effects on health.[47] Finally, when elderly individuals fall ill, overweight might provide a metabolic buffer as previously reported in older people with chronic conditions.[50] Because of these factors, the applicability of the currently used cut-off points of BMI with regard to both overweight and underweight and the cut-off point of WC with regard to abdominal obesity (Table 1.1) in the elderly are under discussion.[51,52] Further exploration of the applicability of these cut-off points in elderly individuals is needed and is highly relevant for clinicians and public health.

So far, only a few studies have examined the impact of BMI and WC on the association with mortality in elderly populations separately and jointly. These studies reported stronger associations for WC with mortality when analysed jointly with BMI than when WC was analysed separately.[53,54] In the model with WC and BMI, BMI had even an inverse association with mortality.[53,54] Thus, the roles of WC and BMI in association with mortality seem different. Because the interpretation of WC and BMI as a continuous variable are –as yet– difficult to translate to practical use, further research including combinations of the currently used WC and BMI categories is needed as these have not been rigorously examined among the elderly.[45,54]

Changes in weight status and health

Besides insight into initial weight status and health among the elderly, it is important to consider weight history over a longer period and assess the potential impact of changes in body weight. Several studies have examined changes in weight in the association with mortality and QoL.[55-58]

Weight loss over a short as well as over a long period is known to be associated with an increased mortality risk.[57-62] For weight gain, the association with mortality is less consistent. In adults, weight gain over a long period (11–41 years) was associated with an increased mortality risk.[59-61] In elderly individuals, weight gain, often assessed over a relatively short period (e.g. 3–6 years), seemed not to be associated with mortality,[57,58] although in persons with overweight or obesity and in particular in the longer term, an increased mortality risk was evident.[62] However, little is known about changes in different anthropometric measures with respect to mortality; this is of importance since in elderly individuals changes in body weight can depend on several factors, e.g. changes in body fluid by oedema, dehydration, or changes in fat mass, or muscle mass. Therefore, more research is needed on mortality and changes measured with different anthropometric measures within one elderly population.

For QoL, many studies have examined the cross-sectional association with weight status and showed consistent results.[63] From intervention studies we know that weight loss is beneficial for QoL in obese adults.[63] However, an important aspect for healthy ageing is the impact of overweight and obesity determined in the longer term. Longitudinal studies on both young and older adults have observed negative associations between their weight gain and QoL compared to persons with a stable weight, whereas for weight loss the results were inconsistent.[55,56,64-66] However, these longitudinal studies failed to examine the associations in the longer term, in men and women separately, or on all aspects of QoL, and/or used self-reported weight, or used only two measurements to define changes in weight over time.[55,56,64-66] Thus, to gain more insight into long-term changes in weight over individuals' life course, further research is needed in a general population with repeated measurements of weight, carried out by trained personnel over a longer period of time.

Objective

The focus of this PhD research is to examine the impact of weight status, using several anthropometric measures, on coronary heart disease (CHD), mortality, and QoL in old age and during ageing.

Methodology and outline of the thesis

To examine the objective of this thesis, data were used from longitudinal cohort studies, including populations from the United States, Australia, Europe, and specifically from the Netherlands. Data on demography, lifestyle, and QoL were obtained by questionnaires or interviews. Anthropometric measurements were in almost all cohort studies measured by trained personnel and were repeated over time. Furthermore, data were available on diseases, date of death, and cause of death. The general descriptives of these studies are presented per chapter in Table 1.2.

Chapter 2 describes the relative risk of CHD in association with BMI, and whether this relative risk is different between studies that started before or in 1985 and after 1985. In addition, this chapter describes how age of the population and follow-up period influences this relative risk. This was examined by means of a meta-regression analysis including international cohort studies.

Chapter 3 describes the association between BMI and cause-specific mortality in an elderly European population, and **Chapter 4** describes the association between WC and cause-specific mortality (taking account of BMI) in an elderly Western population by means of a meta-analysis including international cohort studies. Furthermore, both chapters explore the cut-off points of BMI and WC classifications for use in elderly populations.

Chapter 5 describes the association of changes in eight different anthropometric measures and mortality due to all-causes and due to cardiovascular diseases in an elderly European population and explores which measure might be applicable for the detection of body compositional changes in old age.

In **Chapters 6 and 7**, data from an adult population are used to examine the longitudinal association between changes in weight and changes in QoL, and the association between long-term BMI patterns (i.e. persistent healthy weight (reference pattern), developing overweight, persistent overweight, developing obesity, persistent obesity, and switching between BMI categories) and QoL.

Chapter 8 discusses the main findings and concludes with the implications for public health and clinical practice.

Table 1.2 Study information per chapter

Ch.	Study	Year(s) of assessment	Number of participants	Age at baseline	Exposure	Measured/ Self-reported	Follow-up period	Outcomes	Number of cases
2	Meta-analysis ($n_{cohort\ studies}$=31)	1957–1996	389,212	20–94 years	BMI (kg/m^2)	M (n=27) S (n=4)	1–35 years	Incidence of or mortality from CHD	8–3,503
3	SENECA study	1988–1989	1,970	70–77 years	BMI (kg/m^2)	M	10 years	Mortality due to All-causes CVD Cancer Respiratory disease Other causes	 751 296 172 41 64
4	Meta-analysis ($n_{cohort\ studies}$=29)	1979–2007	58,609 52,639 50,845 36,267	65–74 years	WC (cm), BMI (kg/m^2)	M (n=27) S (n=2)	4–7 years	Mortality due to All-causes CVD Cancer Respiratory disease	 4,798 1,550 1,643 216
5	SENECA study	1988–1989 1993	1,061	70–77 years	Change in weight (kg), BMI (kg/m^2), WC (cm), WHR, WHtR, MUAC (cm), TSF (mm), CAMA (cm^2)	M	6 years	All-cause mortality CVD mortality	274 103
6	DCS	1995–1999 2000–2004 2005–2009	4,135	26–70 years	Change in weight (kg)	M	10 years	Change in quality of life	n.a.
7	DCS	1989–1994 1995–1999 2000–2004 2005–2009	3,408	20–66 years	BMI pattern	M	15 years	Quality of life	n.a.

Abbreviations: BMI: body mass index, CAMA: corrected arm muscle area, CHD: coronary heart disease, CVD: cardiovascular diseases, DCS: Doetinchem Cohort Study, MUAC: mid-upper arm circumference, n.a.: not applicable, SENECA: Survey in Europe on Nutrition and the Elderly: a concerted action, TSF: triceps skin fold, WC: waist circumference, WHR: waist-to-hip ratio, WHtR: waist-to-height ratio.

References

1. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. *Lancet*. 2009;374(9696):1196–1208.
2. van Duin C, de Jong G, Stoeldraaijer L, Garssen J. Bevolkingsprognose 2010–2060: model en veronderstellingen betreffende sterfte. *CBS Bevolkingstrends: Statistisch kwartaalblad over de demografie van Nederland*. 2011;59(2e kwartaal):28–41.
3. Uemura K, Pisa Z. Trends in cardiovascular disease mortality in industrialized countries since 1950. *World Health Stat Q*. 1988;41(3–4):155–178.
4. O'Flaherty M, Allender S, Taylor R, Stevenson C, Peeters A, Capewell S. The decline in coronary heart disease mortality is slowing in young adults (Australia 1976–2006): a time trend analysis. *Int J Cardiol*.2012;158(2):193–198.
5. Tunstall-Pedoe H, Vanuzzo D, Hobbs M, Mahonen M, Cepaitis Z, Kuulasmaa K, et al. Estimation of contribution of changes in coronary care to improving survival, event rates, and coronary heart disease mortality across the WHO MONICA Project populations. *Lancet*. 2000;355(9205):688–700.
6. *The world health report 2002: Reducing risks, promoting healthy life*. Geneva: World Health Organization, 2002.
7. *Europe in figures. Eurostat yearbook 2010*. Luxembourg: European Union, 2010.
8. van der Lucht F, Polder JJ. *Van gezond naar beter: Kernrapport Volksgezondheid Toekomst Verkenning 2010*.Bilthoven: RijksInstituut voor Volksgezondheid en Milieu, 2010.
9. Oeppen J, Vaupel JW. Demography. Broken limits to life expectancy. *Science*. 2002;296(5570):1029–1031.
10. Branca F, Nikogosian H, Lobstein T. *The challenge of obesity in the WHO European Region and the strategies for response*.Denmark: World Health Organization, 2007.
11. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373(9669):1083–1096.
12. Yan LL, Daviglus ML, Liu K, Pirzada A, Garside DB, Schiffer L, et al. BMI and health-related quality of life in adults 65 years and older. *Obes Res*. 2004;12(1):69–76.
13. Lean ME, Han TS, Seidell JC. Impairment of health and quality of life using new US federal guidelines for the identification of obesity. *Arch Intern Med*. 1999;159(8):837–843.
14. *Physical status: the use and interpretation of anthropometry*. Geneva: World Health Organization, 1995.
15. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. *Bmj*. 15 1995;311(6998):158–161.
16. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults--The evidence report. National Institutes of Health. *Obes Res* Sep 1998;6 Suppl 2:51S–209S.

17. *Waist circumference and waist–hip ratio: Report of a WHO expert consultation, Geneva, 8–11 December 2008.* Geneva: World Health Organization, 2011.

18. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres JP. A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. *Am J Clin Nutr.* 1996;64(5):685–693.

19. Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0.5 could be a suitable global boundary value. *Nutr Res Rev.* 2010;23(2):247–269.

20. Eiben G, Dey DK, Rothenberg E, Steen B, Bjorkelund C, Bengtsson C, et al. Obesity in 70-year-old Swedes: secular changes over 30 years. *Int J Obes (Lond).* 2005;29(7):810–817.

21. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet.*2011;377(9765):557–567.

22. Janssen I, Shields M, Craig CL, Tremblay MS. Prevalence and secular changes in abdominal obesity in Canadian adolescents and adults, 1981 to 2007–2009. *Obes Rev.* 2011;12(6):397–405.

23. Petursson H, Sigurdsson JA, Bengtsson C, Nilsen TI, Getz L. Body configuration as a predictor of mortality: comparison of five anthropometric measures in a 12 year follow-up of the Norwegian HUNT 2 study. *PLoS One.* 2011;6(10):e26621.

24. Han TS, Tijhuis MA, Lean ME, Seidell JC. Quality of life in relation to overweight and body fat distribution. *Am J Public Health.* 1998;88(12):1814–1820.

25. Blokstra A, Vissink P, Venmans LMAJ, Holleman P, van der Schouw YT, Smit HA, et al. *Nederland de Maat Genomen, 2009–2010, Monitoring van risicofactoren in de algemene bevolking.*Rijksinstituut voor Volksgezondheid en Milieu (RIVM): Bilthoven, 2011.

26. CBS. Lengte en gewicht van personen, ondergewicht en overgewicht vanaf 1981. 2012; http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=81565NED&D1=a&D2=0&D3=5-12&D4=0&D5=0,10,20,30&HDR=T&STB=G1,G2,G3,G4&VW=T, Accessed 24/03/2013.

27. WHO. Global database on body mass index. http://apps.who.int/bmi/index.jsp. Accessed 24/03/2013.

28. Gezondheidsraad. *Ondervoeding bij ouderen.* Den Haag: Gezondheidsraad, 2011; publicatienr. 2011/32.

29. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. *Jama.* 2005;293(15):1861–1867.

30. Renzaho A, Wooden M, Houng B. Associations between body mass index and health-related quality of life among Australian adults. *Qual Life Res.* 2010;19(4):515–520.

31. Heim N, Snijder MB, Deeg DJ, Seidell JC, Visser M. Obesity in older adults is associated with an increased prevalence and incidence of pain. *Obesity (Silver Spring).* 2008;16(11):2510–2517.

32. Wijnhoven HA, van Bokhorst-de van der Schueren MA, Heymans MW, de Vet HC, Kruizenga HM, Twisk JW, et al. Low mid-upper arm circumference, calf circumference, and body mass index and mortality in older persons. *J Gerontol A Biol Sci Med Sci.* 2010;65(10):1107–1114.

33. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Decreased muscle mass and increased central adiposity are independently related to mortality in older men. *Am J Clin Nutr.* 2007;86(5):1339–1346.

34. Miller MD, Crotty M, Giles LC, Bannerman E, Whitehead C, Cobiac L, et al. Corrected arm muscle area: an independent predictor of long-term mortality in community-dwelling older adults? *J Am Geriatr Soc.* 2002;50(7):1272–1277.

35. Enoki H, Kuzuya M, Masuda Y, Hirakawa Y, Iwata M, Hasegawa J, et al. Anthropometric measurements of mid-upper arm as a mortality predictor for community-dwelling Japanese elderly: the Nagoya Longitudinal Study of Frail Elderly (NLS-FE). *Clin Nutr.* 2007;26(5):597–604.

36. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med.* 2008;359(20):2105–2120.

37. Arnlov J, Ingelsson E, Sundstrom J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation.* 2010;121(2):230–236.

38. van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB. Combined impact of lifestyle factors on mortality: prospective cohort study in US women. *Bmj.* 2008;337:a1440.

39. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med.* 2003;348(17):1625–1638.

40. Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women. *Circulation.* 2008;117(13):1658–1667.

41. Baik I, Ascherio A, Rimm EB, Giovannucci E, Spiegelman D, Stampfer MJ, et al. Adiposity and mortality in men. *Am J Epidemiol.* 2000;152(3):264–271.

42. Simpson JA, MacInnis RJ, Peeters A, Hopper JL, Giles GG, English DR. A comparison of adiposity measures as predictors of all-cause mortality: the Melbourne Collaborative Cohort Study. *Obesity (Silver Spring).* 2007;15(4):994–1003.

43. Heiat A, Vaccarino V, Krumholz HM. An evidence-based assessment of federal guidelines for overweight and obesity as they apply to elderly persons. *Arch Intern Med.* 2001;161(9):1194–1203.

44. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. *Obes Rev.* 2007;8(1):41–59.

45. Price GM, Uauy R, Breeze E, Bulpitt CJ, Fletcher AE. Weight, shape, and mortality risk in older persons: elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. *Am J Clin Nutr.* 2006;84(2):449–460.

46. Reis JP, Macera CA, Araneta MR, Lindsay SP, Marshall SJ, Wingard DL. Comparison of overall obesity and body fat distribution in predicting risk of mortality. *Obesity (Silver Spring).* 2009;17(6):1232–1239.

47. Zamboni M, Mazzali G, Zoico E, Harris TB, Meigs JB, Di Francesco V, et al. Health consequences of obesity in the elderly: a review of four unresolved questions. *Int J Obes (Lond).* 2005;29(9):1011–1029.

48. Hughes VA, Roubenoff R, Wood M, Frontera WR, Evans WJ, Fiatarone Singh MA. Anthropometric assessment of 10-y changes in body composition in the elderly. *Am J Clin Nutr.* 2004;80(2):475–482.

49. Cartwright MJ, Tchkonia T, Kirkland JL. Aging in adipocytes: potential impact of inherent, depot-specific mechanisms. *Exp Gerontol.* 2007;42(6):463–471.

50. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet.* 2006;368(9536):666–678.

51. Flicker L, McCaul KA, Hankey GJ, Jamrozik K, Brown WJ, Byles JE, et al. Body mass index and survival in men and women aged 70 to 75. *J Am Geriatr Soc.* 2010;58(2):234–241.

52. Heim N, Snijder MB, Heymans MW, Deeg DJ, Seidell JC, Visser M. Optimal cutoff values for high-risk waist circumference in older adults based on related health outcomes. *Am J Epidemiol.* 2011;174(4):479–489.

53. Guallar-Castillon P, Balboa-Castillo T, Lopez-Garcia E, Leon-Munoz LM, Gutierrez-Fisac JL, Banegas JR, et al. BMI, waist circumference, and mortality according to health status in the older adult population of Spain. *Obesity (Silver Spring).* 2009;17(12):2232–2238.

54. Janssen I, Katzmarzyk PT, Ross R. Body mass index is inversely related to mortality in older people after adjustment for waist circumference. *J Am Geriatr Soc.* 2005;53(12):2112–2118.

55. Fine JT, Colditz GA, Coakley EH, Moseley G, Manson JE, Willett WC, et al. A prospective study of weight change and health-related quality of life in women. *Jama.* 1999;282(22):2136–2142.

56. Leon-Munoz LM, Guallar-Castillon P, Banegas JR, Gutierrez-Fisac JL, Lopez-Garcia E, Jimenez FJ, et al. Changes in body weight and health-related quality-of-life in the older adult population. *Int J Obes (Lond).* 2005;29(11):1385–1391.

57. Lee CG, Boyko EJ, Nielson CM, Stefanick ML, Bauer DC, Hoffman AR, et al. Mortality risk in older men associated with changes in weight, lean mass, and fat mass. *J Am Geriatr Soc.* 2011;59(2):233–240.

58. Newman AB, Yanez D, Harris T, Duxbury A, Enright PL, Fried LP. Weight change in old age and its association with mortality. *J Am Geriatr Soc.* 2001;49(10):1309–1318.

59. Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. *N Engl J Med.* 2004;351(26):2694–2703.

60. Lee IM, Paffenbarger RS, Jr. Change in body weight and longevity. *Jama.* 1992;268(15):2045–2049.

61. Breeze E, Clarke R, Shipley MJ, Marmot MG, Fletcher AE. Cause-specific mortality in old age in relation to body mass index in middle age and in old age: follow-up of the Whitehall cohort of male civil servants. *Int J Epidemiol.* 2006;35(1):169–178.

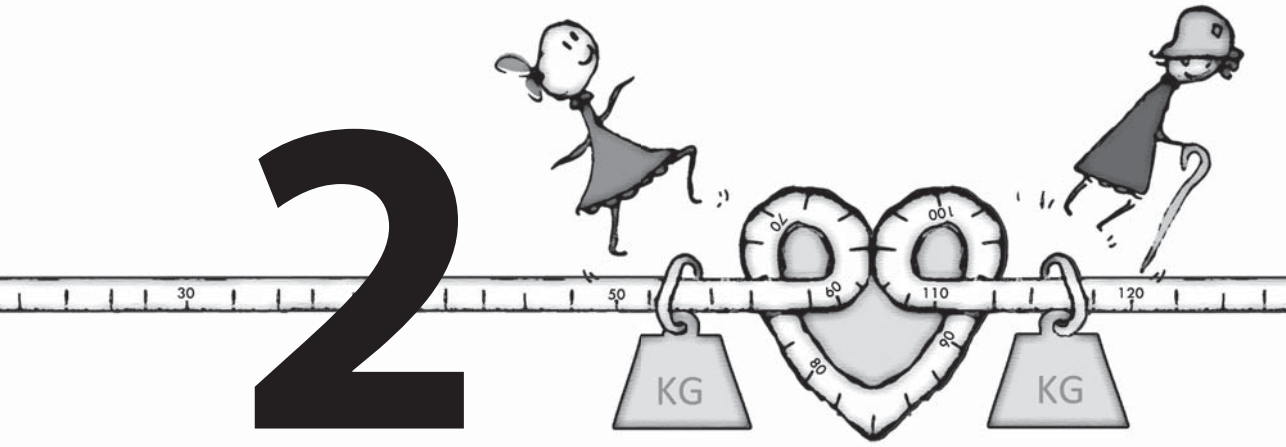
62. Bamia C, Halkjaer J, Lagiou P, Trichopoulos D, Tjonneland A, Berentzen TL, et al. Weight change in later life and risk of death amongst the elderly: the European Prospective Investigation into Cancer and Nutrition-Elderly Network on Ageing and Health study. *J Intern Med.* 2010;268(2):133–144.

63. Fontaine KR, Barofsky I. Obesity and health-related quality of life. *Obes Rev.* 2001;2(3):173–182.

64. Burns CM, Tijhuis MA, Seidell JC. The relationship between quality of life and perceived body weight and dieting history in Dutch men and women. *Int J Obes Relat Metab Disord.* 2001;25(9):1386–1392.

65. Kozak AT, Daviglus ML, Chan C, Kiefe CI, Jacobs DR, Jr., Liu K. Relationship of body mass index in young adulthood and health-related quality of life two decades later: the Coronary Artery Risk Development in Young Adults study. *Int J Obes (Lond).* 2011;35(1):134–141.

66. Verkleij SP, Adriaanse MC, Wendel-Vos GC, Schuit AJ. Longitudinal relation between weight change and quality of life in a community-based population: a prospective cohort study. *Eur J Public Health.* 2013;23(2):285–290.



2

Influence of calendar period on the association between BMI and coronary heart disease: a meta-analysis of 31 cohorts

Ellen L de Hollander, Rik P Bogers, Hendriek C Boshuizen, Annika Rosengren, Martin J Shipley, Paul Knekt, Pierre Ducimetière, Alessandro Menotti, Lisette CPGM de Groot, Wanda JE Bemelmans, for the BMI-CHD collaboration investigators

Obesity (Silver Spring). 2013;21(5):865–880.

Abstract

Objectives: The association between obesity and coronary heart disease (CHD) may have changed over time, for example due to improved pharmacological treatment of CHD risk factors. This meta-analysis of 31 prospective cohort studies explores the influence of calendar period on CHD risk associated with body mass index (BMI).

Design and Methods: The relative risks (RRs) of CHD for a five-BMI-unit increment and BMI categories were pooled by means of random effects models. Meta-regression analysis was used to examine the influence of calendar period (>1985 v ≤1985) in univariate and multivariate analyses (including mean population age as a covariate).

Results: The age, sex and smoking adjusted RR [95% confidence intervals (CI)] of CHD for a five-BMI-unit increment was 1.28 (95%CI: 1.22–1.34). For underweight, overweight and obesity, the RRs (compared to normal weight) were 1.11 (95%CI: 0.91–1.36), 1.31 (95%CI: 1.22–1.41) and 1.78 (95%CI: 1.55–2.04), respectively. The univariate analysis indicated a 31% (95%CI: -56 to 0%) lower RR of CHD associated with a five-BMI-unit increment and a 51% (95%CI: -78 to -14%)) lower RR associated with obesity in studies starting after 1985 (n=15 and n=10, respectively) compared to studies starting in or before 1985 (n=16 and n=10). However, in the multivariate analysis, only mean population age was independently associated with the RRs for a five-BMI-unit increment and obesity [-29% (95%CI: -55 to -5%) and -31% (95%CI: -66 to 3%), respectively] per 10-year increment in mean age).

Conclusion: This study provides no consistent evidence for a difference in the association between BMI and CHD by calendar period. The mean population age seems to be the most important factor that modifies the association between the risk of CHD and BMI, in which the RR decreases with increasing age.

Introduction

The prevalence of both overweight and obesity has increased worldwide over the past decades, especially after the 1980s in Europe and the USA.[1-3] This is a major concern because obesity is associated with increased mortality, disability, decreased quality of life, high health care costs, and morbidity including coronary heart disease (CHD).[1,4]

Despite the rise in the prevalence of obesity, CHD mortality rates have declined since the 1960s–1970s in Western Europe, Australia and the USA.[5,6] This decline can be explained by major improvements in coronary treatments and CHD management since the mid 1980s and by changes in risk factors – even in overweight and obese persons – such as a decrease in the prevalence of smoking, and in blood pressure and cholesterol levels.[7-10] Additional in this period, the lifestyle approach was advocated within healthcare procedures to combat CHD.[11,12] Because of all these developments, we expected that the risk of incidence and mortality of CHD associated with being overweight or obese has decreased over time.

The impact of time on CHD risk associated with obesity in adults has not been examined in a large meta-analysis before. Knowledge of time-dependent shifts in CHD risk associated with obesity not only provides indirect 'evidence' for improved health care procedures in the obese, but is also important for forecasting future deaths from chronic diseases, as presented in leading publications.[13,14] This in turn is fundamental for underpinning the needs for policies on obesity and CVD management.

The present meta-analysis, including 31 prospective cohort studies from various countries, comprising 389,212 persons, examined the influence of calendar period (the year in which the study started) on the association between BMI and CHD, adjusted for age, sex and smoking. The analysis took additional study characteristics (i.e. mean age of the population and length of follow-up) into account that have been proposed to influence the association between body weight and CHD.[15,16] To test for the impact of changes in risk factors over time (induced by treatment developments), we additionally examined the influence of calendar period on the association between BMI and CHD in a subset of 21 cohort studies with additional adjustments for physical activity, blood pressure and cholesterol. We expected that the influence of calendar period would be attenuated by adjusting for CHD risk factors.

Methods

Data sources, study selection and data extraction were previously described in detail.[17] Briefly, studies were identified by a PubMed/Medline search until 2007 by using the following search

strategy: obesity, body mass index, BMI, or overweight in either the title or in the Medical Subject Heading (MeSH) and either coronary heart disease in the title or coronary disease in MeSH, plus either prospective or cohort. Also, we examined reference lists of identified articles, and got suggestions through colleagues. Eligible studies were prospective cohort studies conducted in healthy, mainly Caucasian populations. Seventy cohort studies were identified and 62 investigators were contacted of whom 31 agreed to participate. The 31 cohort studies had data available on BMI, age, sex and smoking and CHD incidence or mortality. Eighteen studies used mortality from CHD and 13 studies used incidence of CHD (both fatal and non-fatal events) as their endpoint. Twenty-one studies had extra data available on physical activity, blood pressure and cholesterol. The investigators from the participating cohort studies were requested to calculate hazard ratios (further on called relative risks (RR)) of CHD for BMI and their 95% confidence intervals (95%CIs) with systematic adjustments for age, sex and smoking, and if available also for physical activity, blood pressure, and cholesterol levels.

Data synthesis

In this study, we examined the influence of calendar period on the pooled RR for BMI as a continuous variable (i.e. risk per five units increase in BMI; n=31) as well as for BMI-categories (i.e. categories underweight (<18.5 kg/m^2; n=17), overweight (25.0–29.9 kg/m^2; n=20) and obesity (≥30.0 kg/m^2; n=20), as compared to the reference category (18.5–24.9 kg/m^2)). For the 10 studies which only provided RRs for BMI categories, the RRs were transformed to their continuous form for each set of adjustments by applying the method of Greenland and Longnecker,[18] using the numbers of cases as observed rather than their fitted values.[19] The adjusted RRs for BMI were plotted to visualize variation in results between studies.

Calendar period was calculated by using the baseline year of each cohort study. Recruitment and data collection at baseline took in most cohort studies more than one year. Therefore, baseline year was defined as the mean of the first year and last year in which baseline measurements were conducted. The studies were then divided into two strata to examine whether the pooled RRs differed by calendar period (≤1985 and >1985). The 1985 cut-point chosen, corresponded with the period when major changes occurred regarding the management of CHD and the increase in advocating lifestyle approaches within healthcare procedures.[7-12] Furthermore, the influence of other important study characteristics on the association between BMI and CHD, i.e. age of the population (defined as the mean age of the population at baseline) and length of follow-up (defined as the mean length in years the population was followed to their endpoint) were examined.

Statistical analysis

Descriptive statistics were used to describe the main characteristics of the cohort studies, i.e. baseline year, mean age of the population and length of follow-up.

The age, sex and smoking adjusted log RRs for BMI as a continuous and categorical variable were pooled by means of a random effects model,[20] using the MIXED procedure in SAS (version 9.1). The pooled RR and the 95% confidence interval was estimated by exponentiating the results from this model. Heterogeneity of RRs between cohort studies was tested using chi-squared tests.

To determine sensitivity of the results, meta-analyses with 30 studies (continuous BMI) and with 16 and 19 studies (BMI categories) were performed, leaving repeatedly each individual study out of the pooled risk. Further, to check for potential bias due to misclassification of BMI based on self-reported weight and height, analyses were repeated after excluding cohorts with self-reported BMI. This meant exclusion of four studies in the analysis for continuous BMI, overweight and obesity and three studies for underweight. Publication bias was investigated using a funnel plot.

To examine the influence of calendar period (>1985 v ≤1985), age of the population and length of follow-up (expressed per 10-year increment), a meta-regression analysis (including the random effects model) was used. In this meta-regression analysis, the age, sex and smoking adjusted log RR of the studies was regressed onto the study characteristics. This was done by using a univariate (i.e. calendar period, age and length of follow-up in separate models) and a multivariate analysis (i.e. calendar period and age of the population adjusted for each other). Calendar period and length of follow-up were not simultaneously entered into the model to prevent multicollinearity since baseline year and length of follow-up were highly correlated (Pearson's r=-0.86; p<0.001). Similar models were used for the categories underweight, overweight and obesity.

These analyses were then repeated in a subset of cohort studies (continuous BMI: n=21, underweight: n=12, overweight and obesity: n=14) with log RRs additionally adjusted for physical activity, blood pressure and cholesterol.

The influence of study characteristics is reported as a percentage change of the RR of CHD associated with BMI by the study characteristic term. To give insight in how the percentage change was calculated, we present the following *hypothetical* example:

Suppose the regression coefficients for the log(RR) are 0.3 for the intercept and -0.1 for the calendar period effect. In that case, the RR of studies starting before and in 1985 is $e^{0.3}$=1.35

and the RR for studies starting after 1985 is $e^{(0.3 + -0.1)}$=1.22. This gives a percentage change of ((1.22-1)-((1.35-1))/(1.35-1)x100%=-37%. To indicate whether the influence of a study characteristic was statistically significant, the accompanying 95% confidence intervals (95%CI) are presented.

Results

Characteristics of cohorts

Table 2.1 presents the characteristics of the study populations, comprising a total of 389,212 persons. During follow-up in total 20,652 CHD events were observed. Some studies provided RRs for a longer length of follow-up than in the original articles. The cohorts used for analysis regarding BMI categories are marked in Table 2.1.

Table 2.2 presents the descriptive statistics of baseline year, age of the population and length of follow-up. For the earlier studies (≤1985), age of the population was lower in comparison with the later studies (>1985). The length of follow-up was longer for the earlier studies.

Relative risks of CHD associated with BMI

For the 31 studies, the age, sex and smoking adjusted RR of CHD was increased for a five-BMI-unit increment, overweight and obesity (Table 2.3). Underweight was not associated with the risk of CHD [RR 1.11 (95%CI: 0.91–1.36)]. After adjustment for physical activity, blood pressure and cholesterol, the RRs for a five-BMI-unit increment, overweight and obesity were lower but still significant as reported previously.[17]

There was substantial heterogeneity between study results of the 31 cohorts ($p<0.001$; Figure 2.1) and between the study results for each BMI category ($p<0.05$; not shown). The sensitivity analysis indicated no strong influence by individual studies as the change in RR of CHD associated with BMI ranged maximally from -0.08 to 0.06 when single studies were excluded. Exclusion of studies that used self-reported BMI resulted in somewhat lower RRs in the remaining cohorts concerning increasing BMI, underweight, overweight and obesity [respectively, 1.26 (95%CI: 1.20–1.32); 1.09 (95%CI: 0.84–1.42); 1.26 (95%CI: 1.18–1.35); 1.66 (95%CI: 1.45–1.91)].

The funnel plot suggested that studies with higher estimates of relative risk were not overrepresented, suggesting that there was no publication bias using the 31 cohorts

Table 2.1 Characteristics of studies included in the pooled analysis

Study	% male	Age range	Baseline year(s)	Median or mean follow-up(yr)	% Current smokers	No. available for analysis	No. cases	Description of endpoint
Australian National Heart Foundation Risk Factor Prevalence Study[21cd]	49	20–70	1989–1990	8.3	24	9,099	76	death from CHD: ICD-9 codes 410–414
Busselton Health Study[22]	49	40–75	1966–1981	10	34	3,891	187	death from CHD: ICD-9 codes 410–414
Caerphilly cohort Study[23,24b]	100	47–67	1984–1988	12	44	2,160/2,357	398	fatal and non-fatal events: death from CHD; clinical non-fatal (definite acute) MI; electrocardiographic MI
Dubbo study of Australian elderly[25b]	44	60–94	1988	13	15	2,805	968	fatal and non-fatal events: hospitalisation or death ICD-9-CM codes 410–414
ECCIS study[26]	100	40–59	1989–1992	5	38	4,850	73	fatal and non-fatal events: definite MI; sudden coronary death; cases judged of coronary origin although manifested only as heart failure, arrhythmia and blocks
Finnish Mobile Clinic Health Examination Survey[27cd]	53	30–69	1967–1972	22	34	30,765	3,319	death from CHD: ICD-8 codes 410–414
Finnish Twin Cohort Study[28,29ad]	50	24–60	1981	19.7	30	15,127	155	death from CHD: ICD-8 410–414, ICD9 410–414, ICD10 I21–25
Fletcher Challenge[30cd]	72	20–89	1992	4.8	24	10,201	110	death from CHD
Gubbio Population Study[31]	45	35–74	1983–1985	6	35	2,963	126	fatal and non-fatal events: definite MI; sudden coronary death; cases judged of coronary origin although manifested only as heart failure, arrhythmia and blocks
Iowa Women's Health Study[32acd]	0	55–69	1986	15.8	15	32,011/30,741	1,121	death from CHD
Italian Rural Areas[33b]	100	40–59	1960	35	61	1,622	214	death from CHD: definite fatal MI; other forms of fatal ischemia; sudden death from CHD

Table 2.1 continues on next page

Table 2.1 *Continued*

Study	% male	Age range	Baseline year(s)	Median or mean follow-up(yr)	% Current smokers	No. available for analysis	No. cases	Description of endpoint
Kuopio Ischaemic Heart Disease Risk Factor Study[34d] (KIHD)	100	42–61	1984–1989	10.6	31	1,597	155	fatal and non-fatal events: definite and probable acute MI; prolonged chest pain episodes
Malmö Preventive Project[35d] (MPP)	100	27–61	1974–1984	17.7	49	22,025	1,727	fatal and non-fatal events: acute MI (ICD code 410); death from chronic CHD (ICD codes 412 and 414)
Manresa Catalonia study[36]	100	30–59	1968	18.5	67	1,059	135	fatal and non-fatal events: fatal MI; other death, sudden or non-sudden, presumed due to CHD (ICDA 410–413, 795, 427.0, 427.2 and 427.9); non-fatal MI
Melbourne Collaborative Cohort Study[37cd]	41	27–75	1990–1994	5.6	11	41,119	323	death from CHD
Multifactor Primary Prevention Study[38cd] (MPPS) Göteborg	100	47–55	1970–1973	22.0	50	7,371	1,688	fatal and non-fatal events: death from CHD (ICD-8/9 codes 410–414); non-fatal MI
NHANES I Epidemiologic Follow-up Study[39cd](NHEFS)	44	25–74	1971–1975	20	45	5,139/5,078	543	death from CHD: ICD-9 codes 410–414.9
Nijmegen Cohort Study[40cd]	48	20–52	1977–1978	18	58	5,898	268	fatal and non-fatal events: MI; angina pectoris
Norwegian Counties Study[41cd]	51	35–49	1974–1978	26	45	43,896	1,564	death from CHD: ICD-8/9 codes 410–414, ICD-10 codes I21–25; sudden deaths (ICD-8 codes: 782.4, 795; ICD-9 codes: 798.1–798.2; ICD-10 codes: R96)
Nurses' Health Study[42acd]	0	34–59	1980	20	28	76,615	1,996	fatal and non-fatal events: death from CHD; nonfatal MI; sudden death within 1 h of onset of symptoms in women with no other plausible cause other than CHD

Perth Cohort[43,44cd]	52	20–90	1979–1994	14.4	25	9,727	187	death from CHD
PRIME study[45b]	100	50–59	1991–1993	5	28	9,757	317	fatal and non-fatal events: MI; death from CHD; angina pectoris
Rome Railroad Cohort[46b]	100	40–59	1962	25	66	726	88	death from CHD: definite fatal MI; sudden death from CHD; cases judged of CHD origin although manifested only as heart failure, arrhythmia and blocks
Scottish Heart Health Study[47cd]	51	40–59	1984–1987	7.6	39	10,262	171	fatal and non-fatal events: MI; coronary artery surgery; death from CHD
SENECA[48cd]	48	70–100	1988–1989	10	18	1,196	55	death from CHD: ICD 410–414
Swedish Annual Level-of-Living Survey[49acd] (SALLS)	51	35–74	1988–1989	11.7	27	5,196	373	fatal and non-fatal events: ICD-9 410–414, ICD10 I20–I25
US Railroad cohort[46b]	100	40–59	1957–1959	25	60	2,415	481	death from CHD: definite fatal MI; sudden death from CHD; cases judged of CHD origin although manifested only as heart failure, arrhythmia and blocks
Ventimiglia di Sicilia Heart Study[50] (VHS)	43	20–69	1989	8	17	835	8	death from CHD: defined MI; sudden death
Western Australian Abdominal Aortic Aneurysm Study[51,52cd]	100	65–84	1996	1.2	11	12,194	240	death from CHD
Whitehall Study[53,54cd]	100	40–64	1967–1969	33	41	17,475	3,503	death from CHD: ICD-8 codes 410–414
Zutphen Elderly Study[55cd]	100	64–84	1985	10.3	33	575	83	death from CHD: ICD-9 codes 410–414

Abbreviations: CHD, Coronary Heart Disease: ICD, International Classification of Disease (-8, -9, -10 indicate the revision number; CM Clinical Modification); MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; PRIME, Prospective Epidemiological Study of Myocardial Infarction.

[a]Body mass index based on self-report of the participants.

[b]No results available for both the categories moderate overweight (body mass index, 25.0–29.9 [calculated as weight in kilograms divided by height in meters squared]) and obesity (body mass index, ≥30.0).

[c]Cohort used for analysis regarding underweight.

[d]Cohort used for analysis regarding overweight and obesity.

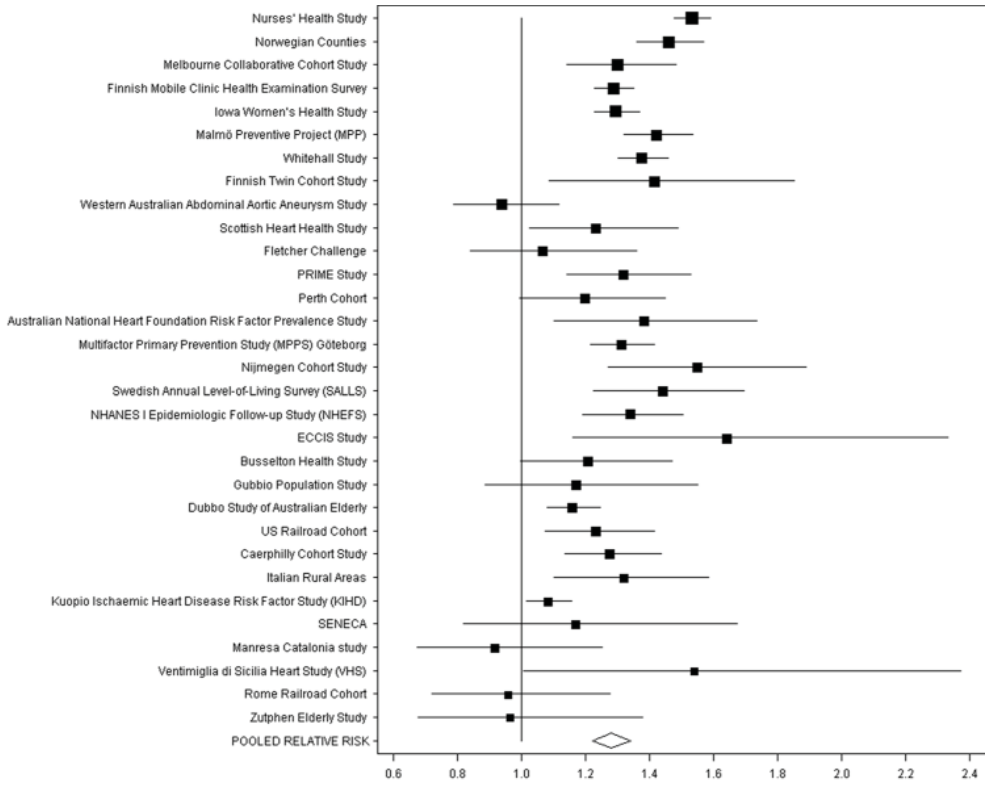


Figure 2.1 Relative risks of coronary heart disease per increment of 5 kg/m^2, adjusted for age, sex and smoking. Horizontal lines indicate 95% confidence intervals.

Table 2.2 Mean (range) study characteristics

	Baseline year	Age of population (yr)	Length of follow-up (yr)
Studies in the body mass index analyses			
All studies (n=31)[a]	1981 (1958–1996)	51.5 (35.0–73.0)	15.0 (1.2–35.0)
Studies ≤1985 (n=16)	1973 (1958–1985)*	48.1 (35.0–71.1)*	20.8 (6.0–35.0)*
Studies >1985 (n=15)	1989 (1986–1996)	55.1 (43.4–73.0)	8.9 (1.2–15.8)
Studies in the overweight and obesity analyses			
Total (N=20)[a]	1983 (1969–1996)	51.0 (35.0–73.0)	15.2 (1.2–33.0)
Studies ≤1985 (n=10)	1976 (1969–1985)*	47.1 (35.0–71.1)	21.3 (15–33.0)*
Studies >1985 (n=10)	1989 (1986–1996)	54.8 (43.4–73.0)	9.0 (1.2–15.8)

*Significant difference between calendar period strata: p<0.05.

[a] The mean study characteristics did not change substantially in the subset of studies used in the model with additional adjustments for physical activity, blood pressure and cholesterol, although the range was slightly reduced with approximately 4 years in baseline year and follow-up period.

(Appendix 1; see publication: http://onlinelibrary.wiley.com/doi/10.1002/oby.20043/abstract).

Influence of calendar period and other factors on the relative risk of CHD for BMI

The relationships between study characteristics and the RR of CHD associated with BMI as a continuous and categorical variable are graphically displayed in Appendix 2 (see publication; http://onlinelibrary.wiley.com/doi/10.1002/oby.20043/abstract).

Table 2.3 presents the percentage changes in the RR of CHD associated with BMI by calendar period, age of the population and length of follow-up for the univariate and multivariate meta-regression analyses. Because underweight was not associated with CHD, the influences of the study characteristics were not examined for this category. Table 2.4 presents the RRs of CHD associated with continuous and categorical BMI stratified by calendar period.

Relative risks adjusted for age, sex and smoking

The difference in the RR of CHD for a five-BMI-unit increment and obesity between calendar periods, that was observed in the univariate analysis [-31% (95%CI: -56 to 0%) and -51% (95%CI: -78 to -14%), respectively] (Table 2.3, 2.4), was no longer observed in the multivariate analysis (Table 2.3). However, in the multivariate analysis, age of the population still (near) significantly lowered the RR by 29% (95%CI: -55 to -5%) and 31% (95%CI: -66 to 3%) respectively for each ten-year increase in age of the population (Table 2.3). No interaction effect between calendar period and mean age was found.

Length of follow-up (only examined in the univariate analysis) had a significant influence on the RR associated with a five-BMI-unit increment [+25% (95%CI: 0 to 52%)] and with obesity [+53% (95%CI: 9 to 109%)] (Table 2.3).

We repeated these analyses in a subset of studies (n=13; n=6 ≤1985; n=7 >1985) with a length of follow-up between 10–19.9 years in order to reduce correlation between baseline year and length of follow-up (Pearson's r=-0.48; p= 0.10) and overlap in time period. In this subset, the results for calendar period and age of the population were similar (data not shown).

Also, to take both baseline year and length of follow-up into account together with age of the population, we repeated the analyses with the variables age of the population and half of the follow-up length added up to baseline year. Then, calendar period had not an

Table 2.3 Relative risks (RR) of coronary heart disease per five body mass index-unit increment, overweight and obesity and the percentage change by covariates: calendar period, age of the population and length of follow-up

BMI measure of interest	Model ($n_{studies}$)	Meta-regression analysis*	Pooled RR‡ (95%CI)	Percentage change (95%CI) in relative risks (%)†		
				Calendar period (>1985 v ≤1985)	Age of population (per 10 yr increment)	Length of follow-up (per 10 yr increment)
Continuous 5-BMI-unit increment	1 (n=31)[a]	Univariate analysis	1.28 (1.22–1.34)	-31 (-56 to 0)	-32 (-52 to -13)	25 (0 to 52)
		Multivariate analysis	-	-9 (-41 to 36)	-29 (-55 to -5)	-
	2 (n=21)	Univariate analysis	1.16 (1.11–1.21)	-36 (-78 to 15)	-44 (-90 to -4)	6 (-29 to 52)
		Multivariate analysis	-	-10 (-61 to 84)	-40 (-105 to 6)	-
Overweight	1 (n=20)[a]	Univariate analysis	1.31 (1.22–1.41)	-27 (-70 to 34)	-48 (-87 to -12)	22 (-19 to 78)
		Multivariate analysis	-	20 (-44 to 145)	-55 (-128 to -11)	-
	2 (n=14)	Univariate analysis	1.17 (1.11–1.23)	6 (-82 to 148)	-24 (-148 to 51)	-12 (-50 to 49)
		Multivariate analysis	-	21 (-87 to 260)	-30 (-220 to 52)	-
Obesity	1 (n=20)[a]	Univariate analysis	1.78 (1.55–2.04)	-51 (-78 to -14)	-43 (-72 to -13)	53 (9 to 109)
		Multivariate analysis	-	-32 (-68 to 26)	-31 (-66 to 3)	-
	2 (n=14)	Univariate analysis	1.49 (1.32–1.67)	-51 (-96 to 10)	-42 (-135 to 28)	29 (-21 to 104)
		Multivariate analysis	-	-45 (-97 to 40)	-25 (-107 to 39)	-

*Univariate analysis: calendar period, age and follow-up period in separate models; Multivariate analysis: calendar period and age adjusted for each other.

†Indicates the percentage change in RR of BMI or BMI category on CHD associated with the specified change in each study characteristic.

‡The pooled RR (intercept) changed slightly in the meta-regression analysis, but not substantially with regard to the magnitude of the RR.

Model 1: the RRs are adjusted for age, sex and smoking at baseline.

Model 2: Model 1 with additional adjustment physical activity, blood pressure and cholesterol at baseline.

[a]The results of percentage change in the age, sex and smoking adjusted RR by each study characteristic in the univariate and multivariate were in the same order when examining this in the subset of studies used in model 2.

Table 2.4 Relative risks (RR) of CHD per five BMI-unit increment, overweight and obesity stratified by calendar period (>1985 v ≤1985)

BMI measure of interest	Model ($n_{studies}$)	Pooled RR (95%CI)*	
		Calendar period ≤1985	Calendar period >1985
Continuous 5-BMI-unit increment	1 (n=31)	1.33 (1.27–1.41)	1.23 (1.16–1.31)
	2 (n=21)	1.19 (1.13–1.24)	1.12 (1.04–1.20)
Overweight	1 (n=20)	1.35 (1.23–1.48)	1.25 (1.11–1.42)
	2 (n=14)	1.17 (1.10–1.24)	1.18 (1.03–1.35)
Obesity	1 (n=20)	2.05 (1.75–2.40)	1.51 (1.26–1.81)
	2 (n=14)	1.57 (1.39–1.78)	1.28 (1.04–1.58)

Model 1: the RRs are adjusted for age, sex and smoking at baseline.

Model 2: Model 1 with additional adjustment physical activity, blood pressure and cholesterol at baseline.

*Calculated from the univariate meta-regression analysis including calendar period, see explanation in text and Table 2.3 for the percentage difference between calendar periods.

influence on the association between BMI and CHD in the univariate or multivariate analysis, while the influence of age of the population remained the same (data not shown).

Relative risks additionally adjusted for physical activity, blood pressure and cholesterol

When the RRs were additionally adjusted for physical activity, blood pressure and cholesterol, the univariate analysis indicated no longer a significant influence of calendar period on the associations between a five-BMI-unit increment and CHD and obesity and CHD, but the percentage changes remained in the same order of magnitude [-36% (95%CI: -78 to 15%) and -51% (95%CI: -96 to 10%), respectively] (Table 2.3, 2.4). Age of the population remained significant for the association between a five-BMI-unit increment and CHD [-44% (95%CI: -90 to -4)], but not for overweight and obesity (Table 2.3).

The multivariate analysis indicated that age of the population did not significantly influence the association between overweight or obesity and CHD, but a trend was still visible for the association between a five-BMI-unit increment and CHD [-40% (95%CI: -105 to 6%)] (Table 2.3).

Length of follow-up had no longer a significant influence on the association between a five-BMI-unit increment and CHD and obesity and CHD (Table 2.3).

Because we used two endpoints, we examined whether there was a difference between incidence and mortality regarding the RR of BMI (categories). We found no differences and also the influence of calendar period, follow-up period or mean age on the RR did not differ by the endpoint used in the analyses (data not shown).

Discussion

In this meta-analysis of 31 cohorts worldwide including 389,212 mainly Caucasian persons and 20,652 CHD events, we explored the hypothesis whether the RR of CHD associated with BMI is lower in later studies compared to earlier studies. Further, we took other important study characteristics, i.e. age of the population and length of follow-up into account. By taking these study characteristics into account and carrying out extra analyses with RRs adjusted for CHD risk factors, we found no longer a difference in the RR of CHD associated with BMI between calendar periods. The most important and consistent cohort characteristic influencing the association between BMI and CHD was age of the population.

Strengths and limitations

The strength of our analysis lies in the large number of cohorts including populations from various countries and the systematic adjustments for relevant cohort variables (i.e. length of follow-up and age of the population). No indication of publication bias was found, as was discussed also in a previous publication.[17]

Another strength of our meta-analysis is that we were able to account for CHD risk factors (i.e. physical activity, blood pressure and cholesterol) which could influence the change in the association between BMI and CHD over time.

Several limitations should be addressed. First, we did not use studies with a baseline year in the 21st century. This limited our time span to examine the influence of calendar period and to give insight on recent developments of the association between BMI and CHD. Second, length of follow-up was found to be a strong confounder, but was also strongly correlated with baseline year and associated with the RR of CHD for BMI (categories). However, in a previous analysis of data from the NHANES study, adjustment for length of follow-up did not affect the outcome of the trend of decreasing RRs of all-cause mortality for obesity over time.[13] Third, for some studies the RRs for categories of BMI were transformed to RRs for BMI as a continuous variable, which may have introduced some inaccuracy. Finally, we did not adjust for important confounders such as dietary variables or weight (loss) history

because these were not available in most studies although those have been shown to be related to BMI and CHD.[56,57] Nevertheless, in the Nurses' Health Study (the largest included study) adjustment for diet had virtually no impact on the association between BMI and risk of CHD.[42]

Findings in the context of the literature

We found increased RRs of CHD for a five-BMI-unit increment, overweight and obesity of 1.28, 1.31, and 1.78, respectively. The accompanying RRs with the additional adjustments were 1.16, 1.17 and 1.49, respectively. This corresponds well with relative risks found in other studies.[58-61]

With regard to time-dependent changes in the association between obesity and health risks, a previous meta-analysis found in overweight and obese elderly an RR of total mortality of 0.47 (95%CI: 0.40–0.55) and 0.66 (95%CI: 0.51–0.71), using 5 cohorts starting in or after 1990.[62] In 13 and 15 cohorts starting before 1990, they found respectively an RR of 1.00 (95%CI: 0.96–1.04) and 1.02 (95%CI: 0.98–1.07).[62] In the National Health and Nutrition Examination Surveys (NHANES I, II and III), a similar trend of decreasing RR of total mortality in obese US adults (≥25 years) was found.[13] Our results also indicated an association between calendar period and the RR of CHD for (increasing) BMI and obesity, but not when study characteristic mean age of the population was taken into account. In addition, we expected that the influence of calendar period would be attenuated by the additional adjustments for physical activity, blood pressure and cholesterol, because of the hypothesis that the blood pressure and cholesterol profile in persons were unfavourable at baseline in studies starting before 1985 compared to studies starting after 1985 due to improvements of treatment of CHD risk factors and lifestyle. However, after the additional adjustments in the univariate analysis, the magnitude of the percentage changes on the RRs for a five-BMI-unit increment and obesity remained in the same order as for the age, sex and smoking adjusted RRs.

In summary, we did not find a clear difference between calendar periods in the association between BMI and CHD. This suggests that earlier studies may not be ruled out for use in predictive models forecasting future deaths of chronic diseases. However, as discussed before, length of follow-up and age of the population might have confounded our results, since these factors were different between calendar periods. Therefore, we cannot conclude beyond doubt that there is no difference between calendar periods. To examine changes by calendar period more thoroughly, a meta-analysis should be performed with similar study

characteristics to exclude this kind of confounding. Also, systematic adjustments including information on medication use should be considered to test our hypothesis.

Nevertheless, our study yields sufficient evidence to draw the conclusion that age of the population is an important factor modifying the association between BMI and CHD. Throughout all analyses, we found a significant influence of age of the population on the association between BMI and CHD, except in the univariate and multivariate analyses with CHD and overweight and obesity adjusted for the additional CHD risk factors. These exceptions can easily be explained by the low number of included studies with an old population (n=1), which in turn made it less accurate to regress the log RR on age for the higher age ranges. All together, our results stress the importance of taking age of a population into account in predictive models forecasting future deaths attributable to overweight and obesity.

The decrease in RR of CHD for a five-BMI-unit increment with each 10 year increment of age was comparable to previous studies who found a decreasing trend in the RR of CHD associated with BMI with increasing age.[58,63] An explanation for the reduction in RR at higher BMI levels with increasing age is complicated. In the elderly, the value of BMI as an indicator of body fatness is reduced because of the higher total fat mass (because of an age-dependent loss of lean body mass), fat redistribution and age-related decline in height.[64] Unintentional age-related weight loss which might be caused by (un)diagnosed illnesses can confound the association between BMI and risk of disease/mortality in the elderly.[64] Also, the ones susceptible for the consequences of obesity might have died earlier in life, while the remaining obese elderly persons survived.[64] Furthermore, several studies reported that the lowest mortality from all-causes or CVD in elderly persons lies within the overweight category, which indicates that a BMI of 18.5–24.9 kg/m^2 is not appropriate for the elderly[65-67] and therefore another anthropometric measure such as waist circumference, waist-hip ratio, body fat or lean body mass might be more useful.[68,69]

In conclusion, we found no consistent evidence for a difference in the association between BMI and the risk of CHD by calendar period, but we cannot conclude beyond doubt that no difference exists. Further research, that excludes the possible influence of follow-up length, is needed to clarify this. A clear finding of our study is, however, that age of the population was consistently associated with the RR of CHD for BMI. In older populations, the RR of CHD associated with BMI is lower than in younger populations. Therefore, for models used to predict mortality and prevalence of CHD in general populations, for example as used by the WHO, data from earlier studies may not be ruled out completely, but applying an age specific approach can be highly recommended.

Acknowledgements

The authors thank Federica Barzi for help with data extraction and analysis of some of the Australian and New Zealand studies. *BMI-CHD collaboration investigators and study sites:* Australian National Heart Foundation Risk Factor Prevalence Study: T Welborn; Busselton Health Study: M Knuiman, School of Population Health, The University of Western Australia, Nedlands, Australia; Caerphilly Prospective Study: JWG Yarnell and Y Ben-Shlomo, Dept of Epidemiology and Public Health, The Queen's University of Belfast, Institute of Clinical Science, Royal Victoria Hospital, N Ireland, United Kingdom; Dubbo Study of Australian Elderly: LA Simons MD FRACP, University of New South Wales Lipid Research Department, St Vincent's Hospital, Sydney, Australia; Finnish Mobile Clinic Health Examination Survey: P Knekt, Department of Health and Functional Capacity, National Public Health Institute, Helsinki, Finland; Finnish Twin Cohort Study: J Kaprio, Department of Public Health, Faculty of Medicine, University of Helsinki, Helsinki, Finland; Fletcher Challenge: S MacMahon, R Norton, M Woodward, The George Institute, University of Sydney, Australia; R Jackson, University of Auckland, New Zealand; Iowa Women's Health Study: AR Folsom and CP Hong, Division of Epidemiology, University of Minnesota, School of Public Health, Minneapolis, MN; Kuopio Ischaemic Heart Disease Risk Factor Study: HM Lakka, Department of Public Health and Clinical Nutrition, University of Kuopio, Kuopio, Finland; Malmö Preventive Project: S Calling and B Hedblad, Dept of Clinical Sciences in Malmö, Epidemiological Research Group, Lund University, Malmö University Hospital, Malmö, Sweden; Manresa Catalonia Study: L Tomas-Abadal, Departamento de Cardiología, Hospital de Sant Pau, Barcelona; Melbourne Collaborative Cohort Study: GG Giles, Cancer Epidemiology Centre, The Cancer Council Victoria, Melbourne, Australia; Multifactor Primary Prevention Study (MPPS) Göteborg: A Rosengren, Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden; NHANES I Epidemiologic Follow-up Study: RJ Thorpe, Jr, The Johns Hopkins Medical Institutions, Baltimore, MD; Nijmegen Cohort Study: JC Bakx, Department of General Practice, University Medical Centre St Radboud Nijmegen, Nijmegen, The Netherlands; Norwegian Counties: B H Strand, Norwegian Institute of Public Health, Division of Epidemiology, Oslo, Norway; Nurses' Health Study: FB Hu, RM van Dam, Department of Nutrition, Harvard School of Public Health, Boston MA, USA; Perth Cohort: K Jamrozik, School of Population Health, The University of Queensland, Herston, Australia, MS Hobbs, School of Population Health, University of Western Australia, Australia; PRIME Study: P Ducimetiere, INSERM Unit 258: Cardiovascular and Metabolic Epidemiology, Villejuif Cedex, France; Scottish Heart Health Study: H Tunstall-Pedoe, M Woodward, Cardiovascular Epidemiology Unit, Ninewells Hospital & Medical School, Dundee, Scotland, UK; SENECA: CPGM de Groot, WA van

Staveren, Division of Human Nutrition, Wageningen University, The Netherlands; Swedish Annual Level-of-Living Survey (SALLS): S-E Johansson, Centrum för Allmänmedicin (Center for Family Medicine), Karolinska Institutet, Huddinge, Sweden; US Railroad Cohort, Rome Railroad Cohort, and Italian Rural Areas of the Seven Countries Study; Gubbio Population Study; ECCIS Study: A Menotti, Associazione per la Ricerca Cardiologica (Association for Cardiac Research), Rome, Italy; Ventimiglia di Sicilia Heart Study (VHS): Carlo M. Barbagallo, Dipartimento di Medicina Clinica e Patologie Emergenti, Università degli Studi di Palermo, Palermo, Italy; Western Australian Abdominal Aortic Aneurysm Study: PE Norman, School of Surgery and Pathology, University of Western Australia, Australia; K Jamrozik, University of Queensland, Australia; Whitehall Study: MJ Shipley, Dept of Epidemiology and Public Health, University College London, London, UK; Zutphen Elderly Study: D Kromhout, IEJ Milder, Centre for Prevention and Health Services Research, National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

References

1. Branca F, Nikogosian H, Lobstein T. *The challenge of obesity in the WHO European Region and the strategies for response.* Denmark: World Health Organization, 2007.
2. Cameron AJ, Welborn TA, Zimmet PZ, Dunstan DW, Owen N, Salmon J, et al. Overweight and obesity in Australia: the 1999–2000 Australian Diabetes, Obesity and Lifestyle Study (AusDiab). *Med J Aust.* 2003;178(9):427–432.
3. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *Jama.* 2002;288(14):1723–1727.
4. Overweight, obesity, and health risk. National Task Force on the Prevention and Treatment of Obesity. *Arch Intern Med.* 2000;160(7):898–904.
5. O'Flaherty M, Allender S, Taylor R, Stevenson C, Peeters A, Capewell S. The decline in coronary heart disease mortality is slowing in young adults (Australia 1976–2006): A time trend analysis. *Int J Cardiol.* 2012;158(2):193–1998.
6. Uemura K, Pisa Z. Trends in cardiovascular disease mortality in industrialized countries since 1950. *World Health Stat Q.* 1988;41(3–4):155–178.
7. Gregg EW, Cheng YJ, Cadwell BL, Imperatore G, Williams DE, Flegal KM, et al. Secular trends in cardiovascular disease risk factors according to body mass index in US adults. *Jama.* 2005;293(15):1868–1874.
8. Kuulasmaa K, Tunstall-Pedoe H, Dobson A, Fortmann S, Sans S, Tolonen H, et al. Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations. *Lancet.* 2000;355(9205):675–687.

9. Rosengren A, Eriksson H, Hansson PO, Svardsudd K, Wilhelmsen L, Johansson S, et al. Obesity and trends in cardiovascular risk factors over 40 years in Swedish men aged 50. *J Intern Med.* 2009;266(3):268–276.

10. Tunstall-Pedoe H, Vanuzzo D, Hobbs M, Mahonen M, Cepaitis Z, Kuulasmaa K, et al. Estimation of contribution of changes in coronary care to improving survival, event rates, and coronary heart disease mortality across the WHO MONICA Project populations. *Lancet.* 2000;355(9205):688–700.

11. *Australia's health.* Canberra: Australian Institute of Health and Welfare, 1992.

12. *The world health report 2002: Reducing risks, promoting healthy life*. Geneva: World Health Organization, 2002.

13. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. *Jama.* 2005;293(15):1861–1867.

14. *Preventing chronic diseases: a vital investment: a global report*. Geneva: World Health Organization, 2005.

15. Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. *N Engl J Med.* 1998;338(1):1–7.

16. Dyer AR, Stamler J, Garside DB, Greenland P. Long-term consequences of body mass index for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. *Ann Epidemiol.* 2004;14(2):101–108.

17. Bogers RP, Bemelmans WJ, Hoogenveen RT, Boshuizen HC, Woodward M, Knekt P, et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. *Arch Intern Med.* 2007;167(16):1720–1728.

18. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol.* 1992;135(11):1301–1309.

19. Hartemink N, Boshuizen HC, Nagelkerke NJ, Jacobs MA, van Houwelingen HC. Combining risk estimates from observational studies with different exposure cutpoints: a meta-analysis on body mass index and diabetes type 2. *Am J Epidemiol.* 2006;163(11):1042–1052.

20. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med.* 2002;21(4):589–624.

21. Welborn TA, Dhaliwal SS, Bennett SA. Waist-hip ratio is the dominant risk factor predicting cardiovascular death in Australia. *Med J Aust.* 2003;179(11-12):580–585.

22. Knuiman MW, Vu HT. Prediction of coronary heart disease mortality in Busselton, Western Australia: an evaluation of the Framingham, national health epidemiologic follow up study, and WHO ERICA risk scores. *J Epidemiol Commun Health.* 1997;51(5):515–519.

23. Yarnell JW, Patterson CC, Sweetnam PM, Lowe GD. Haemostatic/inflammatory markers predict 10-year risk of IHD at least as well as lipids: the Caerphilly collaborative studies. Eur Heart J 2004;25(12):1049–1056.

24. Yu S, Yarnell JW, Sweetnam PM, Murray L. What level of physical activity protects against premature cardiovascular death? The Caerphilly study. *Heart.* 2003;89(5):502–506.

25. Simons LA, Friedlander Y, McCallum J, Simons J. Risk factors for coronary heart disease in the prospective Dubbo Study of Australian elderly. Atherosclerosis 1995;117(1):107–118.

26. Menotti A, Lanti M, Puddu PE, Carratelli L, Mancini M, Motolese M, et al. The risk functions incorporated in Riscard 2002: a software for the prediction of cardiovascular risk in the general population based on Italian data. *Ital Heart J.* 2002;3(2):114–121.

27. Knekt P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. *Am J Epidemiol.* 1994;139(12):1180–1189.

28. Kaprio J, Kujala UM, Koskenvuo M, Sarna S. Physical activity and other risk factors in male twin-pairs discordant for coronary heart disease. *Atherosclerosis.* 2000;150(1):193–200.

29. Kujala UM, Kaprio J, Koskenvuo M. Modifiable risk factors as predictors of all-cause mortality: the roles of genetics and childhood environment. *Am J Epidemiol.* 2002;156(11):985–993.

30. MacMahon S, Norton R, Jackson R, Mackie MJ, Cheng A, Vander Hoorn S, et al. Fletcher Challenge-University of Auckland heart and health study: design and baseline findings. *N Z Med J.* 1995;108(1013):499–502.

31. Menotti A, Lanti M, Puddu PE, Mancini M, Zanchetti A, Cirillo M, et al. First risk functions for prediction of coronary and cardiovascular disease incidence in the Gubbio Population Study. *Ital Heart J.* 2000;1(6):394–399.

32. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. *Arch Intern Med.* 2000;160(14):2117–2128.

33. Menotti A, Lanti M. Coronary risk factors predicting early and late coronary deaths. *Heart.* 2003;89(1):19–24.

34. Lakka HM, Lakka TA, Tuomilehto J, Salonen JT. Abdominal obesity is associated with increased risk of acute coronary events in men. *Eur Heart J.* 2002;23(9):706–713.

35. Jonsson S, Hedblad B, Engstrom G, Nilsson P, Berglund G, Janzon L. Influence of obesity on cardiovascular risk. Twenty-three-year follow-up of 22,025 men from an urban Swedish population. *Int J Obes Relat Metab Disord.* 2002;26(8):1046–1053.

36. Tomas-Abadal L, Varas-Lorenzo C, Bernades-Bernat E, Balaguer-Vintro I. Coronary risk factors and a 20-year incidence of coronary heart disease and mortality in a Mediterranean industrial population. The Manresa Study, Spain. *Eur Heart J.* 1994;15(8):1028–1036.

37. Giles GG, English DR. The Melbourne collaborative cohort study. *IARC Sci Publ.* 2002;156:69–70.

38. Rosengren A, Wedel H, Wilhelmsen L. Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. A prospective population study. *Eur Heart J.* 1999;20(4):269–277.

39. Thorpe RJ, Jr, Ferraro KF. Aging, obesity, and mortality. Misplaced concern about obese people? *Res Aging.* 2004;26:108–129.

40. Bakx JC, Veldstra MI, van den Hoogen HM, Zielhuis GA, Thien T, van Weel C, et al. Blood pressure and cardiovascular morbidity and mortality in a Dutch population: the Nijmegen cohort study. *Prev Med.* 2001;32(2):142–147.

41. Strand BH, Tverdal A. Can cardiovascular risk factors and lifestyle explain the educational inequalities in mortality from ischaemic heart disease and from other diseases? 26 year follow up of 50,000 Norwegian men and women. *J Epidemiol Commun Health.* 2004;58:705–709.

42. Li TY, Rana JS, Manson JE, Willett WC, Stampfer MJ, Colditz GA, et al. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. *Circulation.* 2006;113(4):499–506.

43. *Risk Factor Prevalence Study—Survey No 3, 1989*. National Heart Foundation and Australian Institute of Health of Welfare, 1991.

44. Magnus P, Armstrong B, McCall M. A comparison of populations self-selected and randomly selected for coronary risk factor screening. *Prev Med.* 1983;12(2):340–350.

45. Mahamat A, Richard F, Arveiler D, Bongard V, Yarnell J, Ducimetiere P, et al. Body mass index, hypertension and 5-year coronary heart disease incidence in middle aged men: the PRIME study. *J Hypertens.* 2003;21(3):519–524.

46. Menotti A, Seccareccia F, Blackburn H, Keys A. Coronary mortality and its prediction in samples of US and Italian railroad employees in 25 years within the Seven Countries Study of cardiovascular diseases. *Int J Epidemiol.* 1995;24:515–521.

47. Tunstall-Pedoe H, Woodward M, Tavendale R, A'Brook R, McCluskey MK. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study. *BMJ.* 1997;315(7110):722–729.

48. Haveman-Nies A, de Groot LP, Burema J, Cruz JA, Osler M, van Staveren WA. Dietary quality and lifestyle factors in relation to 10-year mortality in older Europeans: the SENECA study. *Am J Epidemiol.* 2002;156(10):962–968.

49. Sundquist K, Qvist J, Johansson SE, Sundquist J. The long-term effect of physical activity on incidence of coronary heart disease: a 12-year follow-up study. *Prev Med.* 2005;41(1):219–225.

50. Barbagallo CM, Cavera G, Sapienza M, Noto D, Cefalu AB, Pagano M, et al. Prevalence of overweight and obesity in a rural southern Italy population and relationships with total and cardiovascular mortality: the Ventimiglia di Sicilia project. Int J Obes Relat Metab Disord 2001;25(2):185–190.

51. Jamrozik K, Norman PE, Spencer CA, Parsons RW, Tuohy R, Lawrence-Brown MM, et al. Screening for abdominal aortic aneurysm: lessons from a population-based study. *Med J Aust.* 2000;173(7):345-350.

52. Lawrence-Brown MM, Norman PE, Jamrozik K, Semmens JB, Donnelly NJ, Spencer C, et al. Initial results of ultrasound screening for aneurysm of the abdominal aorta in Western Australia: relevance for endoluminal treatment of aneurysm disease. *Cardiovasc Surg.* 2001;9(3):234–240.

53. Batty GD, Shipley MJ, Jarrett RJ, Breeze E, Marmot MG, Davey Smith G. Obesity and overweight in relation to disease-specific mortality in men with and without existing coronary heart disease in London: the original Whitehall study. *Heart.* 2006;92(7):886–892.

54. Jarrett RJ, Shipley MJ, Rose G. Weight and mortality in the Whitehall Study. *Br Med J (Clin Res Ed)*. 1982;285(6341):535–537.

55. Buijsse B, Feskens EJ, Kok FJ, Kromhout D. Cocoa intake, blood pressure, and cardiovascular mortality: the Zutphen Elderly Study. *Arch Intern Med.* 2006;166(4):411–417.

56. Harris TB, Savage PJ, Tell GS, Haan M, Kumanyika S, Lynch JC. Carrying the burden of cardiovascular risk in old age: associations of weight and weight change with prevalent cardiovascular disease, risk factors, and health status in the Cardiovascular Health Study. *Am J Clin Nutr.* 1997;66(4):837–844.

57. Schaefer EJ. Lipoproteins, nutrition, and heart disease. *Am J Clin Nutr.* 2002;75(2):191–212.

58. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet.* 2009;373(9669):1083–1096.

59. Rodriguez C, Calle EE, Patel AV, Tatham LM, Jacobs EJ, Thun MJ. Effect of body mass on the association between estrogen replacement therapy and mortality among elderly US women. *Am J Epidemiol.* 2001;153(2):145–152.

60. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med.* 2008;359(20):2105–2120.

61. Chiuve SE, McCullough ML, Sacks FM, Rimm EB. Healthy lifestyle factors in the primary prevention of coronary heart disease among men: benefits among users and nonusers of lipid-lowering and antihypertensive medications. *Circulation.* 2006;114(2):160–167.

62. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. *Obes Rev.* 2007;8(1):41–59.

63. Ni Mhurchu C, Rodgers A, Pan WH, Gu DF, Woodward M. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310 000 participants. *Int J Epidemiol.* 2004;33(4):751–758.

64. Zamboni M, Mazzali G, Zoico E, Harris TB, Meigs JB, Di Francesco V, et al. Health consequences of obesity in the elderly: a review of four unresolved questions. *Int J Obes (Lond).* 2005;29(9):1011–1029.

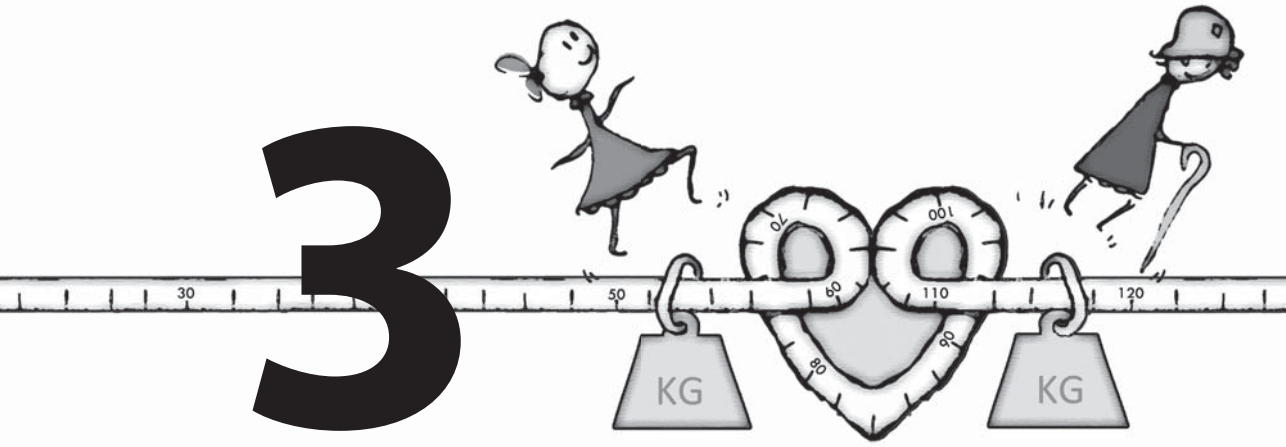
65. Allison DB, Gallagher D, Heo M, Pi-Sunyer FX, Heymsfield SB. Body mass index and all-cause mortality among people age 70 and over: the longitudinal study of aging. *Int J Obes Relat Metab Disord.* 1997;21(6):424–431.

66. De Hollander EL, Van Zutphen M, Bogers RP, Bemelmans WJE, De Groot LCPGM. The impact of body mass index in old age on cause-specific mortality. *J Nutr Health Aging.* 2012;16(1):100–106.

67. Flicker L, McCaul KA, Hankey GJ, Jamrozik K, Brown WJ, Byles JE, et al. Body mass index and survival in men and women aged 70 to 75. *J Am Geriatr Soc.* 2010;58(2):234–241.

68. Heitmann BL, Erikson H, Ellsinger BM, Mikkelsen KL, Larsson B. Mortality associated with body fat, fat-free mass and body mass index among 60-year-old Swedish men-a 22-year follow- up. The study of men born in 1913. *Int J Obes Relat Metab Disord.* 2000;24(1):33–37.

69. Seidell JC. Waist circumference and waist/hip ratio in relation to all-cause mortality, cancer and sleep apnea. *Eur J Clin Nutr.* 2010;64(1):35–41.



3

The impact of body mass index in old age on cause-specific mortality

Ellen L de Hollander, Moniek van Zutphen, Rik P Bogers,
Wanda JE Bemelmans, Lisette CPGM de Groot

J Nutr Health Aging. 2012;16(1):100–106.

Abstract

Objectives: To assess the association between Body Mass Index (BMI) and cause-specific mortality in older adults and to assess which BMI was associated with lowest mortality.

Design: Prospective study.

Setting: European towns.

Participants: 1,970 older adults, aged 70–77 years from the SENECA (*Survey in Europe on Nutrition and the Elderly: a concerted action*) study.

Measurements: BMI, examined in 1988/1989, and mortality rates and causes of death during 10 years of follow-up.

Results: Cox proportional hazards model including both BMI and BMI^2, accounting for sex, smoking status, educational level and age at baseline showed that BMI was associated with all-cause mortality ($p<0.01$), cardiovascular mortality ($p<0.01$) and mortality from other causes ($p<0.01$), but not with cancer or respiratory mortality ($p>0.3$). The lowest all-cause mortality risk was found at 27.1 (95%CI: 24.1–29.3) kg/m^2, and this risk was increased with statistical significance when higher than 31.4 kg/m^2 and lower than 21.1 kg/m^2. The lowest cardiovascular mortality risk was found at 25.6 (95%CI: 17.1–28.4) kg/m^2, and was increased with statistical significance when higher than 30.9 kg/m^2.

Conclusions: In this study, BMI was associated with all-cause mortality risk in older people. This risk was mostly driven by an increased cardiovascular mortality risk, as no association was found for mortality risk from cancer or respiratory disease. Our results indicate that the WHO cut-off point of 25 kg/m^2 for overweight might be too low in old age, but more studies are needed to define specific cut-off points.

Introduction

Two concurring trends in our ageing populations are health problems associated with old age and an increased prevalence of overweight.[1] In the general population overweight has been associated with several diseases,[1] such as cardiovascular diseases (CVD) and certain types of cancer. These diseases are highly prevalent in older people and are one of the main causes of death. However, the impact of weight status at old age on mortality and especially on (cause-specific) mortality remains unclear.

To provide further insight into the association between weight status and all-cause mortality in the elderly, a meta-analysis based on 32 studies was carried out. This study concluded that overweight (BMI: 25–30 kg/m^2) in the elderly did not increase the risk of all-cause mortality and that obesity increased this risk only modestly.[2] However, these results do not necessarily mean that weight status at old age is an unimportant risk factor for mortality. First, it could be hypothesized that overweight increases the risk of CVD mortality, while it decreases the relative risk of other causes of death, on average resulting in no increased all-cause mortality risk. Secondly, because of the use of weight status categories, which have been shown to be restrictive in the elderly,[3,4] it remains unclear at which BMI measurement the mortality risk is increased. For example, if the mortality risk is lowest around a BMI of 25 kg/m^2, thus at the higher end of the WHO healthy weight range and at the lower end of the overweight range, the mortality risk would be similar in both the normal and overweight category. Thirdly, since many studies show a U- or J-shaped association between BMI and mortality risk at an old age,[5-7] it is of importance to investigate both sides of the BMI distribution to see at which BMI measurement the mortality risk increases.

The aim of this study was to assess the association between BMI and cause-specific mortality in elderly people (70–77 years) in a European population. The secondary aim was to assess which BMI is associated with the lowest mortality and at which BMI the cause-specific mortality risk starts to increase. Both a high and a low BMI were considered as potential risk factors for increased all-cause and cause-specific mortality.

Methods

Study population

The SENECA (*Survey in Europe on Nutrition and the Elderly: a concerted action*) study is a prospective study investigating whether diet and lifestyle influence the health of elderly

people in various European countries. At baseline, participants were selected from an age- and sex-stratified sample of inhabitants from the following towns: Hamme, Belgium; Roskilde, Denmark; Haguenau, France; Romans, France; Iraklion, Greece; Monor, Hungary; Padua, Italy; Rome, Italy; Culemborg, the Netherlands; Vila Franca de Xira, Portugal; Betanzos, Spain; Yverdon, Switzerland; Burgdorf, Switzerland; Bellinzona, Switzerland; Marki, Poland. All citizens of these towns born between 1913 and 1918 were eligible for enrolment in the study. The only exclusion criteria were: living in a psychogeriatric nursing home, not being able to speak the country's language fluently, not being able to answer questions independently.

Participation rates varied between towns from 34% to 62%.[8] The follow-up period lasted from the baseline examination in 1988–1989 until April 30, 1999. Participants for whom data was missing for survival time (n=27) or BMI (n=227) were excluded from analyses. Furthermore, in three study centres (Monor, Burgdorf and Bellinzona) no information about cause of death was collected and therefore all people from these centres were also excluded (n=156). Subsequently, subjects for whom data was missing on the confounders age (n=6) and education level (n=4) were also excluded. The excluded group (n=420) differed somewhat from the study population. These subjects were on average 1.0 year older, had a 1.0 point higher BMI and had a higher mortality rate (50% vs. 38%, $p<0.001$) than the included subjects. The age and BMI difference was mainly introduced by excluding the three study centres mentioned earlier, because they only included the 1913 and 1914 birth year cohorts. However, the higher mortality rate was not caused mainly by excluding the three study centres. The total study population consisted of 1,970 subjects. All participants gave written informed consent. Approval of the study was obtained from the participating SENECA centres.

Health and vital status

Baseline information on smoking, educational level, chronic diseases, and alcohol use was obtained through questionnaires. A high level of education comprised secondary or higher education, while a low level of education comprised primary education only or illiteracy. Food consumption data was collected by trained personnel using the modified dietary history method.[9] The Mediterranean diet score[10] was calculated and dichotomized into a low quality (score <4) and high quality diet (score ≥4) and alcohol use was divided into abstainers and users, as described elsewhere.[11] Household, sports, and leisure-time physical activities were estimated using a validated questionnaire.[12] Physical activity was classified

in the total study population by sex-specific tertiles. Body weight was measured to the nearest 0.5 kg on a calibrated scale. Subjects were weighed in the morning after breakfast and after emptying their bladder; they wore light underclothing. Height was measured to the nearest 0.1 cm while the subjects were standing upright with no shoes on. Body mass index (BMI) was calculated by dividing body weight (in kg) by the square of height (m^2).

Information on the vital status and causes of death was collected in 1999–2000. Information on cause of death was obtained through death certificates from towns in which deaths of participants occurred or, if this data was not available, via a medical doctor or first-degree relative. One experienced clinical epidemiologist coded the causes of death by using the 9th revision of the World Health Organization International Classification of Disease (ICD-9).[13] We grouped deaths into four major categories, corresponding with the main causes of death among the elderly: cardiovascular disease (CVD), cancer, respiratory disease and other causes. In cases where there were multiple causes of death, cancer was prioritized above CVD, and CVD was prioritized above the other causes of death. The cause of death was unknown for 23.7% out of the total number of deaths.

Statistical analyses

Survival time was computed from the date of a participant's baseline examination until the date of death for decedents, or until April 30, 1999, for survivors.

The major characteristics of the study population were given as frequencies or mean ± SD. We used Chi-square tests (categorical variables) or Student's t-tests (continuous variables) to compare the characteristics of subjects over BMI categories.

We used a Cox proportional hazards model to investigate the association between BMI and all-cause, and cause-specific mortality. To examine whether the associations between BMI categories and mortality in this elderly population are comparable to previous literature,[2,6] we first calculated Hazard Ratios (HR) for BMI categories: <20 kg/m^2, 25–30 kg/m^2 and ≥30 kg/m^2 compared to the reference category: 20–25 kg/m^2, adjusted for the confounders: sex, smoking status (current smoker/former/never), education level (high/low), age at baseline.

Hypothesizing that mortality risks are increased at both the lower and higher end of the BMI distribution, together with the aforementioned confounders, we analysed BMI as a continuous variable using a Cox regression model including BMI and BMI^2. Also, from a previous study in men (40–69 years), this method was shown to explain more variability in mortality than when only the linear term was included or when the WHO classification was

used.[14] U-shaped associations between BMI and mortality were significant when $p<0.05$ for the test that regression coefficients for BMI and BMI^2 were 0.

In the case of a parabolic relation existing between BMI and mortality, we calculated the BMI associated with the minimum risk of death by: -b/2a, where 'a' represents the coefficients of the quadratic term (BMI^2) and 'b' the coefficient of the linear term (BMI). We also determined the BMI ranges at which the mortality risk was increased by <10%, 10–20% or >20%. We chose an interval of 10–20% because the BMI at which mortality risks are significantly increased highly depends on the number of deaths; with larger numbers of deaths the confidence intervals become smaller, thus narrowing the optimum BMI range. The results were graphically displayed together with 95% confidence intervals.

Interactions between variables were considered for inclusion in the continuous model when $p<0.05$. However, interaction terms did not reach significance in any of the models. Because sex showed no interaction with either BMI or BMI^2, stratification of the results by sex was not necessary. The proportional hazards assumption was checked for all models and no major violations of this assumption were found.

Sensitivity analyses were performed to assess the robustness of the results. We repeated the analyses with extra adjustments for diet, physical activity and alcohol use, and in a subgroup in which the first 2 years of follow-up were excluded, in a subgroup with no major diseases (CVD, cancer or respiratory problems) at baseline and in a subgroup of non-smokers.

Data were analysed using the SAS System for Windows (release 9.1.3) (SAS Institute Inc, Cary, North Carolina). Mortality risk was considered significantly increased if the 95% confidence interval (95%CI) did not include 1. All p-values are 2-sided.

Results

Table 3.1 presents the baseline health and lifestyle characteristics of the participants according to BMI category. Sex, smoking status, educational level, physical activity and alcohol use were not evenly distributed among the BMI categories. People within the highest BMI categories had a chronic disease at baseline more often ($p<0.01$): with diabetes, hypertension and arthritis being more common in people with a BMI ≤30 kg/m^2. In contrast, respiratory problems were more common in people with the lowest BMI category, while osteoporosis was most common in people with a BMI between 20 and 25 kg/m^2. Table 3.2 shows the total number of deaths from each cause in SENECA participants during 10 years of follow-up.

Table 3.1 Baseline characteristics of SENECA participants (n (%))

	Total	BMI <20 kg/m^2	BMI 20–25 kg/m^2	BMI 25–30 kg/m^2	BMI ≥30 kg/m^2	p (Chi^2)
n (%)	1,970	83 (4)	614 (31)	857 (43)	416 (21)	
Age, mean (SD), y	73 (1.9)	73 (1.8)	73 (1.8)	73 (2.0)	73 (1.9)	0.52*
Sex male	979 (50)	31 (37)	314 (51)	474 (55)	160 (38)	<0.01
Smoking						<0.01
Never	1,042 (53)	41 (49)	294 (48)	437 (51)	270 (65)	
Former	579 (29)	18 (22)	185 (30)	283 (33)	93 (22)	
Current	349 (18)	24 (29)	135 (22)	137 (16)	53 (13)	
High education	645 (33)	40 (48)	234 (38)	281 (33)	90 (22)	<0.01
Diet† (Mediterranean score ≥4)	773 (43)	31 (42)	250 (44)	324 (41)	168 (46)	0.54
Physical activity†						
High	587 (33)	19 (26)	192 (34)	281 (36)	105 (29)	0.05
Low	597 (33)	28 (38)	175 (31)	241 (31)	146 (39)	0.02
Alcohol use† (abstainers)	654 (37)	32 (44)	201 (36)	260 (33)	161 (44)	<0.01
Chronic disease present at baseline	1,516 (77)	64 (77)	454 (74)	648 (76)	350 (84)	<0.01
Ischemic heart disease	323 (16)	8 (10)	92 (15)	147 (17)	76 (18)	0.16
Stroke	43 (2)	2 (2)	8 (1)	23 (3)	10 (2)	0.34
Cancer	36 (2)	2 (2)	12 (2)	18 (2)	4 (1)	0.51
Respiratory problems	219 (11)	17 (20)	72 (12)	89 (10)	41 (10)	0.04
Diabetes	162 (8)	4 (5)	32 (5)	82 (10)	44 (11)	<0.01
Hypertension	413 (21)	6 (7)	102 (17)	184 (21)	121 (29)	<0.01
Arthritis	641 (33)	27 (33)	182 (30)	253 (30)	179 (43)	<0.01
Inflammatory bowel disease	137 (7)	7 (8)	54 (9)	47 (5)	29 (7)	0.10
Chronic liver disease	34 (2)	2 (2)	10 (2)	17 (2)	5 (1)	0.74
Osteoporosis	48 (2)	1 (1)	25 (4)	14 (2)	8 (2)	0.02
Other disease	674 (34)	26 (31)	203 (33)	296 (35)	149 (36)	0.74

BMI: Body Mass Index

* ANOVA

† Based on the number of persons used in the sensitivity analyses including the extra covariates (n=1,788): diet, physical activity, alcohol use.

Table 3.2 Cause of death and number of deaths in older adults aged 70–77y (n=1,970) during 10y follow-up (1988/89–1999)

Cause of death	ICD-9 code	No. (%) of deaths
Cardiovascular disease	390–459	296 (39.4)
Cancer	140–239	172 (22.9)
Respiratory disease	460–519	41 (5.4)
Other cause of death*	All other numbers	64 (8.5)
Unknown cause of death	No code assigned	178 (23.7)
Total		751 (100)

ICD-9: International Classification of Diseases, 9th Revision
* The category 'other' mainly comprised injury, ill-defined causes, and diseases of the digestive system.

All-cause mortality

We found no association for any of the BMI categories and all-cause mortality (p>0.3) (Table 3.3). However, for BMI as a continuous variable, we did find a significant association with all-cause mortality (p<0.01). The lowest mortality risk was found at a BMI of 27.1 (95%CI: 24.1–29.3) kg/m^2 and the mortality risk was significantly increased above 31.4 kg/m^2 or below 21.1 kg/m^2 (Figure 3.1a).

Cause-specific mortality

For cause-specific mortality across BMI categories, we only found a significantly increased CVD mortality risk for the category ≤30 kg/m^2 [1.39 (95%CI: 1.00–1.92)] and a significantly increased risk of mortality from other causes for the category <20 kg/m^2 [2.75 (95%CI: 1.00–7.52)] (Table 3.3).

In the analyses with BMI as a continuous variable, we found a significant association between BMI and CVD mortality (p<0.01). For CVD, the lowest mortality risk was found at a BMI of 25.6 (95%CI: 17.1–28.4) kg/m^2 and the CVD mortality risk was significantly increased above BMI 30.9 kg/m^2 (Figure 3.1b).

BMI was not significantly associated with cancer mortality (p=0.75) (Figure 3.1c), nor with respiratory mortality (p=0.36) (Figure 3.1d). BMI was significantly associated with other mortality (p<0.01), with the lowest mortality risk at a BMI of 27.4 (95%CI: 22.7–30.2) kg/m^2. The other mortality risk was significantly increased at a BMI above 32.9 kg/m^2 and below 17.7 kg/m^2 (Figure 3.1e).

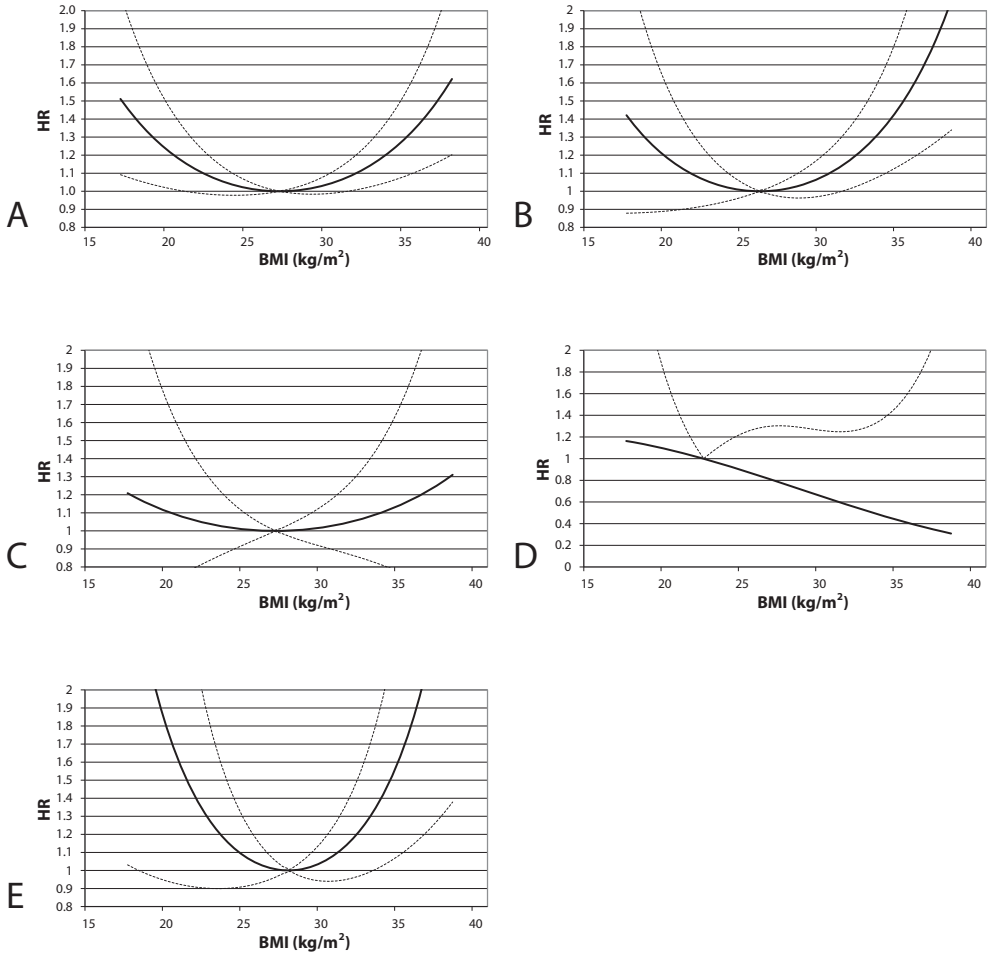


Figure 3.1 Multivariate adjusted hazard ratios for risk of mortality from all-cause mortality (A), cardiovascular disease (B), cancer (C), respiratory disease (D), and other deaths (E) in older adults aged 70–77y by Body Mass Index. In panel A–E solid lines indicate hazard ratios and dashed lines indicate 95% confidence intervals. All models were adjusted for sex, smoking and education level.

The BMI values at which none of the cause-specific mortality risks was significantly increased ranged from 17.7 to 30.9 kg/m^2. The BMI range at which none of the cause-specific mortality risk was increased by more than 20%, was between 23.0 and 31.9 kg/m^2 (Table 3.4). The BMI range at which the mortality risk for all specific causes was increased by less than 10% lay between 24.2 and 30.1 kg/m^2.

Table 3.3 Hazard Ratio (95% Confidence Interval) for the main causes of death per BMI category in older adults aged 70–77y

Cause of death	BMI <20 (n=83)		BMI 20–25 (n=614)		BMI 25–30 (n=857)		BMI ≥30 (n=416)	
	Number of events	HR	Number of events	HR	Number of events	HR	Number of events	HR
All-cause	31	1.06 (0.73–1.55)	234	1 (ref)	328	0.92 (0.78–1.09)	158	1.05 (0.89–1.29)
Cardiovascular	15	1.58 (0.90–2.74)	77	1 (ref)	132	1.12 (0.84–1.49)	72	1.39 (1.00–1.92)
Cancer	6	0.83 (0.36–1.92)	57	1 (ref)	72	0.84 (0.59–1.19)	37	1.11 (0.73–1.69)
Respiratory	1	0.65 (0.09–4.97)	14	1 (ref)	21	0.91 (0.46–1.80)	5	0.51 (0.18–1.42)
Other	5	2.75 (1.00–7.52)	16	1 (ref)	30	1.18 (0.64–2.18)	13	1.13 (0.54–2.38)

BMI: Body Mass Index; HR: Hazard Ratio

Table 3.4 Body mass index cut-off points in older adults aged 70–77y

Cause of death	BMI range with no significant increased risk	Lower BMI range with >20% increased mortality risk	Lower BMI range with 10–20% increased mortality risk	BMI range with <10% increased mortality risk	Higher BMI range with 10–20% increased mortality risk	Higher BMI range with >20% increased mortality risk
All-cause	21.1–31.4	≤20.4	20.3–22.2	22.3–31.9	32.0–33.7	≥33.8
Cardiovascular	<30.9	≤19.5	19.4–21.0	21.1–30.1	30.2–31.8	≥31.9
Cancer	n.a.	≤17.2	17.1–19.6	19.7–33.3	33.4–35.9	≥36.0
Respiratory	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Other	17.7–32.9	≤23.0	22.9–24.1	24.2–30.5	30.6–31.8	≥31.9

n.a.: not applicable
BMI: Body Mass Index

Sensitivity analyses

Adjusting for diet, physical activity and alcohol use (n=1,788) hardly affected the shape of the BMI-mortality association. Only the HR's at both ends of the curves were slightly higher (max. 0.3) for all-cause and CVD mortality compared to our main results (Figure 3.2). For mortality from other causes, however, the HRs at both ends of the range were slightly lower (max. 0.8) when adjusted for diet, physical activity and alcohol use (not shown).

Excluding the first 2 years of follow-up (n=106) did not change the shape of any of the BMI-mortality curves meaningfully, although the exclusion did result in a small (0.2 to 0.6 kg/m^2) reduction in the estimated nadir of the BMI-mortality curve.

Excluding people with chronic diseases at baseline (n=542) again did not change the results meaningfully. Except for CVD mortality, where the increased mortality risk at lower BMI's disappeared and the curve was replaced by an almost monotonic increasing risk, while the association was no longer significant (p=0.39) (Figure 3.3).

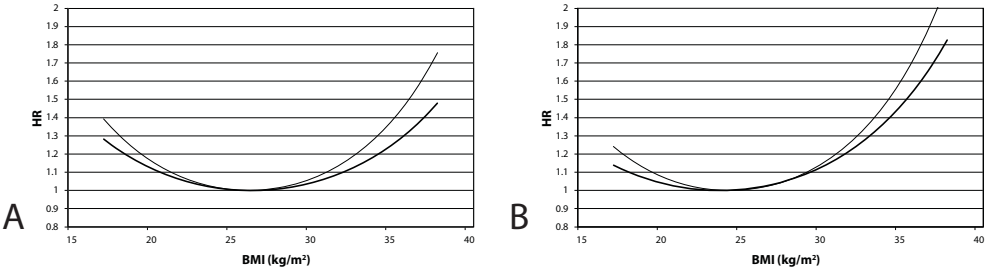


Figure 3.2 Sensitivity analyses of multivariate adjusted Cox models: basic model (n=1,788) compared to model with physical activity, diet and alcohol use (n=1,788) added as extra covariates to the model for all-cause (A) and cardiovascular mortality (B) in older adults aged 70–77y. All models were adjusted for sex, smoking and education level.

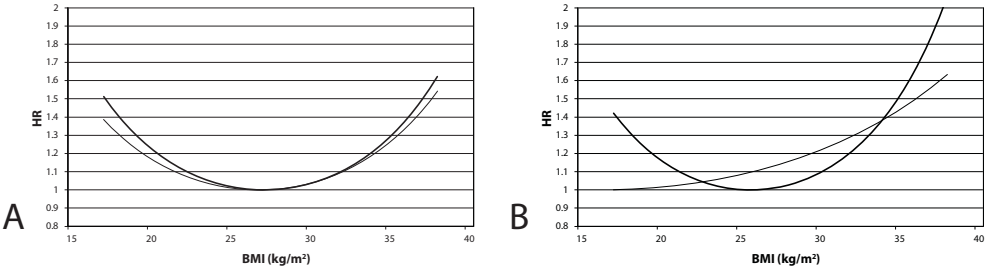


Figure 3.3 Sensitivity analyses of multivariate adjusted Cox models: basic model compared to model with baseline diseases excluded for all-cause (A) and cardiovascular mortality (B) in older adults aged 70–77y. All models were adjusted for sex, smoking and education level.

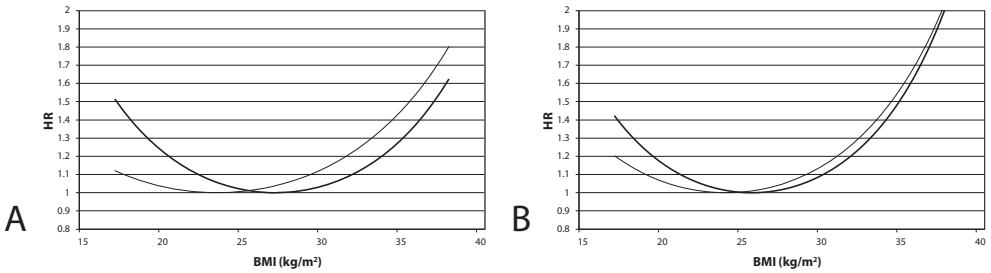


Figure 3.4 Sensitivity analyses of multivariate adjusted Cox models: basic model compared to model with never-smokers for all-cause (A) and cardiovascular mortality (B) in older adults aged 70–77y. All models were adjusted for sex and education level and the basic model was also adjusted for smoking status.

In people who had never smoked (n=1,042), the BMI mortality curves for all-cause and CVD mortality shifted to the left and showed a flattening of the risk on the left hand side of the curve (Figure 3.4). In contrast, the curve for other mortality (not shown) shifted somewhat to the right.

In all sensitivity analyses, the risk of respiratory mortality decreased with higher BMIs, although this association was not significant.

Discussion

This study shows that in older adults aged 70–77 years, BMI is associated with all-cause mortality when BMI is analysed as a continuous variable. The lowest all-cause mortality risk was found around 27 kg/m^2, and this risk was significantly increased above 31 kg/m^2 and below 21 kg/m^2. BMI was also associated with CVD mortality and mortality from other causes, but not with cancer or respiratory mortality during 10 years of follow-up. The increased all-cause mortality risk seemed to be mostly driven by an increased CVD risk. For CVD mortality risk, the lowest risk was found around 25.6 kg/m^2; this mortality risk increased significantly above BMI 30.9 kg/m^2.

Our findings of the associations between BMI (continuous) and mortality and their nadirs seem to be stable when looking at the sensitivity analyses. In general, the sensitivity analyses did not change the HRs substantially. However, excluding people with chronic diseases (CVD, cancer and respiratory diseases) at baseline (resulting in a considerably smaller study

population) mainly affected the association between BMI and CVD mortality risk, which resulted in lower CVD mortality risks in the lower BMI range. This might be due to a loss of power in the analyses, but could also have resulted from less influence of susceptibility for illness and death in the lower BMI ranges. In our main analyses, we did not exclude people with chronic diseases at baseline, because (given the high prevalence of CVD at the age of 70 years and the association of BMI with CVD morbidity[15] this would have underestimated the mortality risk of a high BMI. Additionally, we analysed a subgroup of never-smokers, because of potential residual confounding by smoking.[16] This resulted in BMI nadirs shifting to the left within the 20–25 kg/m^2 range for all-cause and CVD mortality. The shift to the left was similar to the results of a recent study including 1.46 million White adults, although they also excluded people with chronic diseases.[17]

Some limitations of our study should be noted. First, the response rate was low and we had to exclude participants from our analyses. From a bias assessment study, it was shown that non-participants may have been less active and healthy than the participants.[18] However, with mortality as an outcome measure and from our results of the sensitivity analyses, this would probably not influence our results substantially. Also, the 420 people who were excluded from the study were somewhat older and heavier and had a higher mortality rate than the study population. This may have resulted in an underestimation of the relative mortality risk in the higher BMI range. However, when we included a part of the excluded people, namely the participants of the three excluded study centres (Monor, Burgdorf and Bellinzona), in the analyses for all-cause mortality, the nadir and the HRs over the whole BMI range did not change meaningfully. Secondly, no cause of death could be retrieved for 23.7% of the total number of deaths, which might have limited the power to study cause-specific deaths. However, for these cases, the death certificates were randomly not available. Therefore, we do not expect that the unknown cases would affect our findings of the associations between BMI and cause-specific mortality. Also, there was a high level of standardization in our study: one medical doctor coded all causes of death from death certificates. Thirdly, the age-related decline in height among the elderly may induce a false BMI increase of about 2.0 kg/m^2.[19] Because of loss of lean body mass and redistribution of fat inside the body with ageing, BMI in elderly people could be an underestimation of the adiposity.[20] Measures that take into account the distribution of fat mass, such as waist circumference, may be more appropriate in the elderly.[20] However, BMI as a measurement is often used in clinical practice, which makes it important to examine the association between BMI, as a measure of adiposity, and mortality, in the elderly. Finally, the relatively small numbers of persons and deaths in the lower BMI range (<20 kg/m^2), and the small

number of deaths from respiratory diseases led to a limited statistical power for establishing the lower end of the BMI range and for studying the association between BMI and the mortality of respiratory diseases.

Our results are nonetheless comparable with other studies including Western elderly people with regard to several aspects. First, we did not find an increased all-cause mortality risk associated with the BMI categories of overweight and obesity, which is comparable with other studies among the elderly.[2,6,21-23] Results for cause-specific mortality are also much in line with others.[7,24-26] There are few studies that have used BMI as a continuous variable to assess the association with mortality. Previous studies showed increased relative risks of cardiovascular diseases and mortality in the association with continuous BMI in persons aged 70 years and older,[27,28] although the relative risks were lower than those found in younger persons. Two other studies estimated the BMI associated with the lowest all-cause mortality rate among older persons.[3,29] Engeland and colleagues found BMI nadirs 1.5–3 kg/m^2 lower compared to our estimate, depending on sex.[29] This might be explained by differences in methodology, i.e. 1/BMI was used as a proxy for BMI. However, in this study, Engeland and colleagues found an increased BMI nadir with increasing age in their population.[29] The other study by Flicker and colleagues[3] found similar U-shaped associations and nadirs for all-cause and cause-specific mortality risks, although in contrast to our results, they did find a significant association for cancer and respiratory diseases. This might be explained by the limited power in our study population, especially in the lower BMI range.

In conclusion, our results show that in people of older age, weight status is still associated with mortality and seems to be mostly driven by CVD. The minimum mortality risks in our study were between 25 and 27 kg/m^2 and the BMI range at which the cause-specific mortality risk was increased by less than 10%, was between 24 and 30 kg/m^2, indicating that the mortality risk was lowest in the overweight category. Therefore, the WHO cut-off point of 25 kg/m^2 for defining overweight might be too low for older people as well as the cut-off point of 18.5 kg/m^2 or 20 kg/ m^2 for defining underweight. Finally, more studies are needed to define specific cut-off points for BMI measurements in the elderly. In addition to mortality, these studies should also focus on morbidity.

References

1. Branca F, Nikogosian H, Lobstein T. *The challenge of obesity in the WHO European Region and the strategies for response.* Denmark: World Health Organization, 2007.
2. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. *Obes Rev.* 2007;8(1):41–59.
3. Flicker L, McCaul KA, Hankey GJ, Jamrozik K, Brown WJ, Byles JE, et al. Body mass index and survival in men and women aged 70 to 75. *J Am Geriatr Soc.* 2010;58(2):234–241.
4. Heiat A, Vaccarino V, Krumholz HM. An evidence-based assessment of federal guidelines for overweight and obesity as they apply to elderly persons. *Arch Intern Med.* 2001;161(9):1194–1203.
5. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med.* 2006;355(8):763–778.
6. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. *Jama.* 2005;293(15):1861–1867.
7. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA.* 2007;298(17):2028–2037.
8. Van 't Hof MA, Hautvast JG, Schroll M, Vlachonikolis IG. Design, methods and participation. Euronut SENECA investigators. *Eur J Clin Nutr.* 1991;45 Suppl 3:5–22.
9. De Groot C, Van Staveren W. *Nutrition and the elderly: manual of operations. (Report 11)*: Wageningen, the Netherlands, 1988.
10. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med.* 2003;348(26):2599–2608.
11. Knoops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O, Menotti A, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *Jama.* 2004;292(12):1433–1439.
12. Voorrips LE, Ravelli AC, Dongelmans PC, Deurenberg P, Van Staveren WA. A physical activity questionnaire for the elderly. *Med Sci Sports Exerc.* 1991;23(8):974–979.
13. *International Classification of Diseases, Ninth Revision (ICD-9).* Geneva: World Health Organization, 1977.
14. Kivimaki M, Ferrie JE, Batty GD, Davey Smith G, Elovainio M, Marmot MG, et al. Optimal form of operationalizing BMI in relation to all-cause and cause-specific mortality: the original Whitehall study. *Obesity (Silver Spring).* 2008;16(8):1926–1932.
15. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Monson RR, et al. A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med.* 1990;322(13):882–889.
16. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med.* 1999;341(6):427–434.

17. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med.* 2010;363(23):2211–2219.

18. van't Hof MA, Burema J. Assessment of bias in the SENECA study. *Eur J Clin Nutr.* 1996;50 Suppl 2:S4–8.

19. Sorkin JD, Muller DC, Andres R. Longitudinal change in height of men and women: implications for interpretation of the body mass index: the Baltimore Longitudinal Study of Aging. *Am J Epidemiol.* 1999;150(9):969–977.

20. Zamboni M, Mazzali G, Zoico E, Harris TB, Meigs JB, Di Francesco V, et al. Health consequences of obesity in the elderly: a review of four unresolved questions. *Int J Obes (Lond).* 2005;29(9):1011–1029.

21. Al Snih S, Ottenbacher KJ, Markides KS, Kuo YF, Eschbach K, Goodwin JS. The effect of obesity on disability vs mortality in older Americans. *Arch Intern Med.* 2007;167(8):774–780.

22. Locher JL, Roth DL, Ritchie CS, Cox K, Sawyer P, Bodner EV, et al. Body mass index, weight loss, and mortality in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci.* 2007;62(12):1389–1392.

23. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Decreased muscle mass and increased central adiposity are independently related to mortality in older men. *Am J Clin Nutr.* 2007;86(5):1339–1346.

24. Baik I, Ascherio A, Rimm EB, Giovannucci E, Spiegelman D, Stampfer MJ, et al. Adiposity and mortality in men. *Am J Epidemiol.* 2000;152(3):264–271.

25. Breeze E, Clarke R, Shipley MJ, Marmot MG, Fletcher AE. Cause-specific mortality in old age in relation to body mass index in middle age and in old age: follow-up of the Whitehall cohort of male civil servants. *Int J Epidemiol.* 2006;35(1):169–178.

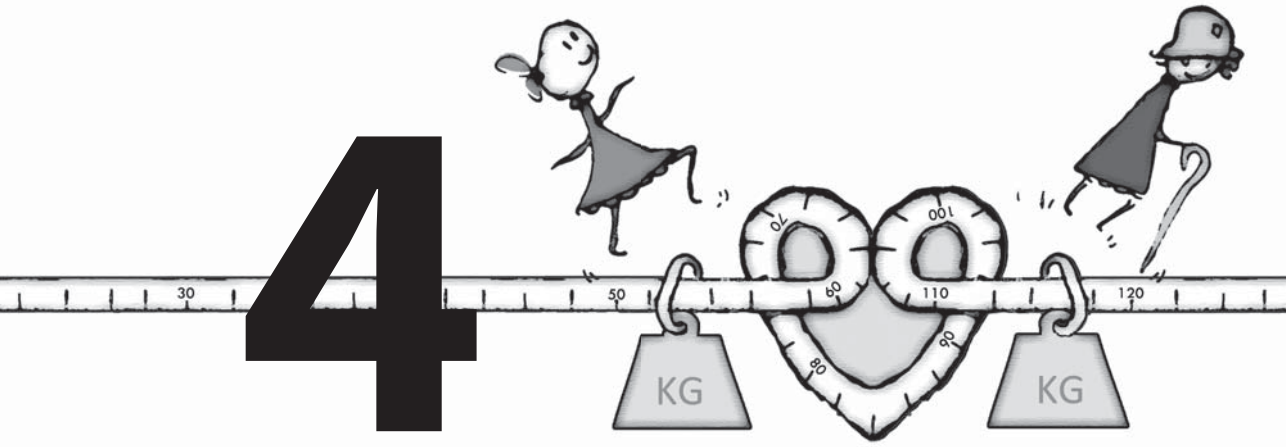
26. Dyer AR, Stamler J, Garside DB, Greenland P. Long-term consequences of body mass index for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. *Ann Epidemiol.* 2004;14(2):101–108.

27. Ni Mhurchu C, Rodgers A, Pan WH, Gu DF, Woodward M. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310 000 participants. *Int J Epidemiol.* 2004;33(4):751–758.

28. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet.* 2009;373(9669):1083–1096.

29. Engeland A, Bjorge T, Selmer RM, Tverdal A. Height and body mass index in relation to total mortality. *Epidemiology.* 2003;14(3):293–299.

4



The association between waist circumference and risk of mortality considering body mass index in 65- to 74-year-olds: a meta-analysis of 29 cohorts involving more than 58,000 elderly persons

Ellen L de Hollander, Wanda JE Bemelmans, Hendriek C Boshuizen, Nele Friedrich, Henri Wallaschofski, Pilar Guallar-Castillón, Stefan Walter, M Carola Zillikens, Annika Rosengren, Lauren Lissner, Julie K Bassett, Graham G Giles, Nicola Orsini, Noor Heim, Marjolein Visser, Lisette CPGM de Groot, for the WC elderly collaborators

Int J Epidemiol. 2012;41(3):805–817.

Abstract

Background: For the elderly, the association between waist circumference (WC) and mortality considering body mass index (BMI) remains unclear, and thereby also the evidence base for using these anthropometric measures in clinical practice. This meta-analysis examined the association between WC categories and (cause-specific) mortality within BMI categories. Furthermore, the association of continuous WC with lowest and increased mortality risks was examined.

Methods: Age- and smoking-adjusted relative risks (RRs) of mortality associated with WC-BMI categories and continuous WC (including WC and WC^2) were calculated by the investigators and pooled by means of random-effects models.

Results: During a 5-year-follow-up of 32,678 men and 25,931 women, we ascertained 3,318 and 1,480 deaths, respectively. A large WC (men: ≥102 cm, women: ≥88 cm) was associated with increased all-cause mortality RRs for those in the 'healthy' weight {1.7 [95% confidence interval (CI): 1.2–2.2], 1.7 (95%CI: 1.3–2.3)}, overweight [1.1 (95%CI: 1.0–1.3), 1.4 (95%: 1.1–1.7)] and obese [1.1 (95%CI: 1.0–1.3), 1.6 (95%CI: 1.3–1.9)] BMI category compared with the 'healthy' weight (20–24.9 kg/m^2) and a small WC (<94 cm, men; <80 cm, women) category. Underweight was associated with highest all-cause mortality RRs in men [2.2 (95%CI: 1.8–2.8)] and women [2.3 (95%CI: 1.8–3.1]. We found a J-shaped association for continuous WC with all-cause, cardiovascular (CVD) and cancer, and a U-shaped association with respiratory disease mortality ($p<0.05$). An all-cause (CVD) mortality RR of 2.0 was associated with a WC of 132 cm (123 cm) in men and 116 cm (105 cm) in women.

Conclusions: Our results showed increased mortality risks for elderly people with an increased WC – even across BMI categories – and for those who were classified as 'underweight' using BMI. The results provide a solid basis for re-evaluation of WC cut-points in ageing populations.

Introduction

The prevalence of overweight has increased for all age groups over the past decades in the Western world, including the elderly.[1,2] For adults, overweight is known to be associated with many health problems and decreases in life expectancy,[1,3] but for the elderly the association is less clear.[4–7]

In clinical practice, body mass index (BMI) and to a lesser extent waist circumference (WC) are widely used measures to assess an individual's health risk. However, WC might be a better measure than BMI, given its relationship with harmful visceral adiposity.[8] This might be particularly important for the elderly since they have more visceral adipose tissue than younger adults for a given WC.[7,8] Several studies have examined the association between WC and mortality risks in elderly people, but findings are inconsistent.[5,6,9–14]

For WC, three categories (men: <94 cm, 94–101 cm and ≥102 cm, women: <80 cm, 80–87 cm and ≥88 cm)[15] have been defined to indicate the increasing health risk with increasing WC.[16,17] However, associations between these WC categories and mortality have not been studied extensively in the elderly. One study reported in never smoking men aged ≥55 years an elevated all-cause mortality risk in the upper two categories (94–101 cm and ≥102 cm) compared with the reference category (79–93 cm).[18]

Furthermore, since BMI is the most commonly used anthropometric measure, it is important to assess mortality risks associated with WC categories, within BMI categories. By studying combined categories, a more complete picture of risks becomes available and insight is gained on the magnitude of relative risks with increasing WC or with increasing BMI categories, keeping the other measurement the same. This has previously been studied, but not by stratifying for all combinations of WC and BMI categories, and in a smaller population of elderly.[6,12]

Given the unclear association between WC and mortality in the elderly, especially when also considering BMI, and the ageing of the population, more research in a large elderly population is needed. This would provide an evidence base for application of these anthropometric indicators. To our knowledge, only data from single cohort studies with limited generalizability have previously studied this association. Therefore, the aims of this meta-analysis, which included over 58,000 people aged 65–74 years, were twofold. The first aim was to examine the association between internationally defined WC categories and all-cause and cause-specific mortality risks, within standard BMI categories. The second aim was to examine the association of WC as a continuous variable with lowest and increased mortality risks.

Methods

Data sources and searches

Studies were identified by a PubMed search from 1984 until 1 November 2010, by examining the reference lists of identified reviews, and by suggestions from colleagues. The following search strategy was used: waist, or WC, or abdominal adiposity in the abstract, title or in the Medical Subject Heading (MeSH), and mortality in the abstract, title or mortality in MeSH, plus either prospective or cohort. This search resulted in 202 abstracts. Additionally, all investigators from a previous collaboration were contacted,[19] and we searched on the website of the United States National Institute of Aging for eligible studies.

Study selection

Eligible studies were prospective cohort studies conducted in predominantly Caucasian populations. The studies had to include at least 400 people in the age range of 65–74 years at baseline, this ensured smaller studies were also included. WC, BMI and all-cause mortality had to be available. Additionally, it had to be possible to calculate hazard ratios [relative risks (RRs)] for a follow-up period of 5–8 years (preferably closest to 5 years). This follow-up range was chosen to ensure most subjects were still alive during follow-up, since life expectancy is about 80 years,[20] and also to reduce heterogeneity between studies. Also, baseline conditions tend to change considerably over a longer follow-up period.

In Appendix 1 (available at http://ije.oxfordjournals.org/content/41/3/805/suppl/DC1), a flowchart of the identified studies is presented. We identified 100 studies as possibly eligible for inclusion in our meta-analysis. The investigators of these studies received an e-mail with an explanation of the purpose of the study, an invitation for participation and a request to ensure their study would meet the inclusion criteria. No financial support was offered to participate in this meta-analysis.

We could not find valid e-mail addresses for four investigators, thus 96 investigators were contacted by e-mail of whom 60 responded. Eighteen of these declined because the data did not fully meet the inclusion criteria. Fourteen investigators declined for financial reasons, due to lack of time or interest, or lost contact after initial response. Finally, 28 investigators responded from whom 29 cohort studies were included in the meta-analysis.

Data extraction

The investigators who agreed to participate were requested to perform Cox regression analyses to calculate RRs of mortality for WC as a categorical and continuous variable following a protocol with instruction. All analyses were stratified by sex.

For the combined WC-BMI categories, WC categories defined by Lean and colleagues and used in practice[15–17] (i.e. <94, 94–101, ≥102 cm in men; <80, 80–87, ≥88 cm in women) and BMI categories underweight (<20 kg/m^2), 'healthy' weight (20–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (≥30 kg/m^2) were used. The investigators used a model to assess mortality risks for the 11 combined WC-BMI categories compared with the reference category ('healthy weight' and small waist) (Table 4.1). This model was adjusted for age and smoking status [current, former and never smokers (reference)].

Since previous studies have shown a U-shaped relation between WC and mortality,[10,11,21,22] the investigators used a model with WC as a continuous variable, including the linear and quadratic term of WC (WC and WC^2). The models were first only adjusted for age and smoking status, and subsequently for BMI as well. All analyses were performed over a follow-up period of ~5 years for all-cause mortality and, if available, for mortality from cardiovascular disease (CVD), cancer and respiratory disease (see Table 4.2 for definitions).

Additional analyses were performed for the models with WC as a categorical variable and WC as a continuous variable (with adjustment for BMI) for the following subgroups: subjects aged 65–69 years and 70–74 years; subjects aged 65–74 years; excluding mortality during the first 2 years of follow-up; excluding those with major chronic diseases (i.e. CVD, cancer and respiratory disease) at baseline; and only including never smokers.

Table 4.1 Sex-specific combinations of waist circumference (WC) and body mass index (BMI) categories used in the analyses

	WC categories (men/women)		
BMI categories	Small waist	Medium waist	Large waist
Underweight <20kg/m^2	<94cm/<80cm	94–101cm/80–87cm	≥102cm/≥88cm
'Healthy' weight 20–24.9kg/m^2	<94cm/<80cm (ref)	94–101cm/80–87cm	≥102cm/≥88cm
Overweight 25–29.9kg/m^2	<94cm/<80cm	94–101cm/80–87cm	≥102cm/≥88cm
Obese >30 kg/m^2	<94cm/<80cm	94–101cm/80–87cm	≥102cm/≥88cm

The investigators were not asked to test the proportional hazard assumption for each requested analysis because it was considered too onerous. Nevertheless, the proportional hazard assumption was tested for each analysis in eight cohort studies and no violations were found [(global) test of Schoenfeld p>0.05].

Descriptive statistics for each cohort (e.g. mean age, BMI and WC, number of subjects, total deaths, deaths from CVD, cancer and respiratory disease and percentage never smokers) were provided by the investigators.

Data synthesis and analysis

First, heterogeneity of the pooled RRs for the combined WC–BMI categories (received from the investigators) was tested by calculating the Cochran's chi-square, its p-value and the I^2 (percentage of variation across studies).[23] Heterogeneity in the continuous analyses was tested by a chi-squared test from the random effects model.[24] To account for any heterogeneity, a random-effects model was used for all models to pool the log RRs. For the combined WC–BMI categories, the log RR for each WC–BMI category was pooled by a univariate meta-analysis.[24] For the continuous analyses, we used a bivariate meta-analysis to pool the log RRs with the variance of each term and the covariance between terms.[25] To assess the association between continuous WC and mortality, we tested if the regression coefficients for both terms were equal to 0. To plot a parabolic function between WC and mortality, the lowest risk was calculated by $-\text{Estimate}_{WC}/(2*\text{Estimate}_{WC^2})$ which was the reference point (RR=1.0) for the function. The RRs associated with the commonly used cut-points of 102 cm in men and 88 cm in women were reported. Also, the values of WC associated with a RR of 2.0 which we consider a clinically relevant increased mortality risk as supported by the National Cancer Institute.[26] For the continuous analyses without and with adjustment for BMI, we tested the effect of BMI by means of a meta-regression analysis.[24]

Results

The 29 cohort studies included 32,678 men and 25,931 women aged 65–74 years of whom, respectively, 3,318 and 1,480 died. Table 4.2 shows the characteristics of the included cohorts by sex.

For the cohort studies where the cause of death was known (n=24), the proportion of deaths assigned to CVD was 40.7% for men and 33.3% for women, the corresponding proportions for cancer were 38.7% and 45.1% and for respiratory diseases, 6.8% and 4.0%.

Table 4.2 Characteristics of studies included in the meta-analysis of men and women (m/w) separately

Study	Mean Age (years)	Mean WC (cm)	Mean BMI (kg/m^2)	% Never smokers	Year(s) of baseline	Mean Follow-up (yr)	Self-reported (S) or Measured (M) BMI and WC	No. Available for analyses	No. All-cause mortality	No. CVD mortality	No. Cancer mortality	No. Respiratory mortality	Definition of end-point cause-specific mortality[a]
1913 Men Birth cohort[27]	67/n.a.	96/.n.a.	25/n.a.	23/n.a.	1980–1981	5.0/n.a.	M	707/n.a.	90/n.a.	53/n.a.	30/n.a.	1/n.a.	A
Aerobics Center Longitudinal Study[28]	67/68	94/79	26/25	64/80	1979–2003	4.9/5.0	M	1780/437	87/9	37/3	36/5	0/0	A,B
Australian National Heart Foundation Study[29]	67/67	95/83	27/26	27/63	1989–1990	4.6/4.9	M	346/384	95/39	39/11	40/14	0/0	B
British Regional Heart Study[30]	70/n.a.	98/n.a.	27/n.a.	28/n.a.	1998–2000	5.0/n.a.	M	2204/n.a.	282/n.a.	unknown	unknown	unknown	n.a.
Catalonia study[31]	69/69	97/71	26/23	23/94	1994–1995	5.0/4.8	M	207/228	21/5	6/0	8/2	5/0	A,B
Cardiovascular Health Study[6]	70/69	98/93	27/27	29/52	1989–90 & 1992–93	4.7/4.9	M	1850/2287	208/134	97/54	71/55	15/9	adjudicated by committee of physicians
Cohort Study in Spain[5]	70/70	103/98	28/30	28/93	2000–2001	4.7/4.8	M	675/1081	90/78	unknown	unknown	unknown	n.a.
Cohort of Swedish Men[32]	69/n.a.	97/n.a.	26/n.a.	37/n.a.	1997	5.1/n.a.	S	9014/n.a.	707/n.a.	359/n.a.	217/n.a.	41/n.a.	A
3C-Dijon Study[33]	70/70	95/83	26/26	29/80	1999–2001	5.8/5.9	M	979/1500	71/53	unknown	unknown	unknown	n.a.

Table 4.2 continues on next page

Table 4.2 *Continued*

Study	Mean Age (years)	Mean WC (cm)	Mean BMI (kg/m^2)	% Never smokers	Year(s) of baseline	Mean Follow-up (yr)	Self-reported (S) or Measured (M) BMI and WC	No. Available for analyses	No. All-cause mortality	No. CVD mortality	No. Cancer mortality	No. Respiratory mortality	Definition of end-point cause-specific mortality[a]
Doetinchem Cohort study[34]	68/68	101/95	27/28	15/56	1998–2002	4.8/4.9	M	236/224	19/7	5/3	8/2	0/0	B
North Carolina Established Populations for Epidemiologic Studies of the Elderly[35]	72/73	99/92	27/28	21/58	1992–1993	4.1/4.6	M	233/295	78/50	26/24	31/12	7/4	CVD: 390 to 459.9 (ICD-9); Cancer: 140 to 208.9 (ICD-9); Respiratory disease: 460 to 519.9 (ICD-9)
Finnish Twin Cohort[36]	n.a/70	n.a /90	n.a /28	n.a /87	1996–2001	4.9	M	n.a /404	n.a /18	n.a /5	n.a./10	n.a./0	A
Gubbio Population Study[37]	69/69	94/86	28/28	18/79	1988–1992	4.7/4.9	M	327/398	41/16	16/6	18/8	0/0	B
Health 2000 Health Examination Survey[38]	69/70	100/94	27/29	34/82	2000–2001	6.2/6.7	M	358/474	81/61	41/17	24/28	5/3	A
Harvard Alumni Health Study[39]	69/n.a.	94/n.a.	25	36/n.a.	1988	4.8/n.a.	M	4416/n.a.	338/n.a.	123/n.a.	152/n.a.	57/n.a.	ICD-7
Hoorn study[40]	69/70	96/89	26/27	8/61	1989–1990	4.7/4.8	M	345/439	49/37	13/13	22/14	1/1	B
Invecchiare in Chianti Study[41]	70/70	96/91	27/28	26/77	1998–2000	4.2/4.3	M	261/289	17/9	8/1	7/6	0/0	B
Longitudinal Aging Study Amsterdam[42]	70/70	99/96	26/28	7/53	1992–1993	4.6/4.8	M	388/415	68/31	26/12	29/11	5/1	A,B

MacArthur Successful Aging Study[43]	72/72	98/88	26/26	31/55	1988	5.9/6.4	M	303/349	79/48	19/16	29/13	10/3	A,B
Melbourne Collaborative Cohort Study[44]	67/67	95/82	27/27	32/72	1990–1994	5.6/5.7	M	3326/3919	305/174	101/47	146/100	15/8	CVD:I00–I99 (ICD-10); 390 to 459 (ICD-9) Cancer: C00–C97 (ICD-10); 140 to 209 (ICD-9) Respiratory disease: J00–J99 (ICD-10); 460 to 519 (ICD-9)
Normative Aging Study[45]	68/n.a.	99/n.a.	28/n.a.	30/n.a.	1990/1998	4.8/n.a.	M	809/n.a.	64/n.a.	11/n.a.	38/n.a.	8/n.a.	ICD-9: CVD: 410–414.9, 430–438.9; Cancer:140–208.9; Respiratory diseases: 460–519.9
Prospective Investigation of the Vasculature in Uppsala Seniors[46]	70/70	95/87	27/27	90/88	2001–2004	7/7	M	500/503	67/44	unknown	unknown	unknown	n.a.
Population Study of Women in Gothenburg[47]	n.a./71	n.a./85	n.a./26	n.a./59	1980–1981, 1992–1993, 2000–2001	n.a./5.0	M	n.a./915	n.a./51	n.a./19	n.a./21	unknown, (between 1 and 6)	Deaths during 1980–1991:Classified from death certificate; From 1991: A,B
Rotterdam study[48]	70/70	95/88	26/27	6/52	1989–1992	4.7/4.9	M	1028/1301	125/87	45/35	53/34	2/1	A

Table 4.2 continues on next page

Table 4.2 *Continued*

Study	Mean Age (years)	Mean WC (cm)	Mean BMI (kg/m^2)	% Never smokers	Year(s) of baseline	Mean Follow-up (yr)	Self-reported (S) or Measured (M) BMI and WC	No. Available for analyses	No. All-cause mortality	No. CVD mortality	No. Cancer mortality	No. Respiratory mortality	Definition of end-point cause-specific mortality[a]
Third Scottish Multinational MONItoring of trends and determinants in CArdiovascular disease study[49]	69/69	95/84	26/27	13/38	1992	4.5/4.6	M	200/212	46/30	unknown	unknown	unknown	n.a.
Survey in Europe on Nutrition and the Elderly: a Concerned Action[50]	72/73	97/89	26/27	20/84	1988–1990	4.5/4.8	M	751/773	163/65	62/28	53/34	14/1	B
Study of Health in Pomerania[51]	70/70	100/90	28/29	15/67	1997–2001	4.7/4.9	M	382/299	58/17	17/3	31/7	0/0	Death certificates and internists
Swedish Mammography Cohort[32]	n.a./69	n.a./85	n.a./25	n.a./65	1997	n.a./5.2	S	n.a./8210	n.a./385	n.a./118	n.a./199	n.a./16	A
Whitehall II study[52]	69/69	95/86	26/28	44/52	2002–2004	5.5/5.6	M	1323/595	101	21/10	31/16	1/4	A

[a] Endpoints defined by the International Classification of Diseases (ICD)-10: Cardiovascular diseases (CVD): I00–I99; Cancer: C00–97; Respiratory disease: J00–J99 are indicated with A. Endpoints defined by the ICD-9: CVD: 390–460; Cancer: 140–240; Respiratory disease: 460–520 are indicated with B. All exceptions are written out.
n.a.: Not available

In general, there was no substantial heterogeneity in the analyses regarding the combined WC-BMI categories resulting in an I^2<17.5% (p=0.22, for the chi-squared test) (Appendix 4, Figure 4.1, 4.2 available at http://ije.oxfordjournals.org/content/41/3/805/suppl/DC1). Similarly, no substantial heterogeneity was found in the continuous analyses (p=0.05 for the chi-squared test from the random-effects model (Appendix 4, Table 4.1 available at http://ije.oxfordjournals.org/content/41/3/805/suppl/DC1).

Associations between combined WC–BMI categories and mortality

For men and women, a large WC (≥102 cm, men; ≥88 cm, women) was associated with increased all-cause mortality RRs for those in the 'healthy' weight, overweight and obese BMI category compared with those classified as 'healthy' weight (20–24.9 kg/m^2) with a small WC (<94 cm, men; <80 cm, women) (Table 4.3). Overall, we observed a tendency for lower all-cause and CVD mortality risks in the overweight category compared with the 'healthy' weight category within WC categories for both men and women (men: $p_{all\text{-}cause}$=0.02, p_{CVD}=0.03; women: $p_{all\text{-}cause}$=0.18, p_{CVD}=0.36), although the RR for overweight men with a small WC in the association with CVD mortality was higher compared with 'healthy' weight men with a small waist (Table 4.3).

The risks of all-cause, CVD and cancer mortality were (although not statistically tested) higher for those with a large WC compared with those having a medium WC, except within the obese category in the association with all-cause and CVD mortality, and for women within the 'healthy' weight category in the association with cancer mortality (Table 4.3).

Underweight was associated with highest all-cause mortality RRs in men {2.2 [95% confidence interval (95%CI): 1.8–2.8]} and women [2.3 (95%CI: 1.8–3.1)]. The RRs for cancer mortality were of the same magnitude. For CVD, an increased risk was found for men [RR=2.9 (95%CI: 2.0–4.2)], but in women the RR was lower [RR=1.5 (95%CI: 0.8–2.8)] (Table 4.3).

Associations between WC as a continuous variable and mortality

All-cause mortality

We observed a J-shaped association between WC and all-cause mortality adjusted for age and smoking status (p<0.01) with the lowest risk at 94 cm and 77 cm for men and women, respectively (Figure 4.1a). The cut-points of 102 cm in men and 88 cm in women were associated with all-cause mortality RRs of 1.03 (95%CI: 1.00–1.07) and 1.06 (95%CI: 0.97–1.15), respectively. An RR of 2.0 was associated with a WC of 132 cm in men and 116 cm in women (Figure 4.1a).

Table 4.3 Relative Risk (95% Confidence Interval) of mortality from all causes, cardiovascular diseases (CVD) and cancer per combined WC-BMI category in men and women aged 65–74 years[a]

All-cause mortality				CVD mortality				Cancer mortality			
	Small waist	Medium waist	Large waist		Small waist	Medium waist	Large waist		Small waist	Medium waist	Large waist
Men				*Men*				*Men*			
Under-weight	2.2 (1.8–2.8)	N.A.	N.A.	Under-weight	2.9 (2.0–4.2)	N.A.	N.A.	Under-weight	2.1 (1.5–3.0)	N.A.	N.A.
Healthy weight	1.0	1.1 (1.0–1.3)	1.7 (1.2–2.2)	Healthy weight	1.0	1.4 (1.1–1.8)	2.6 (1.6–4.1)	Healthy weight	1.0	1.0 (0.7–1.4)	1.7 (0.5–6.2)
Over-weight	0.9 (0.8–1.0)	1.0 (0.9–1.1)	1.1 (1.0–1.3)	Over-weight	1.5 (1.2–1.9)	1.2 (1.0–1.5)	1.4 (1.1–1.8)	Over-weight	0.8 (0.6–1.2)	0.9 (0.8–1.1)	1.3 (1.0–1.6)
Obese	N.A.	1.2 (0.9–1.6)	1.1 (1.0 –1.3)	Obese	N.A.	2.3 (1.5–3.7)	1.7 (1.3–2.4)	Obese	N.A.	0.8 (0.5–1.5)	1.0 (0.8– 1.3)
Women				*Women*				*Women*			
Under-weight	2.3 (1.8–3.1)	N.A.	N.A.	Under-weight	1.5 (0.8–2.8)	N.A.	N.A.	Under-weight	2.6 (1.5–4.4)	N.A.	N.A.
Healthy weight	1.0	1.5 (1.2–1.8)	1.7 (1.3–2.3)	Healthy weight	1.0	1.2 (0.8–1.9)	2.2 (1.3–3.8)	Healthy weight	1.0	1.6 (1.1–2.3)	1.5 (0.9–2.4)
Over-weight	1.0 (0.7–1.4)	1.2 (0.9–1.5)	1.4 (1.1–1.7)	Over-weight	1.1 (0.5–2.3)	1.1 (0.7–1.7)	1.2 (0.8–1.7)	Over-weight	1.2 (0.7–2.1)	1.3 (0.9–1.9)	1.5 (1.1–2.2)
Obese	N.A.	1.6 (0.9–2.8)	1.6 (1.3–1.9)	Obese	N.A.	2.3 (0.9–5.7)	1.5 (1.1–2.2)	Obese	N.A.	1.3 (0.4–3.6)	1.4 (0.9–2.2)

[a] The number of studies used in the analyses differ because some studies did not have sufficient cases in a category. When analyzing all categories with the same number of studies who had information on all categories, the relative risks changed max. with 0.2.

*N.A. Not Available: If the number of studies was <5 then the RR for this category was not calculated, because of the low prevalence of these combinations.

Cause-specific mortality

Mortality from CVD, cancer and respiratory diseases were all associated with WC adjusted for age and smoking status in both men and women (p≤0.03) (Figure 4.1b–d). For CVD mortality, the lowest risk was at 89 cm and 63 cm for men and women, respectively. For men with a WC of 102 cm, the risk of CVD mortality was 1.11 (95%CI: 0.99–1.26) and for women with a WC of 88 cm this was 1.28 (95%CI: 0.92–1.77). An RR of 2.0 was associated with a WC of 123 cm in men and 105 cm in women (Figure 4.1b). For cancer mortality, the lowest risk was at 73 cm and 74 cm for men and women, respectively. For men with a WC of 102 cm, the risk of cancer mortality was 1.13 (95%CI: 0.74–1.71) and for women with a WC of 88 cm this was 1.07 (95%CI: 0.90–1.27) (Figure 4.1c). We observed a U-shaped relationship between WC and mortality from respiratory disease for both men and women. The lowest risk was at 104 cm for men and 99 cm for women. For men with a WC of 102 cm, the risk of mortality from respiratory diseases was 1.00 (95%CI: 0.98–1.03) and for women with a WC of 88 cm this was 1.15 (95%CI: 0.85–1.57) (Figure 4.1d).

Associations between WC as a continuous variable and mortality with adjustment for BMI

After adjusting for BMI, WC remained associated with mortality from all causes, CVD and cancer in both sexes, and with respiratory diseases in men but not in women. The curves for CVD mortality were similar to those that were not adjusted for BMI (p_{men}=0.99; p_{women}=0.62), but the curves for mortality from all causes (p_{men}<0.01; p_{women}<0.01) and respiratory diseases (p_{men}<0.01; p_{women}=0.40) were shifted to the left for both sexes, and for cancer only in women (p=0.15). Thus, the lowest risks were at lower values of WC, and the RRs associated with a similar WC were higher after adjusting for BMI compared with the analyses unadjusted for BMI (Figures 4.1a–d). The curve of cancer mortality in men became linear after adjustment for BMI (Figure 4.1c).

Additional analyses

We restricted our additional analyses to the four most relevant categories (i.e. underweight with a small WC, 'healthy' weight, overweight and obese combined with a large WC), because these categories gave the most consistent and strongest RRs in the main analyses. The associations between the WC-BMI categories and all-cause and CVD mortality did not differ by age group (Appendix 2, Table 2.1, 2.2 available at http://ije.oxfordjournals.org/content/41/3/805/suppl/DC1). Excluding the first 2 years of follow-up, or major chronic

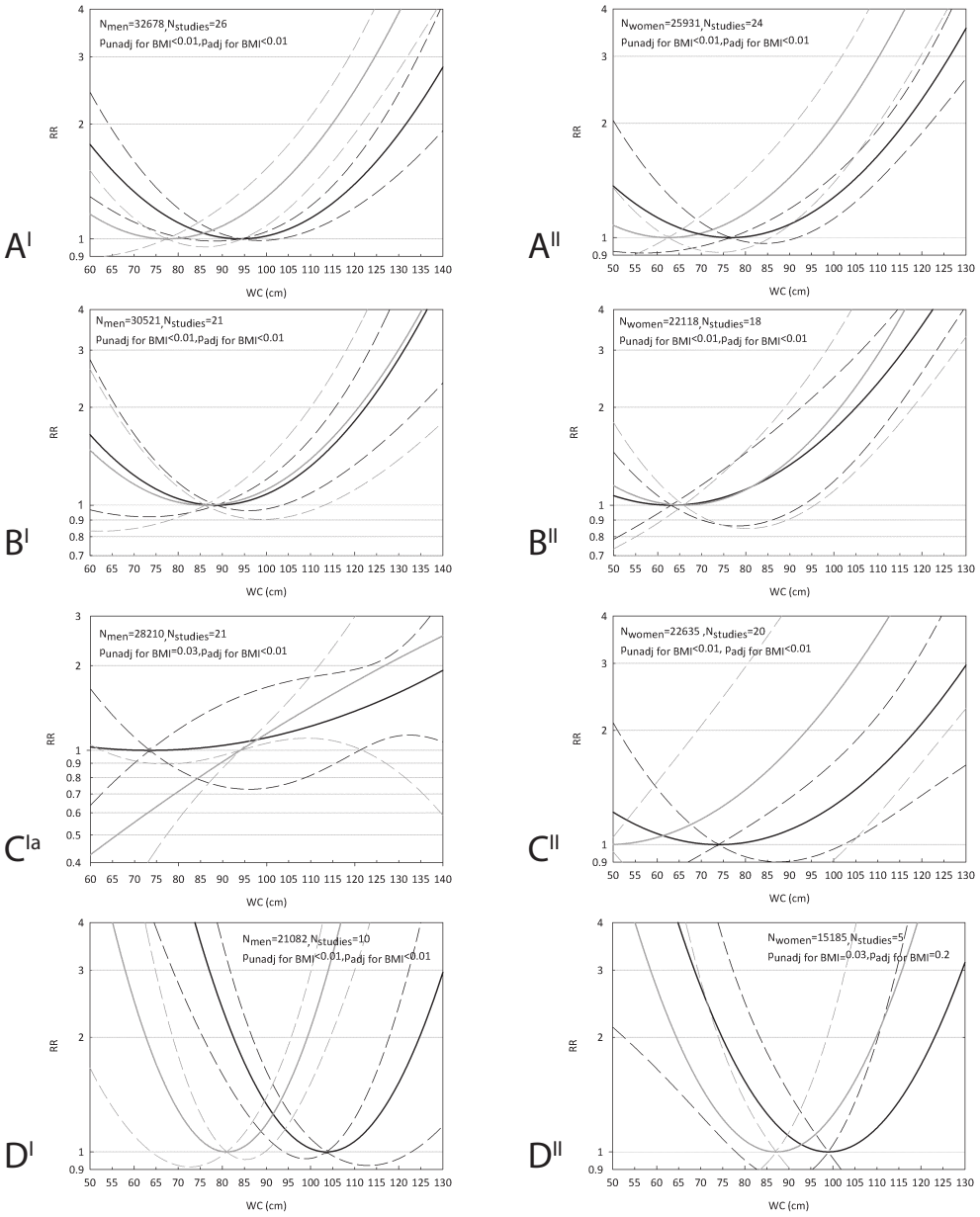


Figure 4.1 Relative risks of mortality from all causes (A), cardiovascular diseases (B), cancer (C), and respiratory disease (D) in men(I) and women(II) aged 65–74 years for waist circumference as a continuous variable. All models were adjusted for age and smoking. In panel A–D solid lines indicate relative risks and dashed lines indicate 95% confidence intervals. The black lines indicate the analyses unadjusted for body mass index and the grey lines indicate the analyses with the adjustment for body mass index. [a]In this figure, for the analysis adjusted for body mass index, a minimum of 94 cm was used, because there was no longer a parabolic association.

diseases at baseline, or only including never smokers did not change the interpretation of our findings (Appendix 3, Table 3.1, Figure 3.1 available at http://ije.oxfordjournals.org/content/41/3/805/suppl/DC1).

We found some differences between the main analyses and additional analyses. After excluding the first 2 years of follow-up, we observed an RR of 1.6 (95%CI: 0.8–3.2) for CVD mortality risk in women with a 'healthy' weight and a large WC, compared with an RR of 2.2 (95%CI: 1.3–3.8) including all subjects. However, the additional analyses confirmed that for those with a large WC being in the 'healthy' weight category is associated with a higher RR (1.6) than the overweight category [RR=1.3; (95%CI: 0.8–2.0)]. Furthermore, the analyses for continuous WC showed a similar pattern for all-cause mortality (Appendix 3, Table 3.1, Figure 3.1 available at http://ije.oxfordjournals.org/content/41/3/805/suppl/DC1).

After exclusion of major chronic diseases at baseline, the RR for CVD mortality in underweight men was 2.5 (95%CI: 0.8–7.7) compared with an RR of 3.3 (95%CI: 1.5–7.3) including all men, but still this confirms that underweight is associated with CVD mortality with an RR of at least 2.0 (Appendix 3, Table 3.1, Figure 3.1 available at http://ije.oxfordjournals.org/content/41/3/805/suppl/DC1).

Results for never smokers were comparable to the total population, except for the CVD mortality risks in men with a large WC and overweight/obesity, which were higher among never smoking men (RR=2.2) than for the total population [RR=1.3 (overweight+large WC]; RR=1.5 (obesity+large WC)]. In women, the patterns of the curves for the continuous analyses of WC were similar, but in men the steepness of the curves differed. As a consequence, in never smoking men, higher WC levels were accompanied by lower RRs for all-cause mortality compared with the RRs in all men (Appendix 3, Table 3.1, Figure 3.1 available at http://ije.oxfordjournals.org/content/41/3/805/suppl/DC1).

Discussion

This meta-analysis of 29 cohort studies, which included a total of 58,609 elderly people of whom 4,798 died during 5 years of follow up, showed that both an increased WC and underweight according to BMI) were associated with an increased risk of all-cause, CVD and cancer mortality risk.

Consistent with our study, others have reported stronger associations between WC (as a continuous variable) and mortality after adjustment for BMI.[5,6,11,14,21,53] We also found that the RR of mortality in persons with a 'healthy' weight combined with a large waist was generally

higher than for those with overweight and a large waist. These findings might be explained by body fat composition, in particular the proportion of hazardous visceral abdominal fat.[54] In contrast to other studies, we also found strong associations with increased risks of mortality, particularly from all causes and CVD, but also from cancer, without adjustment for BMI.[5,6,9,12,13] For respiratory diseases, a U-shaped association was observed between WC and mortality, whereas other studies reported an inverse association.[9,12]

Our results of the combined categories are difficult to compare with other studies as they have used different combined WC-BMI categories, reference categories, study groups or other outcome measures.[6,12,55] However, these studies also found that underweight was associated with higher risks of coronary heart disease in adults,[55] and all-cause and CVD mortality in the elderly.[12]

In our study, all analyses were conducted in a similar manner by the original investigators addressing the specific age-range of 65–74 years. This may be the reason that in general there appeared to be no substantial heterogeneity between studies. We included two cohort studies, one restricted to only men, the other only women, which excluded participants with cancer at baseline in the original data and used self-reported data of WC and BMI. However, excluding these studies from the analyses did not change our results meaningfully (data not shown).

Another strength of the included studies is that no overrepresentation of higher estimates of RR among studies with low precision (i.e. small studies) was detected in our data suggesting no substantial selection bias (Appendix 4 available at http://ije.oxfordjournals.org/content/41/3/805/suppl/DC1). We had a low response, only 28 out of 100 investigators participated but reasons for non-participation depended primarily on lack of time or financial sources. We included cohort studies according to their study characteristics rather than the published analyses. This meta-analysis was conducted according to a specific analysis protocol, requiring new analyses for each cohort; the exact information (required for this study) was not available in the literature already. Therefore, we do not think there is any participation bias in our study. Also, the additional analyses excluding the first 2 years, excluding major chronic diseases at baseline and including only never smokers did not affect our main conclusions.

To keep all analyses as similar as possible, we did not adjust for covariates, such as diet, physical activity and socio-economic status. These variables differ between studies in operationalization, and are often self-reported and thereby less accurate. Furthermore, two studies showed no major differences between the crude and adjusted risks (for these

covariates) of mortality associated with WC.[11,14] However, this might not have been the case if more precise measures were included. Sui and colleagues reported an association between abdominal obesity (≥102 cm, ≥88 cm) and all-cause mortality in adults ≥60 years [RR: 1.3 (95%CI: 1.0–1.6)], similar to our results, but this association attenuated after adjustment for cardiorespiratory fitness [RR: 1.0 (95%CI: 0.8–1.3)].[56] This would imply that WC might not be independently associated with all-cause mortality and that cardiorespiratory fitness may be considered as an indicator instead. More research is needed to confirm these findings of Sui and colleagues, and to add evidence to underpin practical application. Finally, our analyses did not account for weight loss or weight gain prior to baseline, which both can be predictive of mortality risk,[57] possibly due to underlying illnesses. However, the additional analysis when excluding major chronic diseases at baseline, did not affect the interpretation of our findings.

Another methodological issue is that the adjustment for BMI in the continuous analyses might have caused multicollinearity resulting in a less precise estimate with wide confidence intervals. However, in our analyses, the CIs were not substantially wider, which is supported by the lack of a near perfect correlation between BMI and WC (rho<0.95) and the variance inflation factor did not exceed 5.

In our study, underweight was associated with a high RR of mortality, which is commonly explained by underlying diseases or smoking. After excluding those with chronic diseases at baseline, or the first 2 years of follow-up, or including only never smokers this association persisted. This might be explained by the association of low BMI with malnutrition[58] and sarcopenia[59] which are in turn both associated with higher mortality risks.[60,61] In addition, elderly people with underweight may have low-grade inflammation,[62] and might be frailer.[63] These mechanisms might contribute to the vulnerability for external hazards which can lead to death. More research into possible mechanisms is necessary to give more insight into the risk of mortality in underweight persons and give suitable recommendations for the treatment of the elderly.

Interestingly, we found lower all-cause and CVD mortality risks in the overweight category compared with the 'healthy' weight category within WC categories for both men and women, but only in men accompanied by a p<0.05, probably because women had wider CIs. The lower risks within the overweight category are congruent with other studies which found that the lowest mortality risk was associated with overweight and an increased risk was in the 'healthy' weight category, indicating that the 'healthy' weight category might not be appropriate for the elderly.[12,64–67] An explanation for this finding could be the age-

related decline in height among the elderly which might induce a false increase in BMI.[7] Furthermore, as mentioned above for underweight, these elderly persons with low BMI are prone to external hazards, whereas overweight might provide a metabolic buffer for diseases as previously reported in older people with chronic conditions.[68] Therefore, the cut-point of 25 kg/m^2 to indicate excess adiposity might not be appropriate for the elderly.

We found that a large waist (≥102 cm, men; ≥88 cm, women) was consistently associated with all-cause and CVD mortality within the 'healthy' weight, overweight and obese BMI category. This finding was supported by our continuous analyses, which showed that an increased risk was associated with an increased WC either with or without adjustment for BMI. Furthermore, our results provide a solid basis for re-evaluation of currently defined cut-points for WC, which are based on adults aged 20–74 years.[15] From our continuous analysis, we found no relevant elevated mortality risks between the value of the lowest risk and the standard WC cut-points of 102 cm for men and 88 cm for women. This suggests that cut-points for the elderly should be defined at higher WC values. For CVD mortality, a twofold increased risk was seen at WC levels of 123 cm for men and 105 cm for women, which can be considered as clinically relevant (almost) beyond discussion. However, we do not suggest that these levels should be the new WC cut-points. Thresholds to be used in (clinical) guidelines should be based on opinions and consensus about the relevance of increased risks – as found in epidemiological studies – which can differ. For example, Heim and colleagues[69] suggested new WC cut-points of between 100 cm and 106 cm in men and 99 cm in women based on several health outcomes,[69] which especially in women is indeed higher than the currently advocated cut-points.[16,17] In addition, when defining cut-points to be used in clinical guidelines, the absolute prevalence rates need to be considered for practical reasons. We performed additional analyses in seven cohorts (data not shown in the article) to illustrate this issue, which revealed that the prevalence rates sharply increased between a WC level of 123 cm (1–2%) and 102 cm (12–48%) in men, with a similar pattern in women. So, a level of WC in between would include a large part of the population that is at risk and needs to be treated according to clinical guidelines.

In conclusion, in this elderly population, we found increased mortality risks associated with an increased WC – even across BMI categories – and also with being underweight according to BMI. Clinicians should be made aware of the usefulness of WC to measure adiposity in order to determine mortality risk in the elderly. This meta-analysis provides a solid basis for re-evaluation of WC cut-points in ageing populations.

Acknowledgements

We want to thank Rik P Bogers for his contribution to the design of the meta-analysis. Further, we want to thank Joyce van Yperen for analysing the data of the SENECA and Hoorn study. Bogers and van Yperen did not receive any compensation and confirmed their agreement. E.L.de.H. had full access to all of the data in the study (that were provided to her by the collaborating investigators) and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: W.J.E.B., L.C.P.G.M.d.G., Bogers and H.C.B. Acquisition of data: E.L.de.H. Statistical analysis: E.L.de.H., H.C.B. Interpretation of data: E.L.de.H., W.J.E.B., H.C.B., N.F., H.W., P.G.-C., S.W., M.C.Z., A.R., L.L., J.K.B., G.G.G., N.H., M.V., L.C.P.G.M.d.G. Drafting the article: E.L.d.H., W.J.E.B. Critical revision of the article: E.L.d.H., W.J.E.B., H.C.B., N.F., H.W., P.G.-C., S.W., M.C.Z., A.R., L.L., J.K.B., G.G.G., N.H., M.V., L.C.P.G.M.d.G. Study supervision: W.J.E.B. WC elderly collaborators: All other investigators of the collaboration contributed by collecting data and calculating RRs. 1913 Men Birth Cohort: A. Rosengren, V. Sundh; Aerobics Center Longitudinal Study (ACLS): S. Blair, D.C. Lee, X. Sui; Australian National Heart Foundation Study (ANHFS): M. Woodward, T. Welborn, S. Dhaliwal; British Regional Heart Study (BRHS): G. Wannamethee; Catalonia Study: E. Roure, C. Castell; Cardiovascular Health Study (CHS): M.L. Biggs, Cohort of Swedish Men (COSM): A. Wolk, N. Orsini; 3C-Dijon Study: P. Ducimetiere; Doetinchem Cohort Study: M. Verschuren; Finnish Twin Cohort: J. Kaprio; Gubbio Population Study: A. Menotti; Harvard Alumni Health Study (HAHS): I.M. Lee, H. Sesso; Health 2000 Survey: P. Knekt, K. Sääksjärvi; Hoorn Study: J. Dekker, G. Nijpels, C. Stehouwer; Invecchiare in Chianti (InCHIANTI) Study: S. Bandinelli, A.M. Corsi, F. Lauretani; Longitudinal Aging Study Amsterdam (LASA): M. Visser, N. Heim; MacArthur Successful Aging Study: T. Seeman, S. Ishii; Melbourne Collaborative Cohort Study (MCCS): G. Giles, J. Bassett; Normative Aging Study (NAS): A. Spiro; North Carolina Established Populations for Epidemiologic Studies of the Elderly (EPESE): C. Phillips, D. Blazer; Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS): L. Lind; Rotterdam Study: M.C. Zillikens, A. Uitterlinden, A. Hofman, S. Walter, H. Tiemeier; Survey in Europe on Nutrition and the Elderly: a Concerned Action (SENECA): L. de Groot; Study of Health in Pomerania (SHIP): H. Wallaschofski, N. Friedrich, S. Baumeister; Cohort Study in Spain: P. Guallar-Castillón, F. Rodriguez-Artalejo; Study of Women in Gothenburg: L. Lissner, V. Sundh, I. Skoog; Swedish Mammography Cohort: A. Wolk, N. Orsini; Third Scottish MONICA Study: M. Woodward, H. Tunstall-Pedoe; Whitehall II Study: M. Shipley, M. Kivimäki.

References

1. Branca F, Nikogosian H, Lobstein T. *The challenge of obesity in the WHO European Region and the strategies for response.* Denmark: World Health Organization, 2007.
2. Eiben G, Dey DK, Rothenberg E, et al. Obesity in 70-year-old Swedes: secular changes over 30 years. *Int J Obes (Lond)* 2005;29(7): 810–817.
3. Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Ann Intern Med* 2003;138(1): 24–32.
4. Grabowski DC, Ellis JE. High body mass index does not predict mortality in older people: analysis of the Longitudinal Study of Aging. *J Am Geriatr Soc* 2001;49(7): 968–979.
5. Guallar-Castillon P, Balboa-Castillo T, Lopez-Garcia E, et al. BMI, waist circumference, and mortality according to health status in the older adult population of Spain. *Obesity (Silver Spring)* 2009;17(12): 2232–2238.
6. Janssen I, Katzmarzyk PT, Ross R. Body mass index is inversely related to mortality in older people after adjustment for waist circumference. *J Am Geriatr Soc* 2005;53(12): 2112–2118.
7. Zamboni M, Mazzali G, Zoico E, et al. Health consequences of obesity in the elderly: a review of four unresolved questions. *Int J Obes (Lond)* 2005;29(9): 1011–1029.
8. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres JP. A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. *Am J Clin Nutr* 1996;64(5): 685–693.
9. Baik I, Ascherio A, Rimm EB, et al. Adiposity and mortality in men. *Am J Epidemiol* 2000;152(3): 264–271.
10. Dolan CM, Kraemer H, Browner W, Ensrud K, Kelsey JL. Associations between body composition, anthropometry, and mortality in women aged 65 years and older. *Am J Public Health* 2007;97(5): 913–918.
11. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008;359(20): 2105–2120.
12. Price GM, Uauy R, Breeze E, Bulpitt CJ, Fletcher AE. Weight, shape, and mortality risk in older persons: elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. *Am J Clin Nutr* 2006;84(2): 449–460.
13. Reis JP, Macera CA, Araneta MR, Lindsay SP, Marshall SJ, Wingard DL. Comparison of overall obesity and body fat distribution in predicting risk of mortality. *Obesity (Silver Spring)* 2009;17(6): 1232–1239.
14. Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women. *Circulation* 2008;117(13): 1658–1667.
15. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. *Bmj* 1995;311(6998): 158–161.

16. *Obesity : preventing and managing the global epidemic: report of a WHO consultation*. Geneva: World Health Organization, 2000.

17. *Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults*. Canberra: National Health & Medical Research Council, 2003.

18. Visscher TL, Seidell JC, Molarius A, van der Kuip D, Hofman A, Witteman JC. A comparison of body mass index, waist-hip ratio and waist circumference as predictors of all-cause mortality among the elderly: the Rotterdam study. *Int J Obes Relat Metab Disord* 2001;25(11): 1730–1735.

19. Bogers RP, Bemelmans WJE, Hoogenveen RT, et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. *Arch Intern Med* 2007;167(16): 1720–1728.

20. *World Population Prospects, The 2006 Revision, Highlights*. New York: United Nations; 2007.

21. Bigaard J, Tjonneland A, Thomsen BL, Overvad K, Heitmann BL, Sorensen TI. Waist circumference, BMI, smoking, and mortality in middle-aged men and women. *Obes Res* 2003;11(7): 895–903.

22. Folsom AR, Kushi LH, Anderson KE, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. *Arch Intern Med* 2000;160(14): 2117–2128.

23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Bmj* 2003;327(7414): 557–560.

24. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002;21(4): 589–624.

25. Riley RD, Abrams KR, Lambert PC, Sutton AJ, Thompson JR. An evaluation of bivariate random-effects meta-analysis for the joint synthesis of two correlated outcomes. *Stat Med* 2007;26(1): 78–97.

26. National Cancer Institute, US National Institute of Health, *Epidemiology in a nutshell*. 2002. http://benchmarks.cancer.gov/2002/07/epidemiology-in-a-nutshell/(20 December 2011, date last accessed).

27. Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *Br Med J (Clin Res Ed)* 1984;288(6428): 1401–1404.

28. Lee CD, Sui X, Blair SN. Combined effects of cardiorespiratory fitness, not smoking, and normal waist girth on morbidity and mortality in men. *Arch Intern Med* 2009;169(22): 2096–2101.

29. Dhaliwal SS, Welborn TA. Central obesity and multivariable cardiovascular risk as assessed by the Framingham prediction scores. *Am J Cardiol* 2009;103(10): 1403–1407.

30. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Decreased muscle mass and increased central adiposity are independently related to mortality in older men. *Am J Clin Nutr* 2007;86(5): 1339–1346.

31. Castell C, Tresserras R, Serra J, Goday A, Lloveras G, Salleras L. Prevalence of diabetes in Catalonia (Spain): an oral glucose tolerance test-based population study. *Diabetes Res Clin Pract* 1999;43(1): 33–40.

32. Levitan EB, Yang AZ, Wolk A, Mittleman MA. Adiposity and incidence of heart failure hospitalization and mortality: a population-based prospective study. *Circ Heart Fail* 2009;2(3): 202–208.

33. Mahamat A, Richard F, Arveiler D, et al. Body mass index, hypertension and 5-year coronary heart disease incidence in middle aged men: the PRIME study. *J Hypertens* 2003;21(3): 519–524.

34. Verschuren WM, Blokstra A, Picavet HS, Smit HA. Cohort profile: the Doetinchem Cohort Study. *Int J Epidemiol* 2008;37(6): 1236–1241.

35. Cornoni-Huntley J, Ostfeld AM, Taylor JO, et al. Established populations for epidemiologic studies of the elderly: study design and methodology. *Aging (Milano)* 1993;5(1): 27–37.

36. Kaprio J, Kujala UM, Koskenvuo M, Sarna S. Physical activity and other risk factors in male twin-pairs discordant for coronary heart disease. *Atherosclerosis* 2000;150(1): 193–200.

37. Menotti A, Lanti M, Puddu PE, et al. First risk functions for prediction of coronary and cardiovascular disease incidence in the Gubbio Population Study. *Ital Heart J* 2000;1(6): 394–399.

38. Knekt P, Reunanen A, Jarvinen R, Seppanen R, Heliovaara M, Aromaa A. Antioxidant vitamin intake and coronary mortality in a longitudinal population study. *Am J Epidemiol* 1994;139(12): 1180–1189.

39. Lee IM, Paffenbarger RS, Jr. Change in body weight and longevity. *Jama* 1992;268(15): 2045–2049.

40. Wedick NM, Snijder MB, Dekker JM, et al. Prospective investigation of metabolic characteristics in relation to weight gain in older adults: the Hoorn Study. *Obesity (Silver Spring)* 2009;17(8): 1609–1614.

41. Ferrucci L, Bandinelli S, Benvenuti E, et al. Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *J Am Geriatr Soc* 2000;48(12): 1618–1625.

42. Huisman M, Poppelaars J, van der Horst M, et al. Cohort Profile: The Longitudinal Aging Study Amsterdam. *Int J Epidemiol* 2011;40(4): 868–876.

43. Srikanthan P, Seeman TE, Karlamangla AS. Waist-hip-ratio as a predictor of all-cause mortality in high-functioning older adults. *Ann Epidemiol* 2009;19(10): 724–31.

44. Giles GG, English DR. The Melbourne Collaborative Cohort Study. *IARC Sci Publ* 2002;156: 69–70.

45. Bell B, Rose CL, Damon A. The Veterans Administration longitudinal study of healthy aging. *Gerontologist* 1966;6(4): 179–184.

46. Ahlstrom T, Hagstrom E, Larsson A, Rudberg C, Lind L, Hellman P. Correlation between plasma calcium, parathyroid hormone (PTH) and the metabolic syndrome (MetS) in a community-based cohort of men and women. *Clin Endocrinol (Oxf)* 2009;71(5): 673–678.

47. Lissner L, Bjorkelund C, Heitmann BL, Seidell JC, Bengtsson C. Larger hip circumference independently predicts health and longevity in a Swedish female cohort. *Obes Res* 2001;9(10): 644–646.

48. Hofman A, Breteler MM, van Duijn CM, et al. The Rotterdam Study: objectives and design update. *Eur J Epidemiol* 2007;22(11): 819–829.

49. Tunstall-Pedoe H, Woodward M, Tavendale R, A'Brook R, McCluskey MK. Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish Heart Health Study: cohort study. *Bmj* 1997;315(7110): 722–729.

50. Van 't Hof MA, Hautvast JG, Schroll M, Vlachonikolis IG. Design, methods and participation. Euronut SENECA investigators. *Eur J Clin Nutr* 1991;45 Suppl 3: 5–22.

51. Volzke H, Alte D, Schmidt CO, et al. Cohort profile: the study of health in Pomerania. *Int J Epidemiol* 2011;40(2): 294–307.

52. Fransson EI, Batty GD, Tabak AG, et al. Association between change in body composition and change in inflammatory markers: an 11-year follow-up in the Whitehall II Study. *J Clin Endocrinol Metab* 2010;95(12): 5370–5374.

53. Jacobs EJ, Newton CC, Wang Y, et al. Waist Circumference and All-Cause Mortality in a Large US Cohort. *Arch Intern Med* 2010;170(15): 1293–1301.

54. Janssen I, Heymsfield SB, Allison DB, Kotler DP, Ross R. Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fat. *Am J Clin Nutr* 2002;75(4): 683–688.

55. Wormser D, Kaptoge S, Di Angelantonio E, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 2011;377(9771): 1085–1095.

56. Sui X, LaMonte MJ, Laditka JN, et al. Cardiorespiratory fitness and adiposity as mortality predictors in older adults. *Jama* 2007;298(21): 2507–2516.

57. Bamia C, Halkjaer J, Lagiou P, et al. Weight change in later life and risk of death amongst the elderly: the European Prospective Investigation into Cancer and Nutrition-Elderly Network on Ageing and Health study. *J Intern Med* 2010;268(2): 133-144.

58. Venzin RM, Kamber N, Keller WC, Suter PM, Reinhart WH. How important is malnutrition? A prospective study in internal medicine. *Eur J Clin Nutr* 2009;63(3): 430–436.

59. Szulc P, Duboeuf F, Marchand F, Delmas PD. Hormonal and lifestyle determinants of appendicular skeletal muscle mass in men: the MINOS study. *Am J Clin Nutr* 2004;80(2): 496–503.

60. Saletti A, Johansson L, Yifter-Lindgren E, Wissing U, Osterberg K, Cederholm T. Nutritional status and a 3-year follow-up in elderly receiving support at home. *Gerontology* 2005;51(3): 192–198.

61. Roubenoff R. Sarcopenia and its implications for the elderly. *Eur J Clin Nutr* 2000;54 Suppl 3: S40–7.

62. Nakajima K, Yamaoka H, Morita K, et al. Elderly people with low body weight may have subtle low-grade inflammation. *Obesity (Silver Spring)* 2009;17(4): 803–808.

63. Hubbard RE, Lang IA, Llewellyn DJ, Rockwood K. Frailty, body mass index, and abdominal obesity in older people. *J Gerontol A Biol Sci Med Sci* 2010;65(4): 377–381.

64. Allison DB, Gallagher D, Heo M, Pi-Sunyer FX, Heymsfield SB. Body mass index and all-cause mortality among people age 70 and over: the Longitudinal Study of Aging. *Int J Obes Relat Metab Disord* 1997;21(6): 424–431.

65. Flicker L, McCaul KA, Hankey GJ, et al. Body mass index and survival in men and women aged 70 to 75. *J Am Geriatr Soc* 2010;58(2): 234–241.

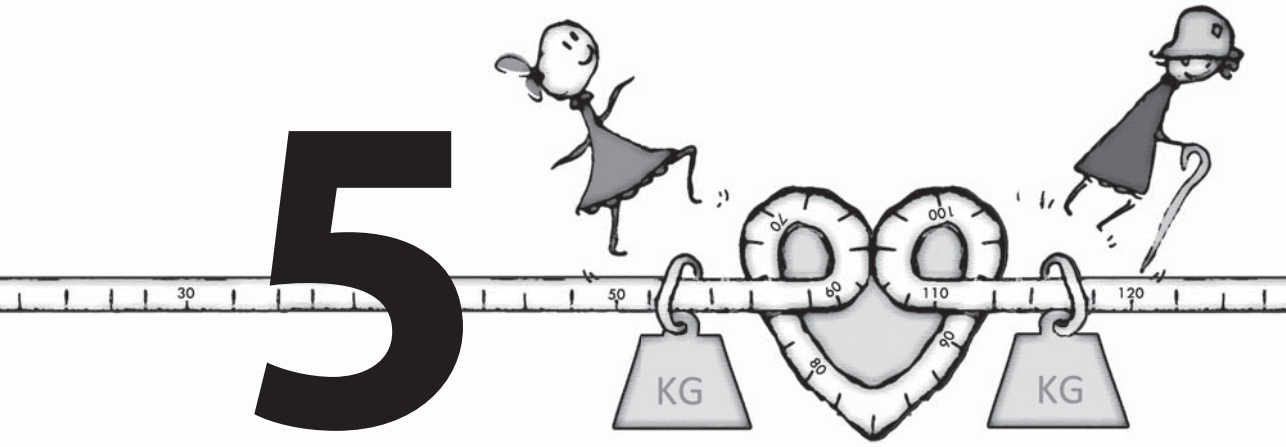
66. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. *Obes Rev* 2007;8(1): 41–59.

67. de Hollander EL, van Zutphen M, Bogers RP, Bemelmans WJE, de Groot LCPGM. The impact of body mass index in old age on cause-specific mortality. *J Nutr Health Aging* 2012;16(1):100–106.

68. Romero-Corral A, Montori VM, Somers VK, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006;368(9536): 666–678.

69. Heim N, Snijder MB, Heymans MW, Deeg DJ, Seidell JC, Visser M. Optimal cutoff values for high-risk waist circumference in older adults based on related health outcomes. *Am J Epidemiol* 2011;174(4): 479–489.

5



Associations between changes in anthropometric measures and mortality in old age: a role for mid-upper arm circumference?

Ellen L de Hollander, Wanda JE Bemelmans, Lisette CPGM de Groot

J Am Med Dir Assoc. 2013;14(3):187–193.

Abstract

Objectives: In elderly individuals, little is known about changes in different anthropometric measure with respect to mortality. We examined the association between changes in eight anthropometric measures and mortality in an elderly population.

Design: Longitudinal study including baseline measurements in 1988–1990 and repeated measures in 1993.

Setting: European towns.

Participants: A total of 1,061 older adults born in 1913–1918 from the *Survey in Europe on Nutrition and the Elderly: a concerted action* study were included in this study.

Measurements: Weight, body mass index, waist circumference, waist-hip ratio, waist-height ratio, mid-upper arm circumference (MUAC), triceps-skinfold and corrected arm muscle area were taken during both measurements.

Results: A Cox regression model was used to examine the association between anthropometric changes (divided into quintiles, smallest change = reference category) and all-cause and cardiovascular disease (CVD) mortality over approximately 6 years of follow-up, adjusted for baseline measurement of application, age, sex, smoking, education, physical activity and major chronic diseases. A decrease in weight (≥3.2 kg), waist circumference (≥3.1 cm), and MUAC (≥1.6 cm and 0.6–1.6 cm) were (near) significantly associated with an all-cause mortality risk of 1.48 (95%CI: 0.99–2.20), 1.52 (95%CI: 1.01–2.31), 1.81 (95%CI: 1.17–2.79) and 1.66 (95%CI: 1.10–2.49), respectively. Also for MUAC, an increase (≥1.3 cm) was significantly associated with an increased all-cause and CVD mortality risk [HR: 1.52 (95%CI: 1.00–2.31) and 1.94 (95%CI: 1.00–3.75)], respectively.

Conclusions: Associations were observed for decreases in only 3 out of 8 anthropometric measures and all-cause mortality. Decreases in MUAC had the strongest associations with mortality and was the only measure in which also an increase was associated with mortality. This suggests a role for MUAC in the prediction of mortality in the elderly.

Introduction

The association between measures of body composition and mortality in elderly persons has been examined in many studies.[1-5] Body mass index (BMI), a measure of overall body fat, is commonly used in practice as a predictor for morbidity and mortality. However, abdominal adiposity measures, such as, waist circumference (WC), waist-hip ratio (WHR) and waist-height ratio (WHtR) have been shown to be better predictors for cardiovascular events and mortality in adults than BMI.[6-8] For elderly people, BMI might not be the strongest predictor of mortality, since body composition changes with increasing age, e.g. muscle mass reduces, height decreases, and fat mass increases, which is redistributed to the stomach area.[9] Nevertheless, for elderly persons an association with mortality has been reported for a high BMI, as well as for a high WC.[1,10] But for an increased WC, adjusted for BMI an increased mortality risk was reported,[1,11,12] while for an increased BMI, adjusted for WC an inverse association was reported.[11,12] Thus, abdominal adiposity measures need to be considered for the elderly in the use of predicting mortality risks with regard to excess body fat.[13]

Other anthropometric measures like the triceps skinfold thickness (TSF), mid-upper arm circumference (MUAC), and corrected arm muscle area (CAMA, calculated from TSF and MUAC) are generally used to assess nutritional status and also body fat. TSF reflects the subcutaneous fat mass, whereas MUAC reflects the muscle mass as well as fat mass, and CAMA reflects only the muscle mass. Several studies found that a low value in these measures was associated with an increased mortality risk in elderly persons.[2,4,5,14] These measures can be valuable for clinical practice; in elderly people problems can occur with standing in an upright position because of frailty or a kyphotic posture, as well as with errors in body weight caused by fluid status (dehydration or oedema).

Next to baseline anthropometric measures, weight changes can be used as predictors for mortality. In elderly persons, especially weight loss was found to be associated with an increased mortality risk, but for weight gain, these findings were less consistent.[15-17]

Because changes in weight can depend on several factors (e.g. changes in body fluid or muscle mass) and the body composition in old age has changed, it is important to examine whether changes of several different anthropometric measures within one elderly population are predictive for mortality. To our knowledge this has not been done before; therefore we examined in a 70–77 year old European population the association between changes in eight anthropometric measures (weight, BMI, WC, WHR, WHtR, MUAC, TSF and CAMA) and all-cause and cardiovascular disease (CVD) mortality.

Methods

Study population

The SENECA (*Survey in Europe on Nutrition and the Elderly, a Concerted Action*) study started in 1988. Elderly persons born between 1913 and 1918 were eligible to participate in the study. The only exclusion criteria were: living in a psycho-geriatric nursing home, not being fluent in the country's language, and not being able to answer questions independently. Participants were selected at baseline from an age- and sex-stratified sample of inhabitants from 19 European towns. The median participation rate of the 19 towns was 51%.[18] Of these towns, Hamme, Belgium; Roskilde, Denmark; Haguenau, France; Romans, France; Padua, Italy; Culemborg, the Netherlands; Vila Franca de Xira, Portugal; Betanzos, Spain; Yverdon, Switzerland; Marki, Poland also participated in the second survey in 1993. All participants gave their written informed consent. Approval of the study was obtained from the participating SENECA centers.

Anthropometric measures

Weight, height, WC, hip circumference (HC), MUAC and TSF were measured in the first and second survey by a trained fieldworker, as described previously.[19] BMI (kg/m^2), WHR (WC/HC) and WHtR (WC/m) were calculated. CAMA was calculated for men and women separately by using MUAC and TSF in the equation developed by Heymsfield and collegaues:[20]

$$CAMA = [(MUAC - \pi \times (TSF / 10)^2) / (4 \times \pi)] - i;$$

i = 10 for men, and 6.5 for women.

Changes in weight, BMI, WC, WHR, WHtR, MUAC, TSF and CAMA were calculated by subtracting the baseline value from the value at the second survey over a mean interval of 4 years (range: 3–6 years). Changes in anthropometric measures were subsequently divided into quintiles. The quintile with the smallest change, including a change of zero, was defined as the reference category.

Covariates

Information on smoking habits, physical activity, education level and chronic diseases at baseline were obtained by questionnaires. Smoking habits were divided into three categories: never smoker, former smoker and current smoker. Physical activity consisted

of household, sports and leisure-time activities, which were estimated using a validated questionnaire.[21] The three categories of physical activity were defined by sex specific tertiles. High education level was defined as secondary or higher education and low education level as primary education only or illiteracy. Chronic diseases (i.e. diabetes, ischemic heart disease, stroke, malignancy and respiratory disease) were measured at baseline with a questionnaire in which having a specific disease could be answered with yes or no.

Mortality

Information on vital status and causes of death was collected in 1999–2000. The follow-up period on which mortality was calculated lasted from the second survey in 1993 until April 30th 1999. Cause of death was obtained through death certificates collected at the local government offices in towns where death had occurred or, if this data was not available, via a medical doctor or first-degree relatives. Cause of death was coded by one experienced clinical epidemiologist using the 9th revision of the World Health Organization International Classification of Disease (ICD-9).[22] Mortality caused by CVD was defined by using ICD-9 codes: 390–459.

Statistical analysis

From the 2,080 participants, 246 participants (12%) died before the second survey and 640 (31%) participants were lost to follow-up, who could therefore not be included in the analysis. One hundred and thirty three participants (6%) had missing values on all anthropometric measures at baseline and second survey, or on one of the covariates and were therefore excluded from the analysis. In total, 1,061 subjects remained left for the analysis with data available at both baseline and the second survey of at least one anthropometric measure. Dependent on the anthropometric measure, the final number of subjects in the analyses varied between 976 and 1,053. Finally, five subjects had one or two anthropometric measure(s) with a very unlikely value, which were set as a missing value, but were not excluded.

Characteristics of the study population are presented as frequencies and percentages or mean and standard deviation. To check for participation or selection bias, we compared the excluded group, without the ones who died before 1993 (n=773), with the included group by means of a Chi-square test for categorical variables and an independent samples t-test for continuous variables. The same tests were used to compare the characteristics between men and women from the included group.

A Cox regression analysis was used to examine the association between the anthropometric changes and all-cause and CVD mortality over a follow-up period of approximately 6 years. The analyses were adjusted for anthropometric measurement of application, age, sex, education level, smoking habits, physical activity, study centre and having diabetes, ischemic heart disease, stroke, malignancy or respiratory disease at baseline. The proportional hazard assumption was tested for all models and no major violations of the assumption were found ($p>0.05$).

Linear and quadratic trends were tested for the exposure variables by using median values of the quintiles in the Cox regression model. Interactions between anthropometric changes and sex were examined to check for possible differences between men and women. In addition, sensitivity analyses were performed by excluding subjects with major chronic diseases (i.e. diabetes, ischemic heart disease, stroke, malignancy or respiratory disease) at baseline.

Data were analysed using SAS System for Windows version 9.2 (SAS Institute Inc., Cary, North Carolina, USA) and statistical significance was established at $p<0.05$.

Results

The baseline characteristics of the included and excluded participants are presented in Table 5.1. The group of excluded participants were 0.2 years older and consisted of more women than the group of included participants ($p<0.05$, Table 5.1). The excluded participants with data on baseline anthropometrics and demographics had a higher BMI (0.5 kg/m^2), WC (1.3 cm), WHtR (1.1), MUAC (0.4 cm) and TSF (1 mm) and consisted of more participants with a low education level and low physical activity level ($p<0.05$, Table 5.1) than the included participants. Finally, excluded participants had a shorter survival time (0.6 years, $p<0.01$) than the included participants (Table 5.1).

From the included participants under study, the percentage of persons with a high education, former and current smokers, and persons with respiratory diseases was higher in men than in women. Women had on average a lower weight, WC, WHR, WHtR, CAMA and a higher TSF (Table 5.1).

All-cause mortality

The hazard ratios (HRs) for all-cause mortality per quintile for the eight anthropometric measures are presented in Table 5.2. For changes in BMI, WHR, WHtR, TSF and CAMA, no

associations with all-cause mortality were found, except for an increase in WC between 0.8 and 3.0 cm [1.61 (95%CI: 1.08–2.39)] and a decrease in TSF between 1.3 and 4.1 mm [0.61 (95%CI: 0.41–0.93)].

For a decrease in weight (≥3.2 kg) and WC (≥3.1 cm), increased all-cause mortality risks of 1.48 (95%CI: 0.99–2.20) and 1.52 (95%CI: 1.01–2.31) were observed.

Table 5.1 Baseline characteristics of included study participants by sex and baseline characteristics of excluded participants

Variable	$Total_{included}$ n=1,061	$Men_{included}$ n=516	$Women_{included}$ n=545	$p\text{-value}_{sex*}$	$Total_{excluded}$ n=773	$p\text{-value}_{incl\ vs\ excl*}$
Sex, n_{men} (%)	516 (49)				337 (44)	0.03
Age, mean (SD), years	72.9 (1.8)	72.9 (1.8)	72.9 (1.7)	0.70	73.1(2.0)	0.01
Weight, mean (SD), kg	69.2 (12.5)	74.3(11.1)	64.4 (11.9)	<0.001	69.9 (12.5)	0.27
BMI, mean (SD), kg/m^2	26.5 (4.1)	26.5 (3.5)	26.6 (4.6)	0.58	27.0 (4.3)	0.02
WC, mean (SD), cm	92.2 (11.6)	96.9 (9.7)	87.7 (11.5)	<0.001	93.4 (11.5)	0.03
WHR, mean (SD)	0.91 (0.08)	0.96 (0.06)	0.86 (0.07)	<0.001	0.91 (0.08)	0.99
WHtR, mean (SD)	57.1 (6.9)	57.9 (5.9)	56.4 (7.6)	<0.001	58.3 (7.2)	0.002
MUAC, mean (SD), cm	29.2 (3.3)	29.2 (2.8)	29.1 (3.6)	0.51	29.5 (3.4)	0.03
TSF, mean (SD), mm	16.5 (7.5)	11.9 (5.2)	21.0 (6.7)	<0.001	17.5 (7.7)	0.01
CAMA, mean (SD), cm^2	38.1 (10.5)	42.1 (9.7)	34.2 (9.9)	<0.001	38.6 (10.8)	0.38
Education, n (%)				<0.001		0.01
Illiteracy/ Primary	681 (64)	293 (57)	388 (71)		537 (70)	
Secondary/ Higher	380 (36)	223 (43)	157 (29)		231 (30)	
Smoking status, n (%)				<0.001		0.44
Never smoker	574 (54)	116 (22)	458 (84)		436 (56)	
Former smoker	310 (29)	261 (51)	49 (9)		205 (27)	
Current smoker	177 (17)	139 (27)	38 (7)		132 (17)	
Physical activity, n (%)				0.90		<0.001
Low	287 (27)	139 (27)	148 (27)		283 (37)	
Moderate	382 (36)	183 (35)	199 (37)		249 (33)	
High	392 (37)	194 (38)	198 (36)		234 (31)	
Chronic diseases, n (%)						
Diabetes	73 (7)	32 (6)	41 (8)	0.40	61 (8)	0.41
Ischemic heart disease	167 (16)	88 (17)	79 (15)	0.25	121 (16)	0.97
Stroke	20 (2)	13 (3)	7 (1)	0.14	16 (2)	0.78
Malignancy	17 (2)	7 (1)	10 (2)	0.54	17 (2)	0.35
Respiratory diseases	97 (9)	65 (13)	32 (6)	<0.001	81 (10)	0.34
One or more disease(s)	314 (30)	131 (25)	119 (22)	0.17	246 (32)	0.31

SD: standard deviation, BMI: body mass index, WC: waist circumference, WHR: waist to hip ratio, WHtR: Waist to height ratio, MUAC: mid-upper arm circumference, TSF: triceps skinfold thickness, CAMA: corrected arm muscle area. *Chi-square test was used for categorical variables and a Student's t-test was used for continuous variables. Statistical difference: p<0.05.

Table 5.2 Hazard Ratios* (95% Confidence Interval) of all-cause mortality for anthropometric changes in older adults aged 70–77yrs

	Weight		BMI		WC		WHR	
n_{total}	1,053		1,031		982		976	
n_{event}	268		261		253		249	
	Quintiles	HR (95%CI)	Quintiles	HR (95%CI)	Quintiles	HR (95%CI)	Quintiles	HR (95%CI)
	≤-3.2 kg	1.48 (0.99–2.20)	≤-1.01 kg/m^2	1.20 (0.81–1.78)	≤-3.1 cm	1.52 (1.01–2.31)	≤-0.04	0.89 (0.57–1.37)
	-3.2 to -1.0 kg	1.25 (0.84–1.88)	-1.01 to -0.21 kg/m^2	1.16 (0.79–1.70)	-3.0 to 0.7 cm	1.0	-0.04 to -0.01	0.83 (0.55–1.25)
	-0.9 to 0.6 kg	1.0	-0.21 to 0.53 kg/m^2	1.0	0.8 to 3.0 cm	1.61 (1.08–2.39)	-0.01 to 0.02	1.0
	0.7 to 2.7 kg	1.14 (0.76–1.72)	0.53 to 1.42 kg/m^2	0.92 (0.62–1.37)	3.1 to 6.9 cm	0.96 (0.62–1.48)	0.02 to 0.05	0.85 (0.57–1.28)
	≥2.8 kg	0.94 (0.62–1.41)	≥1.42 kg/m^2	0.97 (0.66–1.42)	≥7.0 cm	1.25 (0.81–1.94)	≥0.05	1.31 (0.86–1.98)
p_{linear}	0.02		0.17		0.43		0.10	
$p_{quadratic}$	0.79		0.82		0.37		0.20	

	WHtR		MUAC		TSF		CAMA	
n_{total}	959		1,016		1,002		999	
n_{event}	243		263		260		258	
	Quintiles	HR (95%CI)	Quintiles	HR (95%CI)	Quintiles	HR (95%CI)	Quintiles	HR (95%CI)
	≤-1.6	1.26 (0.84–1.90)	≤-1.6 cm	1.81 (1.17–2.79)	≤-4.1 mm	1.03 (0.68–1.57)	≤-6.4 cm^2	1.14 (0.73–1.77)
	-1.6 to 0.5	1.0	-1.6 to -0.6 cm	1.66 (1.10–2.49)	-4.1 to -1.3 mm	0.61 (0.41–0.93)	-6.4 to -1.9 cm^2	1.14 (0.77–1.67)
	0.5 to 2.2	1.21 (0.82–1.80)	-0.5 to 0.3 cm	1.0	-1.3 to 0.4 mm	1.0	-1.8 to 2.2 cm^2	1.0
	2.2 to 4.6	0.72 (0.47–1.11)	0.4 to 1.3 cm	1.30 (0.85–1.98)	0.5 to 2.9 mm	0.68 (0.45–1.02)	2.2 to 6.5 cm^2	0.76 (0.50–1.16)
	≥4.6	1.07 (0.70–1.64)	≥1.3 cm	1.52 (1.00–2.31)	≥2.9 mm	0.94 (0.62–1.43)	≥6.6 cm^2	1.08 (0.73–1.59)
p_{linear}	0.28		0.24		0.94		0.59	
$p_{quadratic}$	0.21		0.05		0.08		0.36	

* The models were adjusted for baseline anthropometrics, age, sex, education level, smoking, physical activity, diabetes, ischemic heart disease, stroke, malignancy, respiratory diseases and study centre.

For MUAC, a decrease of ≥1.6 cm and a decrease between 0.6 and 1.6 cm were associated with all-cause mortality risks of 1.81 (95%CI: 1.17–2.79) and 1.66 (95%CI: 1.10–2.49), respectively. Also, an increase in MUAC of ≥1.3 cm was associated with an increased all-cause mortality risk of 1.52 (95%CI: 1.00–2.31). These findings were accompanied with a significant quadratic trend ($p_{quadratic}$=0.05).

Cardiovascular disease mortality

The HRs for CVD mortality are presented in Table 5.3. No associations were observed for anthropometric changes and CVD mortality, except for a decrease in WHR between 0.01 and 0.04 [0.45 (95%CI: 0.22–0.93)], an increase in WHtR between 2.2 and 4.6 [0.41 (95%CI: 0.18–0.92)] and a decrease in TSF between 4.1 and 1.3 mm [0.43 (95%CI: 0.21–0.86)]. In addition, an increase in MUAC of ≥1.3 cm was associated with an increased CVD mortality risk of 1.94 (95%CI: 1.00–3.75).

Interactions between anthropometric changes and sex

We observed no significant interactions (p>0.05) between anthropometric changes and sex in the association with all-cause and CVD mortality for BMI, WHR, WHtR, TSF and CAMA (data not shown). For weight and WC, we only observed a nearly significant interaction with sex for a decrease in WC of ≥3.1 cm (p=0.07) and an increase in WC between 3.1 and 6.9 cm (p=0.04). The risks for all-cause mortality for these categories were lower in women (Appendix A, Table 4a,b; see publication: http://www.sciencedirect.com/science/article/pii/S1525861012003465). For MUAC, no interactions with sex were observed (p≥0.09). The risks for all-cause mortality for a decrease in MUAC (≥1.6 cm and 0.6–1.6 cm) and the risks for all-cause and CVD mortality for an increase in MUAC (≥1.3 cm) were in the same (positive) direction for men and women (Appendix A, Table 4c and 5; see publication: http://www.sciencedirect.com/science/article/pii/S1525861012003465).

Sensitivity analyses

Our main findings of positive associations for changes in weight, WC and MUAC with all-cause and CVD mortality were still present when excluding subjects with major chronic diseases at baseline, although some associations became weaker (Appendix B; see publication: http://www.sciencedirect.com/science/article/pii/S1525861012003465).

Table 5.3 Hazard Ratios* (95% Confidence Interval) of CVD mortality for anthropometric changes in older adults aged 70–77yrs

	Weight		BMI		WC		WHR	
n_{total}	1,053		1,031		982		976	
n_{event}	100		96		94		93	
	Quintiles	HR (95%CI)	Quintiles	HR (95%CI)	Quintiles	HR (95%CI)	Quintiles	HR (95%CI)
	≤-3.2 kg	1.09 (0.58–2.08)	≤-1.01 kg/m^2	1.08 (0.57–2.06)	≤-3.1 cm	1.41 (0.68–2.93)	≤-0.04	0.62 (0.31–1.21)
	-3.2 to -1.0 kg	0.88 (0.45–1.72)	-1.01 to -0.21 kg/m^2	1.14 (0.60–2.13)	-3.0 to 0.7 cm	1.0	-0.04 to -0.01	0.45 (0.22–0.93)
	-0.9 to 0.6 kg	1.0	-0.21 to 0.53 kg/m^2	1.0	0.8 to 3.0 cm	1.90 (0.98–3.63)	-0.01 to 0.02	1.0
	0.7 to 2.7 kg	0.98 (0.52–1.88)	0.53 to 1.42 kg/m^2	0.98 (0.51–1.89)	3.1 to 6.9 cm	0.87 (0.40–1.89)	0.02 to 0.05	0.66 (0.34–1.28)
	≥2.8 kg	0.85 (0.45–1.60)	≥1.42 kg/m^2	0.99 (0.52–1.89)	≥7.0 cm	1.48 (0.73–2.99)	≥0.05	1.11 (0.57–2.15)
p_{linear}	0.50		0.69		0.89		0.10	
$p_{quadratic}$	0.97		0.92		0.70		0.58	
	WHtR		MUAC		TSF		CAMA	
n_{total}	959		1,016		1,002		999	
n_{event}	90		99		97		97	
	Quintiles	HR (95%CI)	Quintiles	HR (95%CI)	Quintiles	HR (95%CI)	Quintiles	HR (95%CI)
	≤-1.6	0.93 (0.47–1.84)	≤-1.6 cm	1.47 (0.70–3.10)	≤-4.1 mm	0.61 (0.31–1.20)	≤-6.4 cm^2	1.29 (0.59–2.84)
	-1.6 to 0.5	1.0	-1.6 to -0.6 cm	1.45 (0.72–2.91)	-4.1 to -1.3 mm	0.43 (0.21–0.86)	-6.4 to -1.9 cm^2	1.75 (0.93–3.30)
	0.5 to 2.2	1.25 (0.67–2.32)	-0.5 to 0.3 cm	1.0	-1.3 to 0.4 mm	1.0	-1.8 to 2.2 cm^2	1.0
	2.2 to 4.6	0.41 (0.18–0.92)	0.4 to 1.3 cm	1.42 (0.73–2.78)	0.5 to 2.9 mm	0.69 (0.36–1.31)	2.2 to 6.5 cm^2	0.79 (0.39–1.63)
	≥4.6	1.00 (0.52–1.93)	≥1.3 cm	1.94 (1.00–3.75)	≥2.9 mm	0.92 (0.47–1.78)	≥6.6 cm^2	1.52 (0.81–2.86)
p_{linear}	0.78		0.38		0.16		0.85	
$p_{quadratic}$	0.66		0.14		0.86		0.27	

*The models were adjusted for baseline anthropometrics, age, sex, education level, smoking, physical activity, diabetes, ischemic heart disease, stroke, malignancy, respiratory diseases and study centre.

Discussion

In this study of European elderly persons aged 70 to 77 years, we found no consistent associations with all-cause and CVD mortality for changes in 5 out of 8 anthropometric measures. Decreases in 3 anthropometric measures were associated with increased all-cause mortality risks. MUAC showed the most consistent associations with all-cause mortality and was the only measure from which an increase was associated with all-cause and CVD mortality.

The SENECA study provided information from a geographically broad elderly population who were selected according to a standardized methodology to provide a representative sample of the population born in 1913–1918 from 19 towns.[18] This has the advantage to generalize our results on a broader scale than just one country. Although, measurements were taken in different centres, these were carried out by a standardized protocol and thereby controlling for variation. This was supported by no consistent significant interactions between anthropometric changes and centres (data not shown). Nevertheless, we adjusted for centre to rule out any possible confounding. Furthermore, we were able to adjust for many potential confounders.

In our study, we could not distinguish between intentional and unintentional weight loss. This may have important implications in the evaluation of weight loss effects on mortality, since unintentional weight loss may reflect underlying diseases that lead to increased mortality.[9,23] However, measuring intentionality might be prone to bias as it is often measured after the weight loss period.[24] Studies with intentionality measured before the weight loss period showed increased mortality risks regardless of the intention, suggesting underlying mechanisms that can lead to increased long-term mortality, although weight loss was intended.[24]

During the second survey (1993), only 10 towns kept participating in the study and the participants' health had changed, which led to drop out.[25] This resulted in a healthier population than had originally entered the study.[25] Therefore, we expected that anthropometric changes might have been larger in the sample that was lost to follow-up. However, our population did not differ consistently on all baseline anthropometrics from the ones that were lost to follow-up, and the differences were relatively small, although some were statistically significant. Because of the relatively good health of our population, the observed changes could be considered to reflect changes due to ageing, rather than underlying diseases. This was supported by our sensitivity analysis with the exclusion of persons with chronic diseases at baseline that did not affect our main findings as presented

in the results section. Furthermore, we carried out two extra analyses in which persons who died during the first two years of follow-up were excluded and in which we adjusted for having a chronic disease at baseline or the second survey, to account for diseases that might have developed between the two measurements. These extra analyses did not affect our main findings (data not shown).

We found no consistent associations for 5 out of 8 anthropometric (BMI, WHR, WHtR, TSF and CAMA) measures. There were some associations for WHR, WHtR and TSF with mortality, but these were more likely to be caused by chance than can be explained by biological factors or population characteristics. Most of these measures were calculated from two measures, which probably introduce more measuring errors than when it consists of one single measure. BMI and WHtR both include height, which in elderly persons decreases with age, and thus introduces inaccuracy and an overestimation of the body fat measure. This is important since BMI is still a commonly used measure of body fat. TSF can be difficult to measure in elderly people which was demonstrated by the discrepancy that occurred in the measurements by different observers in Roskilde, Denmark.[19] This might explain why we did not find an association with mortality for these measures.

Our result of an increased risk for a weight loss of ≥3.2 kg was similar to previous findings in an elderly population.[15,17,26-28] In contrast to other studies,[17,27,28] we did not find an increased mortality risk associated with weight gain. This might be explained by the use of methods, e.g. the statistical analysis, definition of weight change and especially the period on which weight gain was calculated. Weight gain in the longer term might be more strongly associated with an increased mortality risk than weight gain during a short period, as suggested by Bamia and collegaues.[17]

Because of the redistribution of fat in elderly persons, we expected to find associations between changes in WC and mortality. However, we only found an association between a decrease of ≥3.1 cm in WC and all-cause mortality, which is comparable with the finding of weight loss. The association between changes in WC and mortality was previously studied in a middle-aged population, in which a positive linear association between WC changes (per 5 cm) and mortality was found after adjustment for changes in BMI.[29] We did not combine two measures in our analyses, because the interpretation and application for clinical practice would be difficult. When we adjusted the analyses for changes in WC and all-cause mortality for changes in BMI or weight, an increase of ≥3.1 cm was (near) significantly associated with all-cause mortality [HR: 1.59 (95%CI: 0.96–2.61) and 1.75 (95%CI: 1.07–2.88, respectively)]. These results might be explained by a better reflection of the gain in hazardous abdominal fat, when changes in BMI are fixed.

MUAC was the only measure in which decreases (≤-1.6 cm and -0.6 to -1.6 cm) as well as an increase (≥1.3 cm) were associated with all-cause mortality and in which an increase (≥1.3 cm) was associated with CVD mortality. Our results of an increased all-cause mortality risk associated with a decrease in MUAC is corresponding with previous literature reporting higher mortality risks for a low MUAC.[2,5] The decrease in MUAC probably indicates a decrease in muscle mass, reflecting sarcopenia that is associated with disability, frailty and mortality,[30] but could also reflect a decrease in (subcutaneous) fat that might indicate a lost of metabolic or nutritional buffer to survive a disease.[31] The associations between an increase in MUAC and all-cause and CVD mortality are more difficult to explain. The increase in MUAC probably reflects a gain in subcutaneous fat mass. Subcutaneous fat mass might not be particularly hazardous for the elderly, but MUAC might give a better reflection of changes in overall fat mass since it is less prone to measuring errors and has an exceptionally good reproducibility (intraclass correlation (ICC)=0.98 between observers, ICC=0.99 within observers).[32] In addition, this measure is very practical to use in the elderly as it can be measured in a standing and sitting position.[32] Furthermore, the strength of our findings for MUAC were enforced when we observed that the associations with mortality remained present after adjusting for changes in other anthropometric measures during additional analyses (data not shown).

Conclusion

In this European elderly population of 70–77 years old, we found no consistent associations for changes in 5 out of 8 anthropometric measures. Decreases in three single anthropometric measures were associated with all-cause mortality. This again stresses the importance of preventing weight loss in elderly persons, as reported more often in the elderly literature. Associations between decreases in MUAC and all-cause mortality were the strongest of all single measures and seemed to have better discriminative power as associations for both decrement quintiles were observed. In addition, MUAC was the only measure in which also an increase was associated with all-cause and CVD mortality. Therefore, this highly applicable anthropometric measure can be recommended for clinical practice to observe body compositional changes in elderly people in order to prevent diseases and mortality. Nevertheless, since we are the first examining changes in this anthropometric measure, more research is recommended to confirm these findings in other elderly populations.

Acknowledgements

This study used data from the Survey in Europe on Nutrition and the Elderly, a Concerted Action: the SENECA Study. The authors thank all the SENECA principal investigators. Furthermore, the authors thank Rosemarie Wijnands for her guided contribution to the manuscript during her internship.

References

1. de Hollander EL, Bemelmans WJ, Boshuizen HC, Friedrich N, Wallaschofski H, Guallar-Castillon P, et al. The association between waist circumference and risk of mortality considering body mass index in 65- to 74-year-olds: a meta-analysis of 29 cohorts involving more than 58 000 elderly persons. *Int J Epidemiol.* 2012;41(3):805–817.
2. Enoki H, Kuzuya M, Masuda Y, Hirakawa Y, Iwata M, Hasegawa J, et al. Anthropometric measurements of mid-upper arm as a mortality predictor for community-dwelling Japanese elderly: the Nagoya Longitudinal Study of Frail Elderly (NLS-FE). *Clin Nutr.* 2007;26(5):597–604.
3. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. *Jama.* 2005;293(15):1861–1867.
4. Miller MD, Crotty M, Giles LC, Bannerman E, Whitehead C, Cobiac L, et al. Corrected arm muscle area: an independent predictor of long-term mortality in community-dwelling older adults? *J Am Geriatr Soc.* 2002;50(7):1272–1277.
5. Wijnhoven HA, van Bokhorst-de van der Schueren MA, Heymans MW, de Vet HC, Kruizenga HM, Twisk JW, et al. Low mid-upper arm circumference, calf circumference, and body mass index and mortality in older persons. *J Gerontol A Biol Sci Med Sci.* 2010;65(10):1107–1114.
6. Schneider HJ, Friedrich N, Klotsche J, Pieper L, Nauck M, John U, et al. The predictive value of different measures of obesity for incident cardiovascular events and mortality. *J Clin Endocrinol Metab.* 2010;95(4):1777–1785.
7. Lee K, Song YM, Sung J. Which obesity indicators are better predictors of metabolic risk?: healthy twin study. *Obesity (Silver Spring).* 2008;16(4):834–840.
8. Petursson H, Sigurdsson JA, Bengtsson C, Nilsen TI, Getz L. Body configuration as a predictor of mortality: comparison of five anthropometric measures in a 12 year follow-up of the Norwegian HUNT 2 study. *PLoS One.* 2011;6(10):e26621.
9. Zamboni M, Mazzali G, Zoico E, Harris TB, Meigs JB, Di Francesco V, et al. Health consequences of obesity in the elderly: a review of four unresolved questions. *Int J Obes (Lond).* 2005;29(9):1011–1029.
10. de Hollander EL, Van Zutphen M, Bogers RP, Bemelmans WJ, De Groot LC. The impact of body mass index in old age on cause-specific mortality. *J Nutr Health Aging.* 2012;16(1):100–106.

11. Guallar-Castillon P, Balboa-Castillo T, Lopez-Garcia E, Leon-Munoz LM, Gutierrez-Fisac JL, Banegas JR, et al. BMI, waist circumference, and mortality according to health status in the older adult population of Spain. *Obesity (Silver Spring)*. 2009;17(12):2232–2238.

12. Janssen I, Katzmarzyk PT, Ross R. Body mass index is inversely related to mortality in older people after adjustment for waist circumference. *J Am Geriatr Soc.* 2005;53(12):2112–2118.

13. Seidell JC. Waist circumference and waist/hip ratio in relation to all-cause mortality, cancer and sleep apnea. *Eur J Clin Nutr.* 2010;64(1):35–41.

14. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Decreased muscle mass and increased central adiposity are independently related to mortality in older men. *Am J Clin Nutr.* 2007;86(5):1339–1346.

15. Newman AB, Yanez D, Harris T, Duxbury A, Enright PL, Fried LP. Weight change in old age and its association with mortality. *J Am Geriatr Soc.* 2001;49(10):1309–1318.

16. Myrskyla M, Chang VW. Weight change, initial BMI, and mortality among middle- and older-aged adults. *Epidemiology.* 2009;20(6):840–848.

17. Bamia C, Halkjaer J, Lagiou P, Trichopoulos D, Tjonneland A, Berentzen TL, et al. Weight change in later life and risk of death amongst the elderly: the European Prospective Investigation into Cancer and Nutrition-Elderly Network on Ageing and Health study. *J Intern Med.* 2010;268(2): 133–144.

18. Van 't Hof MA, Hautvast JG, Schroll M, Vlachonikolis IG. Design, methods and participation. Euronut SENECA investigators. *Eur J Clin Nutr.* 1991;45 Suppl 3:5–22.

19. de Groot CP, Perdigao AL, Deurenberg P. Longitudinal changes in anthropometric characteristics of elderly Europeans. SENECA Investigators. *Eur J Clin Nutr.* Jul 1996;50 Suppl 2:S9–15.

20. Heymsfield SB, McManus C, Smith J, Stevens V, Nixon DW. Anthropometric measurement of muscle mass: revised equations for calculating bone-free arm muscle area. *Am J Clin Nutr.* 1982;36(4):680–690.

21. Voorrips LE, Ravelli AC, Dongelmans PC, Deurenberg P, Van Staveren WA. A physical activity questionnaire for the elderly. *Med Sci Sports Exerc.* 1991;23(8):974–979.

22. WHO. *International classification of diseases, ninth revision.*World Health Organization: Geneva, Switzerland, 1987.

23. Wannamethee SG, Shaper AG, Lennon L. Reasons for intentional weight loss, unintentional weight loss, and mortality in older men. *Arch Intern Med.* 2005;165(9):1035–1040.

24. Sorensen TI. Weight loss causes increased mortality: pros. *Obes Rev.* 2003;4(1):3–7.

25. van't Hof MA, Burema J. Assessment of bias in the SENECA study. *Eur J Clin Nutr.* 1996;50 Suppl 2:S4–8.

26. Lee CG, Boyko EJ, Nielson CM, Stefanick ML, Bauer DC, Hoffman AR, et al. Mortality risk in older men associated with changes in weight, lean mass, and fat mass. *J Am Geriatr Soc.* 2011;59(2):233–240.

27. Somes GW, Kritchevsky SB, Shorr RI, Pahor M, Applegate WB. Body mass index, weight change, and death in older adults: the systolic hypertension in the elderly program. *Am J Epidemiol.* 2002;156(2):132–138.

28. Breeze E, Clarke R, Shipley MJ, Marmot MG, Fletcher AE. Cause-specific mortality in old age in relation to body mass index in middle age and in old age: follow-up of the Whitehall cohort of male civil servants. *Int J Epidemiol.* 2006;35(1):169–178.

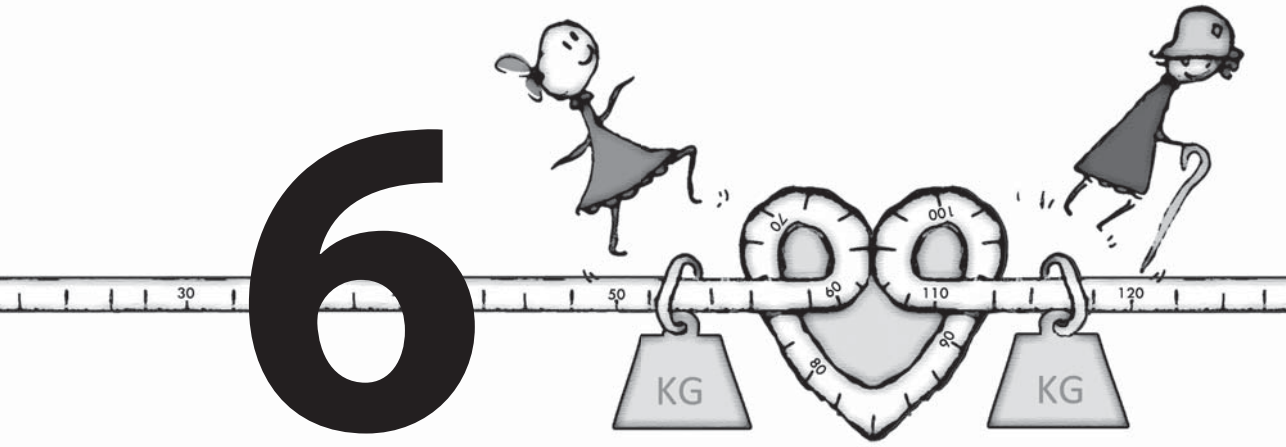
29. Berentzen TL, Jakobsen MU, Halkjaer J, Tjonneland A, Overvad K, Sorensen TI. Changes in waist circumference and mortality in middle-aged men and women. *PLoS One.* 2010;5(9).

30. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc.* 2011;12(4):249–256.

31. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet.* 2006;368(9536):666–678.

32. Burden ST, Stoppard E, Shaffer J, Makin A, Todd C. Can we use mid upper arm anthropometry to detect malnutrition in medical inpatients? A validation study. *J Hum Nutr Diet.* 2005;18(4):287–294.

6



Changes in weight and health-related quality of life: The Doetinchem Cohort Study

Ivon EJ Milder, Ellen L de Hollander, H Susan Picavet,
WM Monique Verschuren, Lisette CPGM de Groot, Wanda JE Bemelmans

Submitted for publication.

Abstract

Background: The cross-sectional association between obesity and a lower health-related quality of life (HRQL) is clear. However, less is known about the association between changes in weight and HRQL. We examined the association between weight changes and changes in HRQL in a population-based sample of 2,005 men and 2,130 women aged 26 to 70 years.

Methods: Weight was measured 2 or 3 times with 5-year intervals between 1995 and 2009; and was categorized as stable (change ≤2kg, 40%), weight loss (19%), or weight gain 2.1–4.0 kg, 4.1–6.0 kg, or >6 kg (41%). Changes in HRQL (SF36 questionnaire, including physical and mental scales) per weight change category were compared with a stable weight using generalized estimating equations.

Results: Weight gain was associated with declines of up to 5 points on five mainly physical scales and holds for different age categories. Especially for women, a dose-response relationship was observed, i.e. larger weight gain was associated with larger declines in HRQL. Changes in HRQL for those with weight loss were small, but particularly on the mental scales, changes were in the negative direction compared to a stable weight.

Conclusions: Both weight gain and weight loss were associated with unfavourable changes in HRQL compared to a stable weight. For weight gain, this was most pronounced on the physical scales and for weight loss, although less consistent, on the mental scales.

Introduction

Overweight, and in particular severe overweight (obesity), is associated with reduced health-related quality of life (HRQL), because of its link with several diseases.[1,2] But, also without apparent morbidity, obesity may impair HRQL, e.g. due to mild physical impairments, negative perceptions of body weight, and stigmatization.[3,4]

The cross-sectional relation between obesity, and to a lesser extent overweight, and impaired HRQL has consistently been shown, especially for the physical scales of HRQL.[1,2] In addition, from surgical and lifestyle intervention studies it is known that intentional weight loss in obese people can lead to substantial improvements in HRQL after 0.5 to 5 years follow-up.[2,4,5]

Less is known on the relation between weight changes and changes in HRQL in the general population over longer periods. A few studies reported associations of weight gain with larger declines,[6-9] lower attained scores on the physical scales and the vitality scale of HRQL at the end of a follow-up period,[10-12] or a higher odds for poor physical functioning[13] compared to stable weight. However, most of these studies did not include all HRQL scales,[6,8,11-13] only used self-reported data on changes in weight,[6,7,12] and/or relatively short periods of 2–5 years for weight change.[6-10,12] Results on the association between weight loss and changes in HRQL in a general population are even more scarce and inconsistent.[6,7,9,10]

Previous research has shown that HRQL scores are dependent on sex and age, with men on average scoring higher on all HRQL scales, and HRQL scores decreasing with age particularly on the physical scales in the older age categories.[14,15] Thus, we expect that the impact of weight change on HRQL differs by age and sex, e.g. due to differences in perceptions of body weight, differences in the occurrence of morbidity/impairments, and differences in the reason(s) for weight change (intentional or unintentional). This emphasizes the need for age and sex stratified analyses when examining associations between weight change and change in HRQL. Insight in these age and sex specific associations may be used to assess public health needs and target public health interventions to specific groups.[16]

The aim of this study was to evaluate the relation between weight change and changes in HRQL in the population-based sample of the Doetinchem Cohort Study over two consecutive 5-year periods, for men and women separately. In addition, we evaluated whether this relation differs between individuals in different age groups.

Methods

Study population

The Doetinchem Cohort Study is a population-based longitudinal study, which currently has four measurement rounds completed and a fifth round in progress.[17] The first round took place from 1987 to 1991 as part of the Monitoring Project on Cardiovascular Disease Risk factors (Peilstations project). In that period, 12,405 inhabitants of Doetinchem (a rural area in the eastern part the Netherlands), aged 20–59 years, were examined (response rate 62%; Figure 6.1). A random sample of 7,769 participants were re-invited for the second

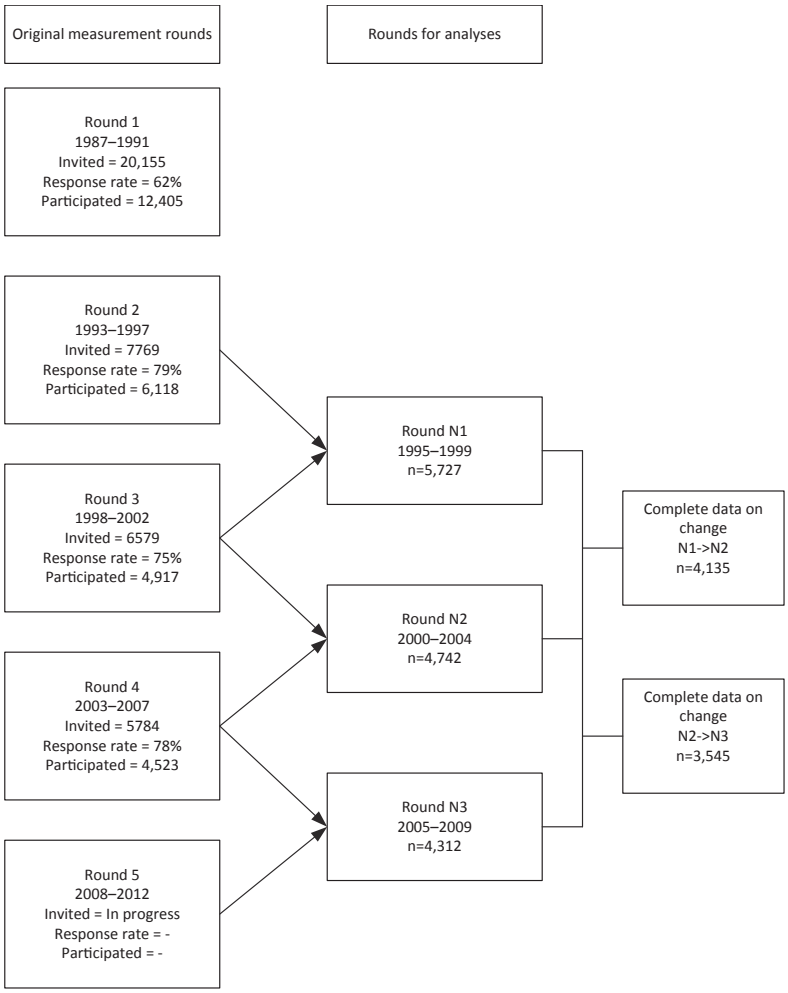


Figure 6.1 Flowchart of data collection in the Doetinchem Cohort Study.

round between 1993 and 1998 (MORGEN project). These participants were then re-invited for an examination five, ten and fifteen years later. Participants who actively refused to participate at any time were not invited again. The response rate for the second, third, and fourth measurement round was ≥75%.

The study was approved according to the guidelines of the Helsinki Declaration by the external Medical Ethics Committee of the Netherlands Organization of Applied Scientific Research Institute and of the University of Utrecht (5th round). All participants gave written informed consent.

For the present study, data were available until 2009. Data on HRQL have been collected since 1995. Thus, for our analyses the first round (baseline) are the data collected between 1995 and 1999 (N1), data collected between 2000 and 2004 represent the first follow-up (N2) and data collected between 2005 and 2009 as the second follow-up (N3) (Figure 6.1).

If participants were pregnant at the time of data collection, data for that round were excluded for the analyses (n=39). Data on HRQL, weight, demographic, and lifestyle variables were available for 4,135 individuals.

Measures

Change in Health-Related Quality of Life (HRQL).

HRQL was evaluated with the Dutch RAND-36 questionnaire,[18] which was adapted from the standardized SF-36 Health Survey.[19] The RAND-36 includes one question on health change in the past year and 35 items on eight scales of HRQL:

1. physical functioning
2. role limitations due to physical problems
3. bodily pain
4. general health perceptions
5. vitality
6. social functioning
7. general mental health
8. role limitations due to emotional problems

In this paper, we consider the first four scales to reflect the 'physical scales', and the last four the 'mental scales'.

For each scale, the crude score was converted to a 0–100 scale, according to international (SF-36) methodology; with higher scores indicating better HRQL.[19] The main outcome variable was change in HRQL over 5 years, for each scale; which could thus range from -100 to 100.

Weight and weight change

All anthropometric measurements were carried out by trained personnel. Subjects wore light clothes with emptied pockets, and without shoes. Height was measured on a wall-mounted stadiometer to the nearest 0.5 cm. Body weight was measured with a calibrated scale to the nearest 100g.

The main independent variable was weight change over 5y, which was categorized into five classes:

1: Weight loss >2 kg
2: Stable (≤2 kg change; reference category)
3: Weight gain 2.1–4.0 kg
4: Weight gain 4.1–6.0 kg
5: Weight gain >6 kg

Demographic, health, and lifestyle characteristics were assessed using self-administered questionnaires that were completed at home preceding the medical examination.[17] Information on chronic diseases was obtained from self-report for cardiovascular diseases, diabetes (type 1 and 2), asthma, and cancer.

Body-mass index (BMI) and BMI category

Before calculating BMI, 1 kg was subtracted from the weight to adjust for clothing. BMI was calculated as weight divided by height squared (kg/m^2). Based on BMI participants were defined as normal weight (BMI <25.0 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2) or obese BMI ≥30.0 kg/m^2).

Physical activity

Physical activity was estimated with the validated physical activity questionnaire for the "European prospective investigation into cancer and nutrition" (EPIC questionnaire), extended with questions on sports and other strenuous leisure activities in the preceding year. All activities were categorized as light, moderate, or vigorous based on the metabolic equivalent value (MET) as reported by Ainsworth and colleagues.[20] Cutoff points for light, moderate, and vigorous were <4.0, 4.0–6.4, and ≥6.5 MET, respectively. Subsequently, the average time spent on low, moderate, and high-intensity activities was used to classify

individuals as inactive (<0.5h per week), semi active (0.5–3.4h per week) and norm active (≥3.5 h per week).

Smoking

Smoking status (current, ex or never smoker) was obtained from questions on past and present cigarette use. Individuals were defined as smoker if they reported smoking at least one cigarette per month.

Alcohol

Alcohol use was also classified as heavy (mean intake ≥3 drinks per day for men, and ≥2 drinks per day for women), moderate (mean intake 0–2 drinks per day for men, and 0–1 drinks per day for women), ex, or never.

Education

Educational level was defined as the highest completed education, and was classified into four categories: primary education or less, low or intermediate secondary education, higher secondary education or intermediate vocational education, and higher vocational education or university.

Job status

Job status was defined as having a paid job (including salaried employment and self-employment) or not having a paid job (including those who reported not to have a job, housewife, retired, unable to work, and other).

Household composition

Household composition was defined as living alone or not living alone (living with a partner, children, parents, or other adults).

Statistical analyses

To study the relationship between changes in weight and changes in HRQL over two consecutive 5-year periods, we used generalized estimating equations (GEE). (Proc GENMOD in SAS, with distribution=normal, link function=identity, and correlation structure=autoregressive; SAS Institute Inc., Cary, North Carolina, USA). The mean change in HRQL for each weight change category was estimated using the least squares means option after adjustment for age, smoking, physical activity, alcohol use, educational level, job status,

household composition, HRQL score, and BMI at the preceding measurement. Then, the change in HRQL per weight change group was compared with the change in HRQL of the reference group, stable weight. All analyses were performed for men and women separately.

To assess how changes in weight affect HRQL in individuals in different age groups, we performed analyses stratified for age category (≤40, 41–50, 51–60, >60 years). Furthermore, we explored the association between weight changes and changes in HRQL for different BMI categories by stratifying for preceding BMI category.

To evaluate the associations between changes in weight and HRQL independently of the development of severe chronic diseases, we performed additional analyses after the exclusion of individuals with self-reported cardiovascular diseases, diabetes, asthma, or cancer at baseline and/or in one of the subsequent two measurement rounds.

Results

Baseline population characteristics and changes in weight and HRQL

The study population consisted of 2,005 men and 2,130 women aged 26 to 70 years at baseline (1995–1999) (Table 6.1). At this time, 50% of the participating men was (moderately) overweight and 10% obese. For women, these percentages were 34% and 12% respectively.

Table 6.1 Baseline[a] characteristics of the study population by sex

	Men (n=2,005)	Women (n=2,130)
Body-mass index (BMI, kg/m^2)	25.9 ± 3.14[c]	25.2 ± 4.14
Normal weight (BMI <25 kg/m^2)	41	54
Overweight (BMI 25–29.9kg/m^2)	50	34
Obese (BMI >30 kg/m^2)	10	12
Waist circumference (cm)	96 ± 10	87 ± 11
Weight (kg)	84.5 ± 11.1	70.9 ± 11.8
5-year weight change (kg)[b]	1.3 ± 4.4	1.4 ± 4.9
5-year weight change category (%)[b]		
Lost >2 kg	18	19
Stable (change ≤2 kg)	41	39
Gain 2.1–4.0 kg	19	18
Gain 4.1–6.0 kg	10	10
Gain >6 kg	12	13

Table 6.1 continues on next page

Table 6.1 *Continued*

	Men (n=2,005)	Women (n=2,130)
Age (%)		
≤40 years	25	30
41–50 years	36	35
51–60 years	26	24
>60 years	13	11
Educational level (%)		
Low	42	59
Moderate	32	24
High	27	18
Smoking (%)		
Current	27	28
Ex	43	34
Never	30	38
Alcohol use (%)[d]		
Heavy	17	8
Moderate	78	77
Ex	2	1
Never	4	14
Leisure time physical activity level (%)		
Inactive (<0.5 h/wk)	4	2
Semi active (0.5–3.4 h/wk)	18	17
Active (>3.5 h/wk)	78	81
Cohabiting status (%)		
Living alone	10	11
Job status (%)		
Paid job	77	49
Perceived health (%)		
Good/excellent	31	25
Intermediate	60	63
Reasonably/poor	10	12
HRQL (score with range 0–100)		
Physical functioning	91 ± 14	87 ± 17
Role limitations due to physical problems	86 ± 28	80 ± 34
Bodily pain	83 ± 21	77 ± 22
General health perceptions	68 ± 17	67 ± 17
Vitality	70 ± 16	65 ± 17
Social functioning	89 ± 18	84 ± 21
Role limitations due to emotional problems	89 ± 26	85 ± 31
General mental health	79 ± 14	74 ± 15

[a] Measurement between 1995 and 1999 (N1); [b] Change between 1995–1999 and 2000–2004 (N1–N2) and 2000–2004 and 2005–2009 (N2–N3) combined (3,733 observations for men and 3,947 observations for women). [c] Mean ± standard deviation; all such values. [d] Heavy: ≥3 drinks per day for men, ≥2 drinks per day for women; moderate: 0–2 drinks per day for men, 0–1 drinks per day for women.

Association between weight change and change in HRQL

Men and women who had a stable weight (40% of the study population) had small changes (declines as well as improvements) ranging from -2 to + 3 on all scales of HRQL (Figure 6.2a,b).

Both men and women who gained weight (41% of the population) had declines in physical functioning, role limitations due to physical problems, pain, general health perceptions, and vitality (Figure 6.2a,b). For these scales, a dose-response relation was apparent, especially in women, i.e. with an increase in weight gain, an increase in the decline in HRQL was

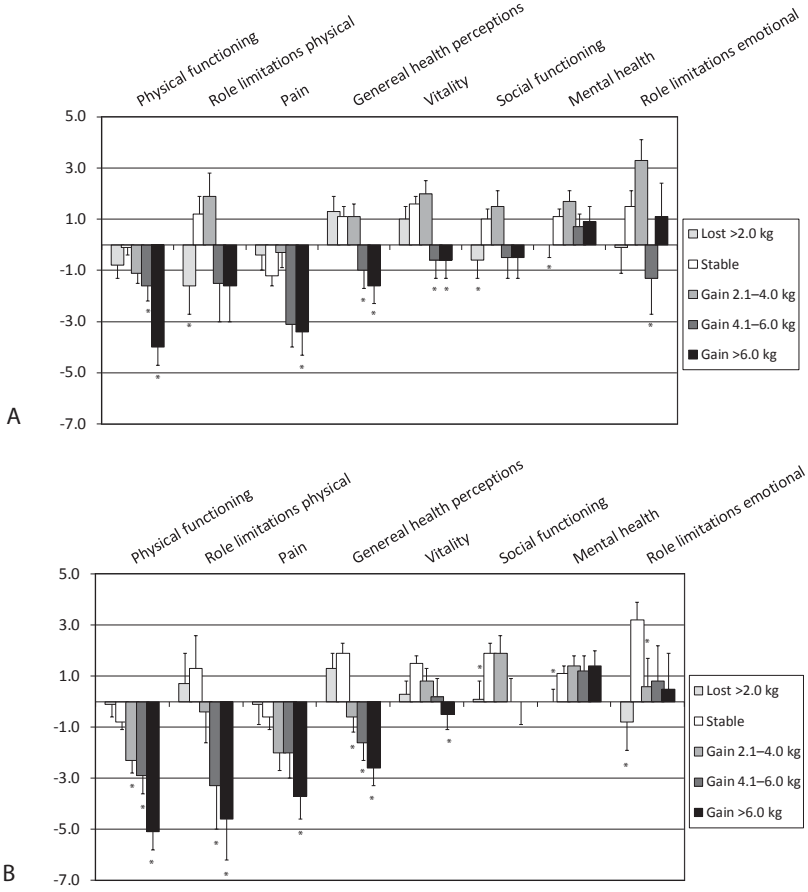


Figure 6.2 Mean change[a] in quality of life score by weight change category in men (A) and women (B). [a] 5-year change in score (0–100) with 100 representing excellent health; Adjusted for preceding age, educational level (low, medium, high), smoking (current, ex, never), alcohol intake (never, ex, moderate, heavy), physical activity category (<0.5h, 0.5–3.4h, >3.5h moderate-to vigorous intensity activity per week), job status (paid job yes/no), cohabiting status (living alone yes/no), quality of life score (0–100) and BMI (kg/m^2). * Significantly different from stable weight.

observed. Individuals who gained more than 6 kg had declines in HRQL scores that were statistically significantly different by 1–5 points in the negative direction from the change in HRQL of individuals with a stable weight. Except for physical functioning, and general health perceptions in women, the statistically significant differences from the stable weight group were limited to the highest weight gain categories (4.1–6.0 kg or >6 kg).

Individuals who lost more than 2 kg over 5 years (19% of the study population) had stable scores or small declines for social functioning, mental health, and role limitations due to emotional problems whereas individuals with a stable weight had small improvements on these HRQL scales. Thus, the statistically significant differences from those with a stable weight were in the negative direction.

Stratification by age group

Both in men and women within all age groups, weight gain >6 kg was associated with declines on most physical HRQL scales (Appendix 6.1, Table A6.1a,b).

For women, this was observed across all ages, but women older than 60 years had the largest declines on the physical scales of up to 15 points.

Men older than 60 years in general had improvements in HRQL, except for those who gained weight for physical functioning and pain. Improvements in HRQL were thus also observed for those who lost weight, but these improvements were smaller than for men in this age category with a stable weight.

Stratification by BMI category

Both in men and women with normal weight, overweight and obesity, weight gain larger than 6 kg over 5 years was associated with declines in HRQL, particularly on the physical scales (Appendix 6.1, Table A6.2a,b). The largest declines were found in obese individuals.

Exclusion of chronic diseases

Exclusion of individuals with chronic diseases at baseline, and/or who developed one or more of these diseases during follow-up did not affect our main findings (data not shown). Observed score differences with individuals with a stable weight changed with less than 1 point, except for role limitations due to physical problems in men, where the difference decreased with up to 1.6 points, and role limitations due to emotional problems in both men and women, where the score difference increased with up to 1.1 points.

Discussion

In this population-based sample, weight gain over two consecutive 5-year periods was associated with declines in physical functioning, role limitations due to physical problems, pain, general health perceptions, and vitality. For these HRQL scales, dose-response relations between the amount of weight gain and the decline in HRQL were observed, especially for women. Among all age categories, weight gain was associated with declines on the physical scales of HRQL. Changes in HRQL for individuals who lost weight did not show a consistent direction, but the difference with individuals with a stable weight was unfavourable, especially for men older than 60 years and the scores on the mental scales.

Comparison with previous research

Consistent with the cross-sectional associations between overweight/obesity and HRQL, weight gain coincided with declines in scores on the physical scales.[2] As compared to studies examining (almost) all dimensions of HRQL, our findings of associations between weight gain and declines in scores on in particular the physical scales of HRQL were similar.[6,7,9] These findings were more marked in women than in men.

However, in contrary to results from interventions,[2,4,5] weight loss in our study did not lead to improvements. In our population-based study, we observed that weight loss was associated with less favourable changes on the mental scales as compared to a stable weight. This was more or less in agreement with the study by Leon-Munoz and colleagues among elderly men and women.[7] They found larger declines on the mental scales as compared to our results, which might be explained by their measurement of weight change. In this study,[7] weight change was not measured, but only investigated with a questions "whether individuals noticed important changes in weight over the past 2 years", which may affect the associations by perception. A negative perception of your weight, either weight gain or loss might negatively influence your perception of HRQL.

Moreover, Fine and colleagues[6] reported that the results for weight loss were dependent on age and baseline BMI. Women younger than 65 years with obesity and weight loss (>9 kg) had larger improvements in physical functioning, pain and vitality than their counterparts with a stable weight. We could not stratify for both age and BMI simultaneously due to the lower number of participants in our study (n=4,135) as compared to Fine and colleagues[6] (n=40,098). In addition, the weight losses in their population were larger, in combination with obesity, this might be due to voluntary weight loss attempts that may have a greater and positive impact on HRQL.

Strengths and limitations

Strengths of our study include the large, population-based sample, and 10 years of follow-up, which allowed us to investigate the relation between changes in HRQL with the 'normal course' of weight change in the general population. Weight change was not self-reported but measured by trained personnel. Data on weight, all scales of HRQL, and several demographic and lifestyle characteristics were available for two or three measurements per person, thus we could adjust for preceding BMI, HRQL and other important characteristics.

Limitations of our study were that we did not know whether the weight change (particularly weight loss) was intentional (dieting) or unintentional. The fact that weight loss for some individuals may have been unintentional and that weight loss in our population was relatively small (e.g. in our population mean weight loss for obese individuals was 7 kg (SD: 5 kg) over 5 years) may explain why we did not find improvements in HRQL with weight loss. Weight loss interventions, especially surgical interventions, among obese people resulted in large weight losses of 33–55 kg and large improvements in HRQL.[2,4,5] In addition, larger improvements in intervention studies may be expected because obese individuals who seek treatment are more (physically) impaired than those who are not trying to lose weight.[2,4,5]

Another limitation was that the period between measurements was relatively long (5 years), thus there may be changes in-between measurements of weight and HRQL that were not captured.

Finally, there may have been selective participation and loss to follow up. Individuals who dropped out on average had lower HRQL scores at baseline, were more often obese, and were more often in the highest age category than individuals who remained in the study (results not shown). In addition, it can be assumed that individuals who have large declines in HRQL, are more likely to drop out. If there is selective loss to follow up related to changes in HRQL, this may lead to bias in the estimated associations between changes in weight and changes in HRQL.

Implications for public health

Individuals who gained more than 6 kg over 5 years had declines in HRQL of 1 to 5 points. The stratified analyses showed that these declines are larger in some groups, e.g. obese individuals and older women these declines were larger (up to 15 points). Compared to the changes in HRQL of individuals in the stable group, the difference was up to 10 points. Changes of 3 to 5 points in HRQL are considered clinically relevant.[21] However, this applies to intra-individual changes in clinical samples, while we examined 'healthy' participants in a population-based study. In population-based samples smaller differences can impact

public health.[22] For the interpretation of our results, it should be kept in mind that we cannot assume that the changes in HRQL are caused by the changes in weight, because the opposite relation of changes in HRQL leading to weight change may also be present.[8]

The declines on the physical scales, associated with weight gain were larger in women than in men. Men older than 60 years in general had improvements in HRQL, whereas women in this age group had the largest declines on the physical scales. This suggests that prevention of weight gain is particularly important for women, and up to higher age than in men. Further research is needed to confirm this difference and/or to establish the reasons behind this difference (e.g. differences in selective dropout or in perceptions of weight change and HRQL between men and women).

Exclusion of individuals with a serious chronic illness (cardiovascular diseases, diabetes, asthma or cancer) did not affect our main findings. This shows that the association between weight change and change in HRQL is partially independent of development of these conditions.

Conclusion

In conclusion, in this population-based sample weight gain over two consecutive 5-year periods was associated with clinically relevant declines in HRQL, particularly for the physical scales. This was observed in all age groups. Nevertheless, older women who gained more than 6 kilograms had the largest declines on the physical scales of HRQL. This stresses again the importance of prevention of weight gain among adults across all ages in order to maintain physical functioning in daily life, especially in women.

The results for weight loss were less consistent, but for the mental scales, we observed that individuals who had a stable weight were better off than those who lost weight, which was most pronounced in men older than 60 years. More research is needed on weight loss in a general population with a distinction between unintentional and intentional weight loss to gain further insight in the impact on HRQL.

Acknowledgements

The authors thank Dr. Maarten A. Schipper for his statistical advice, and we thank the epidemiologists and fieldworkers of the Municipal Health Service in Doetinchem for their contribution to the data collection for his study.

The authors thank the epidemiologists and field workers of the Municipal Health Service in Doetinchem for their contribution to the data collection for this study. Project director is Dr. W. M. M. Verschuren. Logistic management was provided by J. Steenbrink and P. Vissink, and administrative support was supplied by E. P. van der Wolf. Data management was provided by A. Blokstra, A. W. D. van Kessel, and P. E. Steinberger.

The Doetinchem Cohort Study is funded by the National Institute for Public Health and the Environment, which works under the authority of the Ministry of Health, Welfare and Sport of the Netherlands.

References

1. Lean ME, Han TS, Seidell JC. Impairment of health and quality of life using new US federal guidelines for the identification of obesity. *Arch Intern Med.* 1999;159(8):837–843.
2. Fontaine KR, Barofsky I. Obesity and health-related quality of life. *Obes Rev.* 2001;2(3):173–182.
3. Carr D, Friedman MA. Is obesity stigmatizing? Body weight, perceived discrimination, and psychological well-being in the United States. *J Health Soc Behav.* 2005;46(3):244–259.
4. Kolotkin RL, Meter K, Williams GR. Quality of life and obesity. *Obes Rev.* 2001;2(4):219–229.
5. Picot J, Jones J, Colquitt JL, et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. *Health Technol Assess.* 2009;13(41):1–190, 215–357, iii–iv.
6. Fine JT, Colditz GA, Coakley EH, et al. A prospective study of weight change and health-related quality of life in women. *JAMA.* 1999;282(22):2136–2142.
7. Leon-Munoz LM, Guallar-Castillon P, Banegas JR, et al. Changes in body weight and health-related quality-of-life in the older adult population. *Int J Obes (Lond).* 2005;29(11):1385–1391.
8. Cameron AJ, Magliano DJ, Dunstan DW, et al. A bi-directional relationship between obesity and health-related quality of life: evidence from the longitudinal AusDiab study. *Int J Obes (Lond).* 2012;36(2) 295–303.
9. Verkleij SP, Adriaanse MC, Wendel-Vos GC, et al. Longitudinal relation between weight change and quality of life in a community-based population: a prospective cohort study. *Eur J Public Health.* 2013;23(2):285–290.
10. Burns CM, Tijhuis MA, Seidell JC. The relationship between quality of life and perceived body weight and dieting history in Dutch men and women. *Int J Obes Relat Metab Disord.* 2001;25(9):1386–1392.
11. Kozak AT, Daviglus ML, Chan C, et al. Relationship of body mass index in young adulthood and health-related quality of life two decades later: the Coronary Artery Risk Development in Young Adults study. *Int J Obes (Lond).* 2011;35(1):134-41.

12. Williams LT, Young AF, Brown WJ. Weight gained in two years by a population of mid-aged women: how much is too much? *Int J Obes (Lond).* 2006;30(8):1229–1233.

13. Stafford M, Hemingway H, Marmot M. Current obesity, steady weight change and weight fluctuation as predictors of physical functioning in middle aged office workers: the Whitehall II Study. *Int J Obes Relat Metab Disord.* 1998;22(1):23–31.

14. Hopman WM, Berger C, Joseph L, et al. The natural progression of health-related quality of life: results of a five-year prospective study of SF-36 scores in a normative population. *Qual Life Res.* 2006;15(3):527–536.

15. Orfila F, Ferrer M, Lamarca R, et al. Gender differences in health-related quality of life among the elderly: the role of objective functional capacity and chronic conditions. *Soc Sci Med.* 2006;63(9):2367–2380.

16. Hennessy CH, Moriarty DG, Zack MM, et al. Measuring health-related quality of life for public health surveillance. *Public Health Rep.* 1994;109(5):665–672.

17. Verschuren WM, Blokstra A, Picavet HS, et al. Cohort profile: the Doetinchem Cohort Study. *Int J Epidemiol.* 2008;37(6):1236–1241.

18. Zee van der K, Sanderman R. *Het meten van de algemene gezondheidstoestand met de RAND-36: een handleiding (in Dutch). [Measuring general health status with the RAND-26: a manual.].* Groningen (the Netherlands) 1993.

19. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30(6):473–483.

20. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc.* 1993;25(1):71–80.

21. Samsa G, Edelman D, Rothman ML, et al. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics.* 1999;15(2):141–155.

22. Rose G. Sick individuals and sick populations. *Int J Epidemiol.* 2001;30(3):427–432; discussion 433–424.

Appendix 6.1

Mean change in quality of life score by weight change category, stratified for age and BMI

Table A6.1a Mean change[‡] in quality of life score by weight change category in men after stratification for age category (n=3,733 observations for 2,005 men)

QoL scale	Weight change category	26–40y		41–50y		51–60y		>60y	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
Physical functioning	Lost >2 kg	-1.1	1.3	0.4	0.9	-0.2	0.8	-3.2^{bc*}	1.2
	Stable (change ≤2 kg)	0.2	0.7	-0.3	0.5	-0.2	0.5	-0.3	0.9
	Gain 2.1–4.0 kg	-0.5^{a}	0.7	-1.3^{b}	0.6	-0.4^{ab}	0.8	-1.9^{ab}	1.5
	Gain 4.1–6.0 kg	0.9	0.7	-2.9^{a*}	1.1	-1.1	1.2	-1.9	2.2
	Gain >6 kg	-1.0	0.9	-4.5^{a*}	1.2	-6.2^{a*}	1.6	-4.5	2.5
Role limitations physical	Lost >2 kg	-3.6	2.7	-4.0	2.2	0.3	1.6	2.2*	2.7
	Stable (change ≤2 kg)	-0.7^{a}	1.6	-1.8^{a}	1.2	0.5^{a}	1.2	9.8^{b}	1.8
	Gain 2.1–4.0 kg	0.9	1.9	-1.0	1.5	1.7	2.0	8.5^{abc}	2.8
	Gain 4.1–6.0 kg	-2.9	2.5	-8.0*	2.6	2.6^{b}	3.0	10.1^{ab}	4.6
	Gain >6 kg	-0.3	2.1	-6.7	2.5	-4.3	3.1	7.4^{b}	5.0
Bodily pain	Lost >2 kg	-1.0	1.5	-1.2	1.4	-0.0	1.1	1.2	1.4
	Stable (change ≤2 kg)	-2.9	1.2	-2.3	0.8	-1.0	0.7	1.7^{abc}	1.2
	Gain 2.1–4.0 kg	-0.5	1.3	-2.2	1.1	1.1^{b}	1.3	1.8^{b}	1.7
	Gain 4.1–6.0 kg	-3.7	1.7	-4.0	1.4	-0.9	2.2	-3.7	3.1
	Gain >6 kg	-1.3	1.4	-6.3^{a*}	1.6	-3.9	2.1	-2.4	2.8
General health perceptions	Lost >2 kg	-1.0	1.6	1.8	1.2	2.6	1.0	3.0*	1.3
	Stable (change ≤2 kg)	-1.9	1.1	0.4	0.7	1.0^{a}	0.7	5.8^{abc}	1.0
	Gain 2.1–4.0 kg	-2.8	1.2	-0.4	0.8	2.5^{ab}	1.0	6.3^{abc}	1.4
	Gain 4.1–6.0 kg	-3.9	1.3	-3.0*	1.0	-0.2	1.8	5.2^{abc}	1.8
	Gain >6 kg	-4.8	1.1	-2.3*	1.2	-3.6*	1.6	6.0^{abc}	2.2
Vitality	Lost >2 kg	-1.4	1.2	0.4	1.2	3.0^{a}	0.9	2.1^{a}	1.1
	Stable (change ≤2 kg)	-0.4	0.9	-0.1	0.6	3.3^{ab}	0.5	4.2^{ab}	0.9
	Gain 2.1–4.0 kg	0.1	1.1	0.3	0.8	4.3^{ab}	1.0	3.7^{ab}	1.3
	Gain 4.1–6.0 kg	-2.4	1.2	-1.8	1.2	1.9^{a}	1.6	-0.4*	1.8
	Gain >6 kg	-1.8	1.3	-2.2	1.2	-0.3*	1.4	1.9	2.8
Social functioning	Lost >2 kg	-1.7	1.9	-1.3	1.5	0.6	1.1	1.0*	1.5
	Stable (change ≤2 kg)	1.2	0.9	-1.0^{a}	0.7	1.3^{b}	0.7	4.4^{abc}	1.1
	Gain 2.1–4.0 kg	-0.1	1.3	-0.5	1.0	2.6^{b}	1.0	5.9^{ab}	1.4
	Gain 4.1–6.0 kg	-4.6*	1.5	-2.3	1.4	1.5^{a}	1.9	7.7^{abc}	1.9
	Gain >6 kg	-2.0*	1.4	-3.1	1.5	-1.5	1.7	9.3^{abc}	2.8

Table A6.1a continues on next page

Table A6.1a *Continued*

QoL scale	Weight change category	26–40y		41–50y		51–60y		>60y	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
General mental health	Lost >2 kg	-2.6*	1.3	-0.4	1.0	1.2[a]	0.8	1.5[a*]	0.9
	Stable (change ≤2 kg)	0.6	0.7	-0.2	0.5	1.4b*	0.5	3.9[abc]	0.7
	Gain 2.1–4.0 kg	-0.2	0.9	0.8	0.7[a]	3.5[ab]	0.7	2.4	1.2
	Gain 4.1–6.0 kg	-1.8*	1.0	-0.2	0.9	2.6[a]	1.2	3.5[ab]	1.4
	Gain >6 kg	0.1	1.0	-1.0	1.0	2.8[b]	1.2	1.2	1.9
Role limitations emotional	Lost >2 kg	-0.2	2.4	-1.0	2.0	-0.1	1.7	3.5*	2.0
	Stable (change ≤2 kg)	1.8	1.4	-2.7[a]	1.2	1.8[b]	1.0	9.0[abc]	1.4
	Gain 2.1–4.0 kg	1.1	1.8	0.5	1.5	4.6[b]	1.3	8.9[abc]	1.7
	Gain 4.1–6.0 kg	-4.5*	2.5	-4.9	2.4	2.5	2.9	6.0[ab]	3.4
	Gain >6 kg	-0.3	2.0	-3.3	2.4	0.5	2.7	11.1[abc]	3.6

[a] p<0.05 for difference with age 26–40y; [b] p<0.05 for difference with age 41–50y; [c] p<0.05 for difference with age 51–60y. * p<0.05 for difference with stable weight. ‡ 5-year change in score (0–100) with 100 representing excellent health; Adjusted for preceding educational level (low, medium, high), smoking (current, ex, never), alcohol intake (never, ex, moderate, heavy), physical activity category (<0.5h, 0.5–3.4.h, ≥3.5h moderate-to vigorous intensity activity per week), job status (paid job yes/no), cohabiting status (living alone yes/no), quality of life score (0–100) and BMI (kg/m^2).

Table A6.1b Mean change‡ in quality of life score by weight change category in women after stratification for age category (n=3,947 observations for 2,130 women)

QoL scale	Weight change category	26–40y		41–50y		51–60y		>60y	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
Physical functioning	Lost >2 kg	1.6	1.1	1.2	0.9	-1.1	1.0	-4.3[ab]	1.4
	Stable (change ≤2 kg)	0.8	0.6	-0.4	0.6	-0.3	0.6	-5.3[abc]	0.9
	Gain 2.1–4.0 kg	0.2	0.9	-2.1	0.9	-3.8[a*]	1.1	-3.8[a]	1.6
	Gain 4.1–6.0 kg	0.3	1.1	-2.1	1.0	-3.8[a*]	1.4	-9.1[ab]	3.0
	Gain >6 kg	-2.7*	1.2	-2.6	1.0	-6.8[ab*]	1.3	-15.1[abc*]	3.1
Role limitations physical	Lost >2 kg	3.7	2.7	-0.9	2.2	2.4	2.0	-3.4	3.1
	Stable (change ≤2 kg)	2.9	1.7	1.7	1.4	2.7	1.4	-4.4[abc]	2.1
	Gain 2.1–4.0 kg	3.0	2.2	-2.4	2.1	0.5	2.3	-1.8	3.4
	Gain 4.1–6.0 kg	-1.7	3.0	-1.6	2.7	-2.4	3.6	-11.7	6.2
	Gain >6 kg	-3.4	2.9	-1.1	2.3	-7.9*	3.5	-10.9	6.7
Bodily pain	Lost >2 kg	0.9	1.7	0.2	1.4	-0.2	1.4	-2.5	1.7
	Stable (change ≤2 kg)	2.5	1.0	-0.7[a]	0.8	-0.3[a]	0.8	-4.7[abc]	1.1
	Gain 2.1–4.0 kg	-1.3*	1.3	-2.8	1.3	-1.8	1.4	-0.8	2.0
	Gain 4.1–6.0 kg	-0.6	1.8	-1.2	1.6	-3.6	2.0	-3.2	2.9
	Gain >6 kg	-2.5*	1.5	-1.8	1.4	-4.4	2.0	-11.6[abc*]	2.9
General health perceptions	Lost >2 kg	-1.2	1.3	1.7	1.0	3.1[a]	1.0	1.8	1.3
	Stable (change ≤2 kg)	-1.2	0.9	1.8[a]	0.7	3.4[a]	0.7	4.0[a]	1.0
	Gain 2.1–4.0 kg	-3.8*	1.1	-1.5*	1.0	2.3[ab]	1.1	1.1[a]	1.7
	Gain 4.1–6.0 kg	-5.5*	1.3	-2.0[a*]	1.0	2.2[ab]	1.5	-0.9*	2.3
	Gain >6 kg	-5.7*	1.1	-2.8*	1.0	-1.4[a*]	1.6	-1.0*	2.2
Vitality	Lost >2 kg	0.6	1.3	0.4	0.9	1.8	0.9	-2.0[c*]	1.1
	Stable (change ≤2 kg)	0.9	0.8	1.4	0.6	2.3	0.6	1.4	0.8
	Gain 2.1–4.0 kg	-0.7	0.9	0.3	1.0	1.5	1.0	3.1[a]	1.3
	Gain 4.1–6.0 kg	-0.6	1.4	-0.8	1.1	3.0[b]	1.4	-0.4	2.0
	Gain >6 kg	-1.0	1.1	-1.0*	1.0	0.9	1.3	-1.3	2.2
Social functioning	Lost >2 kg	0.2	1.8	1.8	1.3	-0.7*	1.3	-1.7	1.6
	Stable (change ≤2 kg)	1.4	1.1	1.3	0.8	3.6[b]	0.7	0.5[c]	1.1
	Gain 2.1–4.0 kg	1.5	1.3	0.9	1.2	3.1	1.1	2.9	1.9
	Gain 4.1–6.0 kg	0.8	1.6	-0.9	1.5	1.9	1.7	-3.1	3.2
	Gain >6 kg	-1.5	1.6	1.0	1.3	1.8	1.9	-4.3	3.9
General mental health	Lost >2 kg	-0.5	1.2	0.9	0.8	0.1	0.8	-1.6	1.1
	Stable (change ≤2 kg)	1.0	0.7	1.2	0.5	1.3	0.5	0.6	0.6
	Gain 2.1–4.0 kg	1.1	0.8	1.5	0.7	2.0	0.9	1.0	1.1
	Gain 4.1–6.0 kg	1.0	1.2	1.4	1.0	2.3	1.1	-0.8	2.0
	Gain >6 kg	1.6	0.9	1.3	0.9	2.0	1.2	-0.0	2.5

Table A6.1b continues on next page

Table A6.1b *Continued*

QoL scale	Weight change category	26–40y		41–50y		51–60y		>60y	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
Role limitations emotional	Lost >2 kg	-2.4*	2.6	-0.0	2.0	1.3	1.9	-3.3	2.9
	Stable (change ≤2 kg)	3.4	1.5	1.3	1.3	5.6[b]	1.1	2.9	1.6
	Gain 2.1–4.0 kg	-3.2*	2.4	1.8	1.8	1.0*	2.1	3.4	2.9
	Gain 4.1–6.0 kg	-0.3	2.6	-0.7	2.4	5.1	2.8	-1.6	4.1
	Gain >6 kg	-1.1	2.5	1.3	2.1	-0.4	3.0	3.2	5.3

[a] $p<0.05$ for difference with age 26–40y; [b] $p<0.05$ for difference with age 41–50y; [c] $p<0.05$ for difference with age 51–60y. * $p<0.05$ for difference with stable weight. ‡ 5-year change in score (0–100) with 100 representing excellent health; Adjusted for preceding educational level (low, medium, high), smoking (current, ex, never), alcohol intake (never, ex, moderate, heavy), physical activity category (<0.5h, 0.5–3.4.h, ≥3.5h moderate-to vigorous intensity activity per week), job status (paid job yes/no), cohabiting status (living alone yes/no), quality of life score (0–100) and BMI (kg/m^2).

Table A6.2a Mean change‡ in quality of life score by weight change category in men after stratification for preceding BMI category (n=3,733 observations for 2,005 men)

QoL scale	Weight change category	BMI <25 kg/m²		BMI 25–29.9 kg/m²		BMI >30 kg/m²	
		Mean	SE	Mean	SE	Mean	SE
Physical functioning	Lost >2 kg	-1.8	1.1	-0.3	0.6	-2.5	1.6
	Stable (change ≤2 kg)	-0.0	0.4	-0.1	0.4	0.4	1.1
	Gain 2.1–4.0 kg	-0.2	0.6	-1.2	0.5	-3.7	1.9
	Gain 4.1–6.0 kg	-1.4	0.7	-1.3	1.0	-2.9	1.8
	Gain >6 kg	-3.1*§	0.9	-3.0*	0.9	-9.9ab*	2.1
Role limitations physical	Lost >2 kg	-2.3	2.0	-2.5*	1.4	1.8	2.6
	Stable (change ≤2 kg)	1.2	1.0	1.0	1.0	3.2	2.3
	Gain 2.1–4.0 kg	2.4	1.3	1.5	1.3	2.0	3.3
	Gain 4.1–6.0 kg	-2.9	2.4	-1.3	2.2	1.9	3.6
	Gain >6 kg	-0.8	2.1	0.4	2.0	-10.1ab*	4.1
Bodily pain	Lost >2 kg	-0.5	1.2	-0.2	0.8	-1.5	1.8
	Stable (change ≤2 kg)	-0.7	0.7	-1.7	0.6	0.5	1.5
	Gain 2.1–4.0 kg	-0.5	1.0	-0.5	0.9	1.8	2.3
	Gain 4.1–6.0 kg	-2.9	1.4	-3.3	1.4	-2.8	2.6
	Gain >6 kg	-1.4	1.4	-3.2	1.4	-9.4ab*	2.3
General health perceptions	Lost >2 kg	0.6	1.2	2.1	0.8	-1.3b	1.5
	Stable (change ≤2 kg)	2.2	0.7b	0.4a	0.6	0.5	1.4
	Gain 2.1–4.0 kg	1.4	1.4	0.9	0.7	2.1	1.7
	Gain 4.1–6.0 kg	-0.9*	1.1	-1.1	1.0	-0.8	1.9
	Gain >6 kg	-0.7*	1.1	-2.1*	1.0	-2.5	2.1
Vitality	Lost >2 kg	1.1	1.1	0.8	0.7	1.3	1.2
	Stable (change ≤2 kg)	2.2	0.5	1.1	0.4	2.8	1.1
	Gain 2.1–4.0 kg	2.1	0.7	2.0	0.7	1.7	1.8
	Gain 4.1–6.0 kg	-0.9*	1.1	-1.0*	0.9	1.6	1.7
	Gain >6 kg	0.1	1.2	0.4	1.0	-5.6ab*	2.1
Social functioning	Lost >2 kg	-1.1	1.5	-1.0	0.9	0.6	1.6
	Stable (change ≤2 kg)	1.8	0.6	0.7	0.5	0.3	1.4
	Gain 2.1–4.0 kg	2.5	0.8	0.7	0.8	2.8	1.9
	Gain 4.1–6.0 kg	-1.9*	1.3	0.5	1.2	0.4	2.1
	Gain >6 kg	-0.3	1.3	1.1	1.2	-6.0ab*	2.5
General mental health	Lost >2 kg	0.0	0.9	-0.3	0.6	0.3	1.1
	Stable (change ≤2 kg)	1.5	0.4	1.0	0.4	0.5	1.0
	Gain 2.1–4.0 kg	1.8	0.6	1.7	0.6	0.8	1.5
	Gain 4.1–6.0 kg	0.5	0.9	0.3	0.8	3.1	1.5
	Gain >6 kg	1.5	0.9	1.7	0.8	-2.8ab	1.8

Table A6.2a continues on next page

Table A6.2a *Continued*

QoL scale	Weight change category	BMI <25 kg/m²		BMI 25–29.9 kg/m²		BMI >30 kg/m²	
		Mean	SE	Mean	SE	Mean	SE
Role limitations emotional	Lost >2 kg	-0.6	1.9	-0.3	1.3	0.3	2.4
	Stable (change ≤2 kg)	2.2	0.8	0.9	0.8	2.6	1.9
	Gain 2.1–4.0 kg	3.5	1.2	3.5*	1.1	1.0	2.8
	Gain 4.1–6.0 kg	-3.3*	2.3	0.2	1.9	0.3	3.7
	Gain >6 kg	1.5	2.1	2.2	1.8	-3.7	3.6

[a] $p<0.05$ for difference with BMI<25 kg/m²; [b] $p<0.05$ for difference with BMI 25–29.9 kg/m². * $p<0.05$ for difference with stable weight. ǂ 5-year change in score (0–100) with 100 representing excellent health; Adjusted for age, and preceding educational level (low, medium, high), smoking (current, ex, never), alcohol intake (never, ex, moderate, heavy), physical activity category (<0.5h, 0.5–3.4.h, ≥3.5h moderate-to vigorous intensity activity per week), job status (paid job yes/no), cohabiting status (living alone yes/no), quality of life score (0–100).

Table A6.2b Mean change‡ in quality of life score by weight change category in women after stratification for preceding BMI category (n=3,947 observations for 2,130 women)

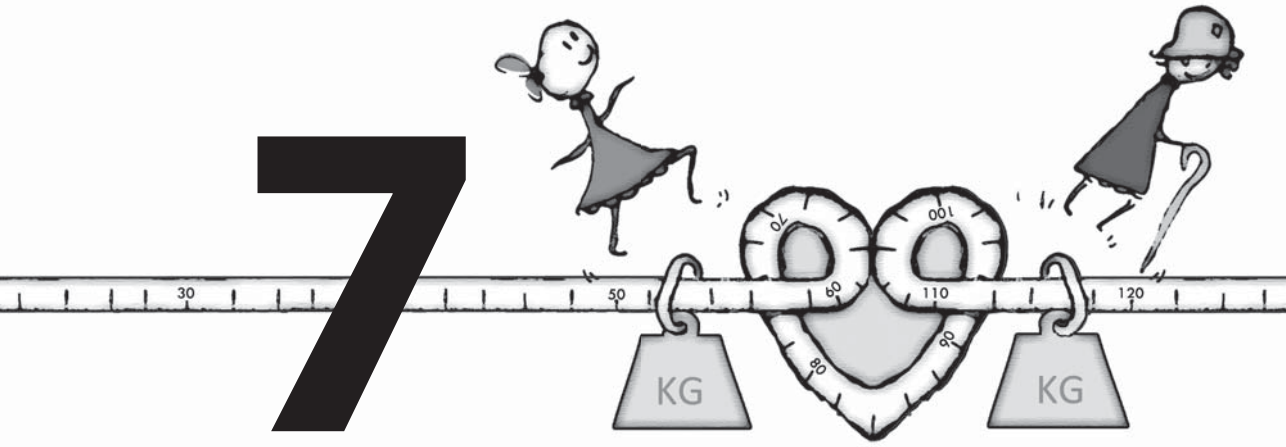
QoL scale	Weight change category	BMI <25 kg/m²		BMI 25–29.9 kg/m²		BMI >30 kg/m²	
		Mean	SE	Mean	SE	Mean	SE
Physical functioning	Lost >2 kg	-0.5	0.8	-0.3	0.8	-1.5	1.2
	Stable (change ≤2 kg)	0.8	0.4	-2.0[a]	0.6	-3.6[a]	1.2
	Gain 2.1–4.0 kg	-1.8[*]	0.6	-1.7	1.0	-5.3	2.0
	Gain 4.1–6.0 kg	-1.6[*]	0.8	-2.5	1.0	-9.5[ab*]	2.6
	Gain >6 kg	-3.3[*]	0.9	-6.3[a*]	1.2	-8.9[a*]	1.9
Role limitations physical	Lost >2 kg	-0.3	2.0	0.9	1.8	0.3	2.7
	Stable (change ≤2 kg)	2.7	1.0	1.4	1.3	-5.7[ab]	2.9
	Gain 2.1–4.0 kg	0.3	1.6	-1.2	2.1	-0.2	3.4
	Gain 4.1–6.0 kg	-2.8[*]	2.4	-1.4	2.7	-11.5	5.4
	Gain >6 kg	-3.4[*]	2.3	-6.1[*]	2.7	-5.6	3.6
Bodily pain	Lost >2 kg	-0.6	1.2	-0.2	1.1	-0.9[*]	1.6
	Stable (change ≤2 kg)	0.6	0.6	-0.4	0.8	-5.9[ab]	1.6
	Gain 2.1–4.0 kg	-1.5	0.9	-1.4	1.3	-5.2	2.3
	Gain 4.1–6.0 kg	-1.6	1.3	-1.5	1.7	-5.2	3.2
	Gain >6 kg	-1.6	1.2	-5.8[a*]	1.6	-6.4	2.3
General health perceptions	Lost >2 kg	1.8	0.9	0.3	0.9	0.3	1.1
	Stable (change ≤2 kg)	2.9	0.6	1.3	0.7	-0.9[a]	1.3
	Gain 2.1–4.0 kg	-0.0[*]	0.8	0.4	1.0	-4.8[ab*]	1.7
	Gain 4.1–6.0 kg	-0.8[*]	1.0	-1.7[*]	1.1	-4.7	1.9
	Gain >6 kg	-2.3[*]	0.9	-1.7[*]	1.1	-6.3[ab*]	1.8
Vitality	Lost >2 kg	0.7	0.8	-0.0	0.8	-0.7	1.1
	Stable (change ≤2 kg)	2.2	0.4	1.2	0.6	-0.5[a]	1.1
	Gain 2.1–4.0 kg	1.4	0.7	-0.1	1.0	0.9	1.3
	Gain 4.1–6.0 kg	0.9	1.0	-0.3	1.1	-1.1	2.2
	Gain >6 kg	-0.4[*]	0.9	-1.0	1.1	-0.0	1.4
Social functioning	Lost >2 kg	-0.2[*]	1.1	0.4	1.1	-0.3	1.8
	Stable (change ≤2 kg)	2.4	0.5	1.6	0.8	0.1	1.6
	Gain 2.1–4.0 kg	2.2	0.9	1.4	1.2	1.8	2.1
	Gain 4.1–6.0 kg	0.7	1.3	-0.5	1.4	-1.3	2.7
	Gain >6 kg	-0.7[*]	1.3	0.3	1.4	1.0	2.0
General mental health	Lost >2 kg	-0.2	0.7	-0.1	0.7	0.7	1.0
	Stable (change ≤2 kg)	1.2	0.4	1.4	0.5	-0.3	1.1
	Gain 2.1–4.0 kg	1.1	0.6	1.5	0.7	3.0	1.0
	Gain 4.1–6.0 kg	2.2	0.8	0.3	1.0	-0.3	2.0
	Gain >6 kg	1.0	0.8	1.2	0.9	3.2	1.2

Table A6.2b continues on next page

Table A6.2b *Continued*

QoL scale	Weight change category	BMI <25 kg/m^2		BMI 25–29.9 kg/m^2		BMI >30 kg/m^2	
		Mean	SE	Mean	SE	Mean	SE
Role limitations emotional	Lost >2 kg	-1.7[*]	1.8	1.0	1.7	-3.4	2.7
	Stable (change ≤2 kg)	4.5	0.8	2.1	1.3	-0.7	2.4
	Gain 2.1–4.0 kg	1.5	1.5	-2.0	2.1	3.7[a]	2.4
	Gain 4.1–6.0 kg	0.7	2.0	1.1	2.2	-0.3	3.9
	Gain >6 kg	-1.5[*]	2.1	0.5	2.2	6.4[a*]	2.4

[a] p<0.05 for difference with BMI<25 kg/m^2; [b] p<0.05 for difference with BMI 25–29.9 kg/m^2. [*] p<0.05 for difference with stable weight. [‡] 5-year change in score (0–100) with 100 representing excellent health; Adjusted for age, and preceding educational level (low, medium, high), smoking (current, ex, never), alcohol intake (never, ex, moderate, heavy), physical activity category (<0.5h, 0.5–3.4.h, ≥3.5h moderate-to vigorous intensity activity per week), job status (paid job yes/no), cohabiting status (living alone yes/no), quality of life score (0–100).



7

The impact of long-term body mass index patterns on health-related quality of life: The Doetinchem Cohort Study

Ellen L de Hollander, H Susan J Picavet, Ivon E Milder,
WM Monique Verschuren, Wanda JE Bemelmans,
Lisette CPGM de Groot

Am J Epidemiol. First published online: July 2, 2013, DOI: 10.1093/aje/kwt0533.

Abstract

Overweight is associated with a reduced health-related quality of life (QOL), but less is known about the impact of long-term body mass index [BMI, calculated as weight (kg)/height (m)^2] patterns on QOL in adults. In the Dutch Doetinchem Cohort Study (1989–2009) that included 1,677 men and 1,731 women aged 20–66 years, 6 BMI patterns were defined by using 4 measurements over a 15-year period: 1) persistent healthy weight (18.5–24.9, reference pattern); 2) persistent overweight (25.0–29.9); 3) persistent obesity (≥30.0); 4) developing overweight; 5) developing obesity; and 6) switching between BMI categories. For each BMI pattern, adjusted QOL (measured on a 0–100 scale) was estimated at the end of this period. The lowest QOL was observed for persistent obesity of all BMI patterns. It was 5.0 points ($p=0.02$) lower for 1 mental dimension in men and 6.2–11.6 points ($p<0.05$) lower for 5 (mainly physical) dimensions in women. Developing overweight or obesity scored 1.8–6.3 points ($p<0.05$) lower on 2–5 (mainly physical) dimensions. Persistent overweight hardly differed from a persistent healthy weight. In women, switching between BMI categories resulted in a lower QOL on the mental dimensions. Studying long-term BMI patterns over a 15-year period showed that persistent obesity, developing overweight, and developing obesity resulted in a lower QOL – particularly on the physical dimensions – compared with a persistent healthy weight.

Introduction

Overweight and obesity are known to be associated with a shorter life expectancy, many chronic diseases, and lower quality of life.[1-5] Health-related quality of life (QOL), often measured with the standardized 36-item Short-Form Health Survey (SF-36) that includes 8 dimensions regarding physical and mental aspects of health,[6] is considered a more general health indicator than mortality or disease rates[7] and therefore a relevant indicator for healthy ageing.

The association between weight status and QOL has been explored by both cross-sectional and longitudinal studies. Cross-sectional studies showed that obesity (≥30.0 kg/m^2) was associated with lower QOL scores compared with a healthy weight (18.5–24.9 kg/m^2), even without apparent diseases.[3,5] However, an important aspect for healthy ageing is the impact of overweight and obesity determined on the longer term. So far, longitudinal studies showed that gaining weight {within body mass index [BMI, calculated as weight (kg)/height (m)^2] categories} over time was associated with a lower QOL or with larger declines in QOL than having a stable weight.[8-12] However, these studies on longitudinal associations between weight and QOL were based on relatively short periods of 2–6 years and/or used self-reported weight.[8-12] Thus, the impact of (measured) overweight or obesity over long periods of time on QOL is not known.

One study examined the association between QOL and changing BMI categories over a longer period, that is, 20 years.[13] They found that persons who remained obese or developed overweight or obesity had a lower QOL on the physical domain, but not on the mental domain, than persons who remained a healthy weight.[13] However, in this study, only two measurements were used to classify persons into long-term BMI patterns, and no information was available on (changes in) BMI between these measurements.[13] To gain insight into long-term BMI patterns, more measurements are needed. In addition, a number of studies[9-13] failed to examine the association between weight and QOL for men and women separately, although previous studies showed differences in QOL between the sexes[14,15] and/or did not include all dimensions of QOL. Therefore, we studied, for both men and women, the impact of long-term BMI patterns, that is, over a period of 15 years, on all 8 dimensions of QOL at the end of this period, by using 4 measurements with 5-year intervals.

Methods

Population and measurement rounds

The Doetinchem Cohort Study is a Dutch prospective population-based study. The baseline measurement was carried out between 1987 and 1991 involving 12,405 respondents from Doetinchem (initial response of the invitees: 62%). For the second measurement round (1993–1997), a random sample of 7,769 men and women was invited and reinvited for the third (1998–2002) and fourth (2003–2007) rounds. Response rates of the second, third, and fourth rounds were 79%, 75%, and 78%, respectively. The fifth round started in 2008 and was finished at the end of 2012. The Doetinchem Cohort Study is described in detail elsewhere.[16] Assessment of QOL has been available since 1995; therefore, for the current paper, measurement rounds were shifted into the following 4 consecutive analysis rounds: 1989–1994 (baseline, round A), 1995–1999 (round B), 2000–2004 (round C), and 2005–2009 (round D) (Figure 7.1).

The study was approved by the external Medical Ethics Committee of the Netherlands Organization of Applied Scientific Research Institute and the University of Utrecht according to the guidelines of the Helsinki Declaration. All participants gave written, informed consent.

Body mass index

Trained staff measured body weight and height. The participants wore light clothing and no shoes and had empty pockets. Body weight was measured with a calibrated scale to the nearest 100 g. To adjust for clothing, 1 kg was subtracted from the weight before calculating the BMI. The participants were classified into 4 BMI categories: 1) underweight (<18.5 kg/m^2), 2) healthy weight (18.5–24.9 kg/m^2), 3) overweight (25–29.9 kg/m^2), and 4) obesity (≥30.0 kg/m^2).

Health-related quality of life (Short-Form 36)

Health-related quality of life was not measured at baseline (round A). Therefore, we used QOL data from round B to adjust for previous QOL. QOL was evaluated with the Dutch RAND-36 questionnaire,[17] which is an adapted version of the standardized SF-36.[6] The RAND-36 includes 8 dimensions of QOL: 1) physical functioning, 2) role limitations due to physical health problems (role, physical), 3) bodily pain, 4) general health perceptions, 5) vitality, 6) social functioning, 7) role limitations due to emotional problems (role, emotional), and 8)

mental health. The first four dimensions are considered to reflect the "physical dimensions," and the last four dimensions, the "mental dimensions." The crude score of each dimension was converted to a 0–100 scale, according to international (SF-36) methodology, with higher scores indicating better QOL.[6]

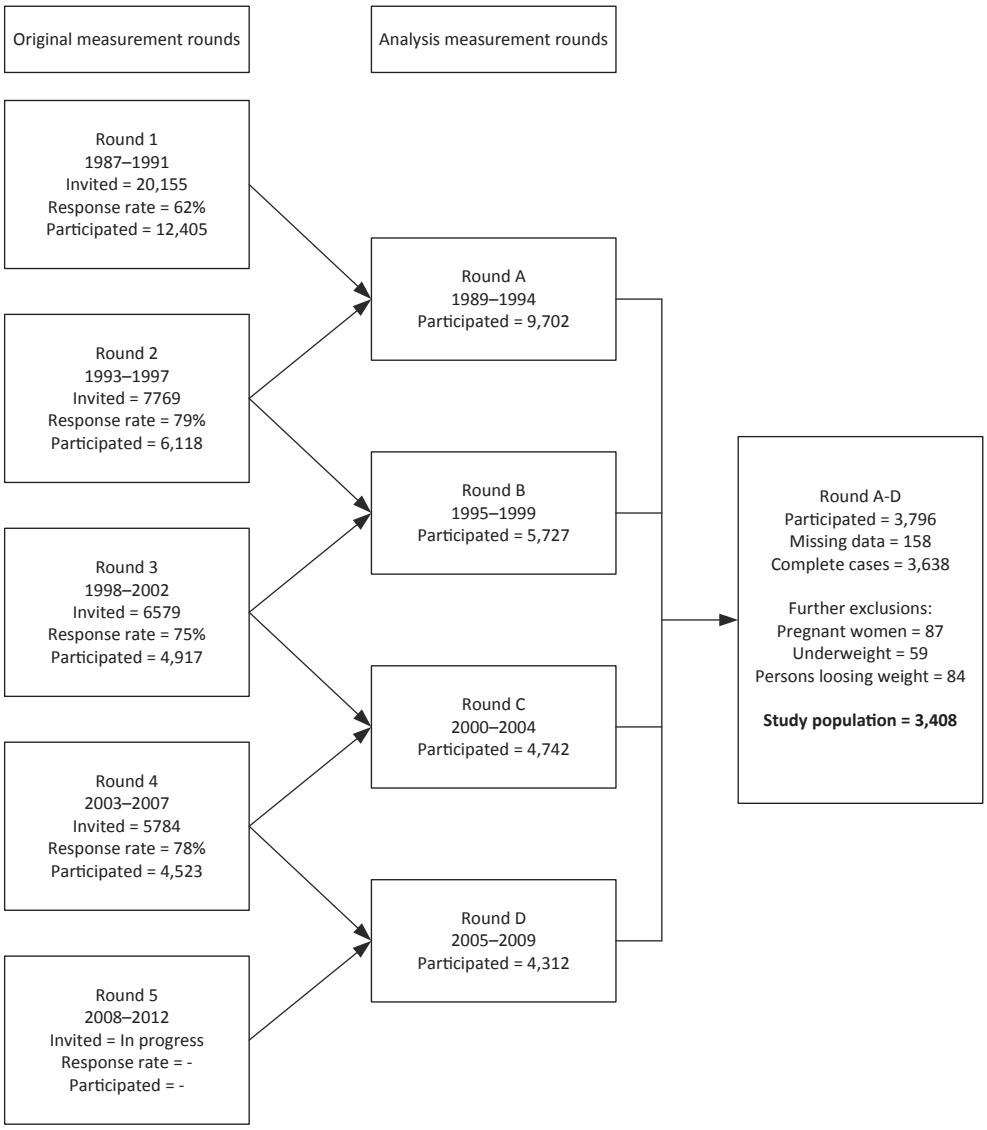


Figure 7.1 Flow chart of the shifted rounds, the Doetinchem Cohort Study, the Netherlands, 1989–2009.

Potential confounders

Data from round D were used to evaluate potential confounders, because attained levels of a confounder or risk factor are suggested to be more relevant for a health outcome than initial levels.[18,19] Smoking status was categorized as never smoker, former smoker, and current smoker, on the basis of questions referring to past and present cigarette use. Educational level was defined as the highest completed education and was classified into three categories: 1) intermediate secondary education or less, 2) intermediate vocational or higher secondary education, and 3) higher vocational education or university. Work status was defined as having a job or not. Household composition was defined as living alone or not living alone (i.e., living with a partner, child(ren), a parent(s) or other adult(s)). Physical activity was assessed with the validated physical activity questionnaire developed for the European Prospective Investigation into Cancer and Nutrition (EPIC), extended with questions on sports and other strenuous leisure-time activities in the preceding year.[20] All activities were categorized as light, moderate, or vigorous on the basis of the metabolic equivalent value of task (MET) as reported by Ainsworth and colleagues.[21] Cutoff points for light, moderate, and vigorous activities were <4.0 METs, 4.0–6.5 METs, and >6.5 METs, respectively. Subsequently, the average time spent on moderate and vigorous intensity activities was used to classify persons as inactive (<0.5 hour/week), semiactive (0.5–3.4 hours/week), and normal active (≥3.5 hours/week). Alcohol use was classified as current, former, or never. Current alcohol users were classified as heavy users (mean intake: ≥3 drinks/day for men and ≥2 drinks/day for women), and moderate users (mean intake: 0–2 drinks/day for men and 0–1 drink/day for women).

Statistical analyses

As we carried out a complete case analysis, data had to be available on BMI at all four rounds, demographics and lifestyle variables at round D, and QOL at rounds B and D (n=3,638). In total, 4,131 respondents were excluded, mainly due to nonresponse at follow-up (Figure 7.1). The proportion of men did not differ between the excluded respondents and the included respondents (p=0.14). However, the excluded respondents were slightly older by 0.9 years (p<0.01) and had a higher BMI of 0.7 kg/m^2 (p<0.01) at baseline (round A). Women who were pregnant (n=87) and underweight persons (n=59) at one of the measurement rounds were excluded from analyses. The number of underweight participants at one of the four measurements was too low (n=59) to classify them in a separate pattern, and they could not be combined with those with a persistent healthy weight as from exploratory analysis we observed structurally lower QOL scores (data not shown).

The remaining participants (n=3,492) were classified in one of the following BMI patterns by using the BMI status of each round: "persistent healthy weight," "developing overweight," "persistent overweight," "developing obesity," "persistent obesity," "switching between categories," "becoming healthy weight," and "becoming overweight" (Figure 7.2). The latter

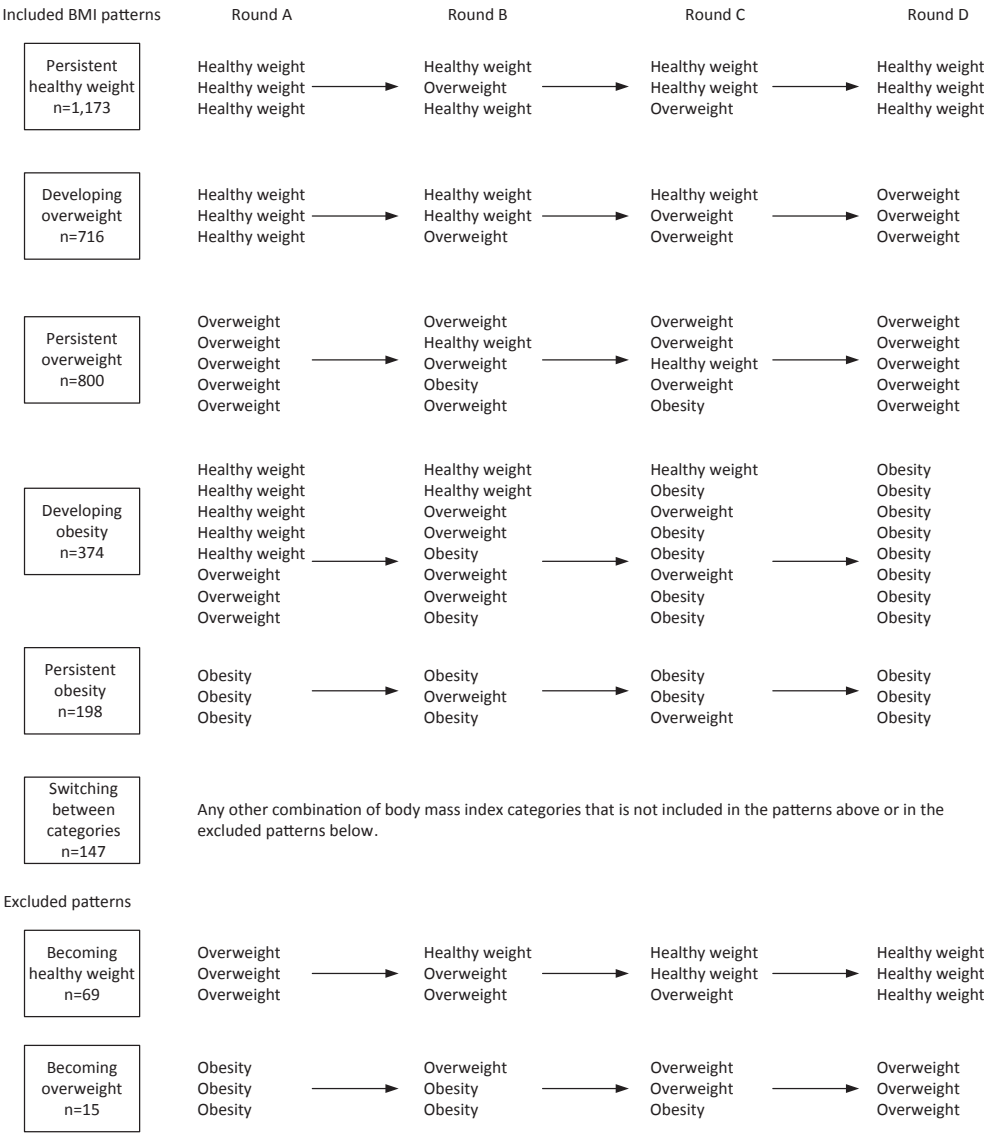


Figure 7.2 Defined long-term body mass index (BMI) patterns, the Doetinchem Cohort Study, the Netherlands, 1989–2009.

two patterns with participants losing weight were excluded from the analysis because of the low number of participants (n=69 and n=15, respectively). In all, we analysed the data of 3,408 participants who were classified into six long-term BMI patterns.

Descriptive statistics were carried out for study characteristics and QOL, and the differences between sexes were examined with an independent-samples *t* test for continuous variables and a χ^2 test for categorical variables.

To examine the differences between the reference BMI pattern "persistent healthy weight" and the other five BMI patterns in QOL at round D, we carried out multivariable linear regression analyses. We used generalized estimated equations with the estimation of robust standard errors to account for the skewed distribution of QOL. The least-squares-means method was used to estimate the adjusted mean of QOL for each BMI pattern. Adjustments were made for age, smoking status, educational level, physical activity, alcohol use, work status, and household composition at round D and for QOL at round B (SAS, version 9.2, software; SAS Institute, Inc., Cary, North Carolina; 2-tailed p-values are reported for all analyses).

Interaction terms between age (<60 years and ≥60 years at round D) and BMI patterns were entered into the model to test for interaction (significant at p≤0.05 (2 sided)), since age was expected to be highly associated with (changes in) QOL.[22,23]

Sensitivity analyses were carried out by repeating the analyses by further adjusting for the presence of a chronic disease at each round and by excluding persons who had a chronic disease at ≥1 measurement round(s). These chronic diseases were self-reported at each measurement round and included diabetes, myocardial infarction, stroke, cancer, and asthma.

Results

A persistent healthy weight was found more often among women (40.8%) than among men (27.8%), while persistent overweight was found more often among men (31.2%) than among women (16.0%) (Table 7.1). Men had higher scores on all eight QOL dimensions assessed at round B than women did (p<0.05) (Table 7.1). Furthermore, men differed from women in all study characteristics assessed at round D (p<0.01), except for physical activity (p=0.57) (Table 7.1).

The following results are reported as score differences from the mean score of the reference BMI pattern, "a persistent healthy weight" (for men and women separately). In general,

Table 7.1 Study characteristics, the Doetinchem Cohort Study, the Netherlands, 1989–2009

	Men (n=1,677)		Women (n=1,731)		
	%	Mean (SD)	%	Mean (SD)	p-value*
BMI patterns					<0.01
Persistent healthy weight	27.8		40.8		
Developing overweight	22.9		19.2		
Persistent overweight	31.2		16.0		
Developing obesity	10.0		11.9		
Persistent obesity	5.0		6.6		
Switching between categories	3.1		5.5		
8 dimensions of QOL at round B					
Physical functioning		91.1 (13.9)		87.6 (16.7)	<0.01
Role, physical		86.2 (28.0)		81.4 (32.9)	<0.01
Bodily pain		83.5 (20.2)		77.9 (22.1)	<0.01
General health perceptions		68.4 (16.8)		67.3 (16.9)	0.04
Vitality		70.1 (16.2)		65.3 (16.7)	<0.01
Social functioning		89.4 (17.6)		84.3 (20.8)	<0.01
Role, emotional		89.9 (25.0)		85.7 (30.9)	<0.01
Mental health		79.3 (14.0)		74.9 (14.8)	<0.01
Age[a]		57.8 (10.0)		57.2 (9.9)	0.09
Smoking status[a]					<0.01
Current smoker	17.6		19.4		
Former smoker	50.9		40.1		
Never smoker	31.5		40.6		
Educational level					<0.01
Low	32.3		49.6		
Moderate	36.8		27.6		
High	31.0		22.8		
Physical activity[a]					0.57
Inactive	3.6		3.0		
Semiactive	15.9		16.4		
Normal active	80.4		80.7		
Alcohol use[a]					<0.01
Never drinker	4.7		14.7		
Former drinker	2.2		1.7		
Moderate use	80.0		76.1		
Heavy use	13.2		7.5		
Job[a]					<0.01
No	39.2		51.4		
Yes	60.8		48.6		
Living alone[a]					<0.01
No	89.4		85.0		
Yes	10.6		15.0		

BMI, body mass index; QOL, health-related quality of life; SD, standard deviation.
* p<0.05 (2 sided). [a] Study characteristics were displayed for round D (2005–2009), because our analyses were adjusted for these variables at round D.

persistently obese adults had the lowest scores on all QOL dimensions, and this was most marked for the physical dimensions, especially in women (Web Figure 1 available at http://aje.oxfordjournals.org/). Persistently obese women had statistically significant lower scores ($p<0.05$) on physical functioning (9.2 points), role limitations due to physical health problems (11.6 points), general health perceptions (6.6 points), vitality (6.2 points), and role limitations due to emotional problems (6.8 points) (Table 7.2; Web Figure 1A). Persistently obese men had lower scores on all QOL dimensions, but the difference was statistically significant only for social functioning (5.0 points; $p=0.02$) and borderline statistically significant ($p\leq0.10$) for physical functioning (3.4 points) and general health perceptions (3.4 points) (Table 7.3; Web Figure 1B).

Also, adults who developed obesity had lower scores on the physical dimensions, and this was more pronounced in women than in men. Women who developed obesity scored from 3.9 to 6.3 points lower on the physical dimensions ($p<0.05$) and 3.2 points lower on vitality ($p<0.01$) (Table 7.2; Web Figure 1A). Men who developed obesity scored statistically significant lower ($p<0.05$) on physical functioning (3.5 points), general health perceptions (3.2 points), and borderline statistically significant lower on bodily pain (3.0 points) ($p=0.08$) (Table 7.3; Web Figure 1B).

Persistently overweight adults did not score statistically significant lower on QOL, except for a 3.2-points-lower mean score on physical functioning in women ($p<0.01$) (Tables 7.2 and 7.3; Web Figure 1).

For developing overweight, lower scores on some of the QOL dimensions were observed. Women who developed overweight had statistically significant lower scores ($p<0.05$) on physical functioning (2.8 points), general health perceptions (3.1 points), vitality (2.4 points), and role limitations due to emotional problems (3.9 points) (Table 7.2; Web Figure 1A). For men who developed overweight, statistically significant lower scores ($p<0.05$) were observed only on physical functioning (1.8 points) and general health perceptions (3.3 points) (Table 7.3; Web Figure 1B).

Women who switched between BMI categories had statistically significant lower scores (3.6–9.8 points) on the four mental dimensions ($p<0.05$) (Table 7.2; Web Figure 1A). In men, higher scores were observed on physical role limitations (6.5 points) ($p=0.03$) (Table 7.3; Web Figure 1B).

Table 7.2 Adjusted mean difference in eight dimensions of health-related quality of life at the end of the 15-year period compared with persons with a persistent healthy weight by body mass index pattern in women, the Doetinchem Cohort Study, the Netherlands, 1989–2009

	Mean persistent healthy weight score (SE)	Developing overweight		Persistent overweight		Developing obesity		Persistent obesity		Switching	
		Mean difference[a]	p-value	Mean difference[a]	p-value	Mean difference[a]	p-value	Mean difference[a]	p-value	Mean difference[a]	p-value
Physical functioning	86.7 (0.5)	-2.8*	<0.01	-3.2*	<0.01	-6.3*	<0.01	-9.2*	<0.01	-1.2	0.44
Role, physical	83.2 (1.2)	-2.5	0.25	-3.7	0.14	-5.8*	0.03	-11.6*	<0.01	-2.5	0.47
Bodily pain	76.2 (0.7)	-1.6	0.20	-1.9	0.19	-4.6*	<0.01	-3.3	0.17	-0.6	0.80
General health perceptions	71.1 (0.6)	-3.1*	<0.01	-0.3	0.76	-3.9*	<0.01	-6.6*	<0.01	-1.9	0.23
Vitality	68.5 (0.5)	-2.4*	0.01	-0.8	0.42	-3.2*	<0.01	-6.2*	<0.01	-5.2*	<0.01
Social functioning	87.8 (0.7)	-1.8	0.11	-1.2	0.34	-0.9	0.52	-2.7	0.18	-4.8*	0.05
Role, emotional	90.1 (1.0)	-3.9*	0.04	0.0	0.98	0.0	0.98	-6.8*	0.03	-9.8*	0.01
Mental health	76.9 (0.5)	-0.2	0.80	0.5	0.59	0.3	0.76	-1.0	0.43	-3.6*	0.02

SE, standard error.

* $p<0.05$ (2 sided). [a] Difference compared with reference category: Persistent healthy weight, adjusted for age, smoking status, educational level, physical activity, alcohol use, work status, and household composition at round D and for health-related quality of life at round B.

Table 7.3 Adjusted mean difference in eight dimensions of health-related quality of life at the end of the 15-year period compared with persons with a persistent healthy weight by body mass index pattern in men, the Doetinchem Cohort Study, the Netherlands,1989–2009

	Mean persistent healthy weight score (SE)	Developing overweight		Persistent overweight		Developing obesity		Persistent obesity		Switching	
		Mean difference[a]	p-value	Mean difference[a]	p-value	Mean difference[a]	p-value	Mean difference[a]	p-value	Mean difference[a]	p-value
Physical functioning	89.8 (0.6)	-1.8*	0.03	1.4	0.07	-3.5*	<0.01	-3.4	0.10	0.5	0.74
Role, physical	86.6 (1.3)	0.8	0.67	0.7	0.72	0.7	0.76	-4.3	0.26	6.5*	0.03
Bodily pain	81.9 (0.8)	-1.3	0.30	-0.1	0.92	-3.0	0.08	-2.5	0.26	1.8	0.43
General health perceptions	71.6 (0.7)	-3.3*	<0.01	0.1	0.94	-3.2*	0.03	-3.4	0.08	1.6	0.41
Vitality	73.2 (0.6)	-1.1	0.26	-1.1	0.24	0.0	0.97	-2.5	0.15	-0.8	0.64
Social functioning	91.4 (0.7)	-0.4	0.68	-0.7	0.53	-0.3	0.83	-5.0*	0.02	-0.3	0.90
Role, emotional	92.8 (1.0)	0.2	0.89	-0.3	0.84	-1.0	0.64	-3.8	0.24	-6.5	0.13
Mental health	81.9 (0.5)	-0.1	0.90	-1.2	0.10	0.2	0.85	-2.5	0.12	-1.6	0.34

SE, standard error.

* $p<0.05$ (2 sided). [a] Difference compared with reference category: Persistent healthy weight, adjusted for age, smoking status, educational level, physical activity, alcohol use, work status, and household composition at round D and for health-related quality of life at round B.

Interaction between age and BMI patterns

We found no overall interactions between age and BMI patterns in the association with QOL, with the exception of women and general health perceptions (p=0.02) and role, emotional (p=0.04). However, in persistently obese women aged ≥60 years, we observed consistently (larger) negative differences in QOL scores compared with their persistently healthy weight peers than in women aged <60 years. For physical functioning, role, physical, bodily pain, vitality, social functioning, role, emotional, and mental health, this difference for women aged ≥60 years was -12.5, -16.4, -6.6, -7.7, -3.0, -12.2, and -1.9, while for women aged <60 years this difference was -6.4, -7.2, 0, -3.9, -2.0, 1.1, and 0.4, respectively. For men, no consistent differences between age groups were found (data not shown).

Sensitivity analyses

Adjustment for the presence of a chronic disease did not affect our main findings (data not shown). After exclusion of persons with a chronic disease, most observed score differences changed with a decrease in score difference of up to 1.6 points, and with an increase in score difference of up to 2.2 points. A larger change was found for persistently obese women and emotional role limitations, which decreased by 4.5 points.

Discussion

Persistently obese men and women had the lowest scores on almost all QOL dimensions compared with other long-term BMI patterns. Men and women who developed obesity or overweight had lower scores on mainly the physical QOL dimensions than did those with a persistent healthy weight. These findings were most pronounced in women. Women who switched between BMI categories had lower scores on the mental QOL dimensions than persistently healthy weight women.

Our findings of an association between long-term BMI patterns and the physical dimensions of QOL were comparable to the findings by Kozak and colleagues.[13] They examined the association between six BMI patterns and QOL, comparable to our patterns, over a 20-year period by using the change in BMI category from two measurements.[13] In contrast to Kozak and colleagues,[13] we also found an association between lower scores on mental dimensions (one in men and two in women). This might be explained by the difference in population (i.e., younger, other country) and applied methods (e.g., defining patterns by only two measurements and adjusting for different variables, such as general health instead of an earlier QOL score). Our

results as to developing overweight or obesity were also in agreement with studies that found an association between weight gain and a lower QOL on the physical dimensions compared with a stable weight.[10-12] In addition, in women, we found consistent associations between the switching BMI pattern and lower scores on the mental dimensions compared with a persistent healthy weight. These associations have not been examined before.

The differences in QOL between a persistent healthy weight and other BMI patterns were strikingly larger in women than in men and were in agreement with previous cross-sectional and longitudinal studies.[22,24,25] The sex difference was largest for the switching BMI pattern. An explanation for the sex difference regarding the mental dimensions might be that, compared with men, women have a greater drive to look thin because of external pressure (e.g., media) and the stigmatization of obesity is more pronounced.[26-28] Thus, women are more likely to try to lose weight through dieting and, when dieting fails, their self-esteem and body image may get negatively affected.[26,27]

In addition to the factors mentioned for the mental dimensions, the sex difference for the physical dimensions might also be explained by men being physically stronger than women, with men being more likely to recover from disabilities, with the possibility that men have more muscle mass than women for the same BMI, and the tendency by men to underreport health problems.[29-31]

Strengths of our study include the large, population-based sample that allowed us to investigate the relation between six long-term BMI patterns and QOL in the general population. Trained personnel measured the participants' weight and height. We had data on all eight dimensions of QOL at several measurement rounds, as well as data on demographics and lifestyle. Therefore, we were able to adjust for important characteristics and an earlier score of QOL.

A limitation of our study is the loss to follow-up that resulted in a relatively healthy population that remained in the Doetinchem Cohort Study.[32] Because of the higher BMI at baseline in the excluded respondents, as presented in Materials and Methods, we examined whether the cross-sectional associations (at round B) between BMI status and QOL were different for included and excluded persons by examining the interaction between inclusion and BMI. We found only small and mostly insignificant differences, which suggest that the lack of data for the excluded respondents had little effect on our findings.

Our study did not have data on stressful life events, which have been shown to be associated with weight gain[33] and could be an explanatory factor for the finding of the lower scores on the mental dimension of QOL in women who switched between BMI categories. However, illness-related life events have been shown to be an important predictor of BMI in a British

population.[34] We accounted for the presence of chronic diseases at each round, which did not affect our main findings.

Because of the observational nature of our study, we cannot establish the underlying pathway or direction of the association between the BMI patterns and QOL. A recent study by Cameron and colleagues[22] found associations between baseline BMI and changes in QOL and between baseline QOL and changes in BMI over 5 years, which suggests a bidirectional relationship between BMI and QOL. However, for the physical dimensions, a clear dose-response relationship between baseline BMI and changes in QOL was observed, while for baseline QOL and changes in BMI, this was not observed.[22] We also observed a dose-response relationship between the BMI patterns (excluding switching pattern) in women especially and QOL on the physical dimensions. With each increasing pattern, thus from becoming overweight to having persistent obesity, the QOL at the end of the 15-year period became lower, and thus the difference with those who had a persistent healthy weight became larger (Web Figure 1).

In our study, the period between measurements was 5 years, which can be assumed to be more accurate than an interval of 20 years. However, the amount of measurements needed to capture relevant BMI changes in order to explain the impact on health is unknown. In addition, the definition of our BMI patterns was not overly restrictive (Figure 7.2). We allowed, for example, one deviation to another BMI category at round B or C in the persistent weight patterns. In preliminary analyses, we also examined other definitions of persistent weight patterns in which no deviation was allowed, or of developing patterns in which progression to a higher BMI category that occurred at the final round was not allowed. This did not change our results substantially, indicating that our results are robust. Therefore, we think that we captured the global changes in BMI during the life course that give a good indication of the consequences of exposure or developments of overweight or obesity on the longer term.

Differences in the eight QOL dimensions are considered clinically important if between 3 and 5 points.[35] However, this applies to clinical samples, while we examined "healthy" participants in a population-based study. In population-based samples, smaller differences can impact public health.[36] Therefore, our results of several BMI patterns scoring at least 3 points lower compared with a persistent healthy weight may be of importance for public health. Moreover, in persistently obese women aged ≥60 years, we observed larger negative differences in QOL scores compared with their persistently healthy weight peers than in women aged <60 years. This might be explained by a longer exposure to obesity in the elder group. This stresses again the importance of prevention of overweight and especially obesity and implies that prevention should be implemented early in adulthood.

Furthermore, women who switched between BMI categories had lower scores on the mental dimensions, ranging from -4 to -10, than persistently healthy weight women. This indicates that prevention of weight cycling is especially relevant for women.

Only persistently overweight persons did not show lower scores on QOL than persistently healthy weight persons, except for women. This suggests that, to retain a good QOL in later life for persons who are overweight, they do not necessarily have to lose weight, although they should avoid the development of obesity.

In conclusion, in this population-based study, adults who developed overweight or obesity or who were persistently obese over 15 years had lower QOL scores – particularly on the physical dimensions – compared with those who were persistently of healthy weight. Women who switched between BMI categories had lower scores on the mental dimensions of QOL than did persistently healthy weight women. Thus, in particular for women, prevention of developing overweight and especially obesity is important not only for preventing specific diseases but also for QOL in general.

Acknowledgements

The Doetinchem Cohort Study was financially supported by the Ministry of Health, Welfare, and Sport of the Netherlands and the National Institute of Public Health and the Environment.

The authors thank the epidemiologists and field workers of the Municipal Health Service in Doetinchem for their contribution to the data collection for this study. Project director is Dr. W. M. M. Verschuren. Logistic management was provided by J. Steenbrink and P. Vissink, and administrative support was supplied by E. P. van der Wolf. Data management was provided by A. Blokstra, A. W. D. van Kessel, and P. E. Steinberger.

References

1. Bjorge T, Engeland A, Tverdal A, et al. Body mass index in adolescence in relation to cause-specific mortality: a follow-up of 230,000 Norwegian adolescents. *Am J Epidemiol*. 2008;168(1):30–37.
2. Branca F, Nikogosian H, Lobstein T, eds. *The Challenge of Obesity in the WHO European Region and the Strategies for Response*. Copenhagen, Denmark: World Health Organization; 2007:1–12.
3. Jia H, Lubetkin EI. The impact of obesity on health-related quality-of-life in the general adult US population. *J Public Health (Oxf)*. 2005;27(2):156–164.
4. Lean ME, Han TS, Seidell JC. Impairment of health and quality of life using new US federal guidelines for the identification of obesity. *Arch Intern Med*. 1999;159(8):837–843.

5. Yan LL, Daviglus ML, Liu K, et al. BMI and health-related quality of life in adults 65 years and older. *Obes Res*. 2004;12(1):69–76.

6. Ware JJ, Sherbourne C. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473–483.

7. Hennessy CH, Moriarty DG, Zack MM, et al. Measuring health-related quality of life for public health surveillance. *Public Health Rep*. 1994;109(5):665–672.

8. Burns CM, Tijhuis MA, Seidell JC. The relationship between quality of life and perceived body weight and dieting history in Dutch men and women. *Int J Obes Relat Metab Disord*. 2001;25(9):1386–1392.

9. Fine JT, Colditz GA, Coakley EH, et al. A prospective study of weight change and health-related quality of life in women. *JAMA*. 1999;282(22):2136–2142.

10. Stafford M, Hemingway H, Marmot M. Current obesity, steady weight change and weight fluctuation as predictors of physical functioning in middle aged office workers: the Whitehall II Study. *Int J Obes Relat Metab Disord*. 1998;22(1):23–31.

11. Williams LT, Young AF, Brown WJ. Weight gained in two years by a population of mid-aged women: how much is too much? *Int J Obes (Lond)*. 2006;30(8):1229–1233.

12. Strandberg TE, Strandberg A, Salomaa VV, et al. Impact of midlife weight change on mortality and quality of life in old age. Prospective cohort study. *Int J Obes Relat Metab Disord*. 2003;27(8):950–954.

13. Kozak AT, Daviglus ML, Chan C, et al. Relationship of body mass index in young adulthood and health-related quality of life two decades later: the Coronary Artery Risk Development in Young Adults Study. *Int J Obes (Lond)*. 2011;35(1):134–141.

14. Garner RE, Feeny DH, Thompson A, et al. Bodyweight, gender, and quality of life: a population-based longitudinal study. *Qual Life Res*. 2012;21(5):813–825.

15. Orfila F, Ferrer M, Lamarca R, et al. Gender differences in health-related quality of life among the elderly: the role of objective functional capacity and chronic conditions. *Soc Sci Med*. 2006;63(9):2367–2380.

16. Verschuren WMM, Blokstra A, Picavet HSJ, et al. Cohort profile: the Doetinchem Cohort Study. *Int J Epidemiol*. 2008;37(6):1236–1241.

17. van der Zee KI, Sanderman R. *Measuring General Health Status with the RAND-36, a Manual* [in Dutch]. Groningen, the Netherlands: Noordelijk Centrum voor Gezondheidsvraagstukken, Rijksuniversiteit Groningen; 1993.

18. Gast GCM, Spijkerman AMW, van der A DL, et al. Five-year changes in biologic risk factors and risk of type 2 diabetes: Are attained but not initial risk factor levels of importance? *Am J Epidemiol*. 2012;176(8):720–725.

19. Jacobs-van der Bruggen MAM, Spijkerman A, van Baal PHM, et al. Weight change and incident diabetes: addressing an unresolved issue. *Am J Epidemiol*. 2010;172(3):263–270.

20. Pols MA, Peeters PH, Ocke MC, et al. Estimation of reproducibility and relative validity of the questions included in the EPIC Physical Activity Questionnaire. *Int J Epidemiol*. 1997;26(suppl 1):S181–S189.

21. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*. 1993;25(1):71–80.

22. Cameron AJ, Magliano DJ, Dunstan DW, et al. A bi-directional relationship between obesity and health-related quality of life: evidence from the longitudinal AusDiab study. *Int J Obes (Lond)*. 2012;36(2):295–303.

23. Franco OH, Wong YL, Kandala NB, et al. Cross-cultural comparison of correlates of quality of life and health status: the Whitehall II Study (UK) and the Western New York Health Study (US). *Eur J Epidemiol*. 2012;27(4):255–265.

24. Bentley TGK, Palta M, Paulsen AJ, et al. Race and gender associations between obesity and nine health-related quality-of-life measures. *Qual Life Res*. 2011;20(5):665–674.

25. Wang R, Wu MJ, Ma XQ, et al. Body mass index and health-related quality of life in adults: a population based study in five cities of China. *Eur J Public Health*. 2012;22(4):497–502.

26. Grivetti L. Psychology and cultural aspects of energy. *Nutr Rev*. 2001;59(1 Pt 2):S5–S12.

27. McCarthy M. The thin ideal, depression and eating disorders in women. *Behav Res Ther*. 1990;28(3):205–215.

28. Roehling MV, Roehling P, Pichler S. The relationship between body weight and perceived weight-related employment discrimination: the role of sex and race. *J Vocat Behav*. 2007;71(2):300–318.

29. Oksuzyan A, Juel K, Vaupel JW, et al. Men: good health and high mortality. Sex differences in health and aging. *Aging Clin Exp Res*. 2008;20(2):91–102.

30. Walter S, Kunst A, Mackenbach J, et al. Mortality and disability: the effect of overweight and obesity. *Int J Obes (Lond)*. 2009;33(12):1410–1418.

31. Wong E, Stevenson C, Backholer K, et al. Adiposity measures as predictors of long-term physical disability. *Ann Epidemiol*. 2012;22(10):710–716.

32. Blokstra A, Picavet HSJ, Verschuren WMM. *De Doetinchem Cohort Studie 4e ronde 2003–2007 Onderzoek naar volksgezondheid en veroudering* (in Dutch). Bilthoven, the Netherlands: National Institute for Public Health and the Environment (RIVM); 2010.

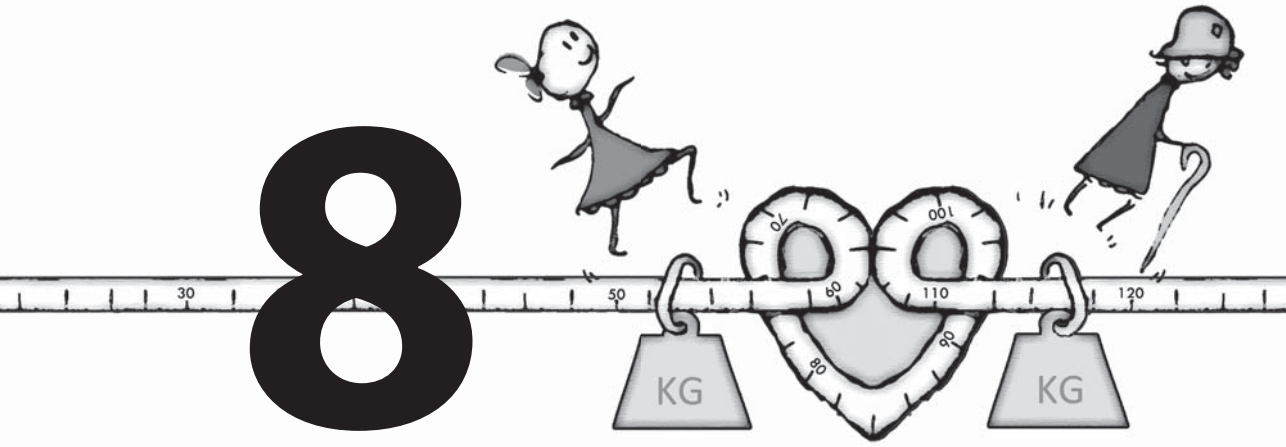
33. Block JP, He Y, Zaslavsky AM, et al. Psychosocial stress and change in weight among US adults. *Am J Epidemiol*. 2009;170(2):181–192.

34. Stewart-Knox B, Duffy ME, Bunting B, et al. Associations between obesity (BMI and waist circumference) and socio-demographic factors, physical activity, dietary habits, life events, resilience, mood, perceived stress and hopelessness in healthy older Europeans. *BMC Public Health*. 2012;12:424.

35. Samsa G, Edelman D, Rothman ML, et al. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics*. 1999;15(2):141–155.

36. Rose G. Sick individuals and sick populations. *Int J Epidemiol*. 2001;30(3):427–432; discussion 433–434.

8



General discussion

In this thesis, using several anthropometric measures and national and international cohort studies, we focused on the impact of weight status on coronary heart disease (CHD), all-cause and cause-specific mortality, and quality of life (QoL) in old age and during ageing. This topic is important because underweight and overweight are important factors in healthy ageing and body composition changes during ageing.[1-4]

First, we examined whether the association between body mass index (BMI) and CHD was consistent over time, and whether age of the population influenced this association.

Secondly, we focused on anthropometric measures as predictors of mortality in elderly populations.

Thirdly, we examined changes and developments in anthropometric measures and their association with mortality and QoL in old age and in an ageing population.

In this chapter, the main findings (Table 8.1) on these topics are critically reviewed. We conclude with a discussion on the consequences for public health and clinical practice.

CHD risks associated with weight status consistent over calendar time but decreasing with increasing age

We hypothesized that the risk of CHD in the association with body mass index (BMI) would be higher before 1985 (earlier studies) than after 1985 (later studies) because of improved health care procedures. However, from our meta-regression analysis, we found no consistent evidence for this hypothesis. When age of the population was added to the model, this appeared an important determinant, and the impact of calendar period on the association between BMI and CHD did not remain (Chapter 2).

Our finding of no consistent evidence for the impact of calendar period on the association between BMI and CHD is in line with previous studies examining the impact of calendar period on the association between BMI and all-cause mortality.[5-7] In our study as well as in previous studies,[6,7] there was an overlap between the follow-up years (on which the mortality risk was calculated) of the earlier studies and the baseline years of the later studies. This makes it difficult to disentangle the influence of calendar period and the influence of follow-up period on the association between BMI and CHD, and thus to filter out the impact of calendar period.

We adjusted for health care procedures by indirect measures, i.e. baseline blood pressure, cholesterol, and physical activity; this did not alter our findings. A more optimal way would

have been to adjust – for example – for the use of medication, like in the Cancer Prevention Study II, where adjustments were made for aspirin use and no impact of calendar time was observed.[5] However, data on medication use were not available in our study.

On the basis of our results, we conclude that calendar period has no impact on the risk of CHD associated with BMI.

From this meta-regression analysis, we found that mean age of the population strongly influenced the association between BMI and CHD. With increasing age of the population, the risk of CHD for a 5-BMI-unit increment and obesity decreased by 29% (95%CI: -55 to -5) and 31% (95%CI: -66 to 3), respectively. We were able to study this properly in the 31 studies, as the range of mean age of the population was 35–73 years. Previous studies that stratified their analyses to age found the lowest risk of mortality in the oldest age stratum; in other words, the risk of mortality associated with BMI decreased with increasing age.[6,8-12] Thus, age is an important modifying factor in the association between BMI and CHD, and mortality.

We conclude that the risk of CHD associated with BMI decreases with increasing age.

Body mass index and waist circumference are both associated with mortality in elderly individuals

It can be questioned whether cut-off points for BMI and waist circumference (WC) classifications should be age-specific, as it is evident that the mortality risk decreases with increasing age. Several factors might underlie this phenomenon, e.g. body compositional changes;[1-4] the survival effect, i.e. individuals who are susceptible to the adverse effects of obesity have probably died before reaching old age; shorter exposure to obesity when obesity has developed at an old age;[1] overweight (fat and lean mass) might provide a reserve when elderly individuals fall ill.[13] Therefore, we examined the association between BMI and all-cause and cause-specific mortality among 1,970 70–77-year olds using both continuous and categorical measures for BMI (Chapter 3) and the association between continuous WC and mortality among approximately 58,000 65–74-year olds (Chapter 4).

In addition, we used a combination of commonly used WC categories and BMI categories (Table 8.2, Chapter 4) in line with the WHO guidelines based on the associated disease risks of increased abdominal fat relative to BMI.[14]

Table 8.1 Main findings of the associations between anthropometric measures and health outcomes

Ch	Population	Exposure	Outcome measure	Main results
2	31 international cohort studies; n = 389,212; 20–94 years		**Univariate model**	**% Change (95%CI) in relative risk of CHD associated with BMI**
		5-BMI-unit increment	Calendar period	-31 (-56 to 0)
		Obesity	Calendar period	-51 (-78 to -14)
			Multivariate model, calendar period, and age of the population	
		5-BMI-unit increment	Calendar period	-9 (-41 to 36)
		Obesity	Calendar period	-32 (-68 to 26)
		5-BMI-unit increment	Age of the population	-29 (-55 to -5)
		Obesity	Age of the population	-31 (-66 to 3)
3†	SENECA study; n = 979 ♂, 991 ♀; 70–77 years	*BMI classification*		**Hazard ratio (95%CI)**
		Underweight	All-cause mortality	1.06 (0.73–1.55)
		Underweight	Mortality due to other causes	2.75 (1.00–7.52)
		Overweight	All-cause mortality	0.92 (0.78–1.09)
		Overweight	CVD mortality	1.12 (0.84–1.42)
		Obesity	All-cause mortality	1.05 (0.89–1.29)
		Obesity	CVD mortality	1.39 (1.00–1.92)
				Lowest mortality risk (95%CI)
		Continuous BMI (kg/m^2)	All-cause mortality	27.1 (24.1–29.3)
		Continuous BMI (kg/m^2)	Cause-specific mortality	25.6 (17.1–28.4) – 27.4 (22.7–30.2)
				BMI range with <10% increased mortality risk
		Continuous BMI (kg/m^2)	All-cause mortality	22.3–31.9
		Continuous BMI (kg/m^2)	Cause-specific mortality	24.2–30.1

4†	29 international cohort studies; n = 32,678 ♂, 25,931 ♀; 65–74 years	*WC-BMI classification*		**Relative risk (95%CI)**
		Underweight	All-cause mortality	2.2 (1.8 – 2.8) ♂, 2.3 (1.8–3.1) ♀
		Underweight	CVD mortality	2.9 (2.0 – 4.2) ♂, 1.5 (0.8–2.8) ♀
		Underweight	Cancer mortality	2.1 (1.5 – 3.0) ♂, 2.6 (1.5–4.4) ♀
		Large-WC-healthy weight	All-cause mortality	1.7 (1.2–2.2) ♂, 1.7 (1.3–2.3) ♀
		Large-WC-healthy weight	CVD mortality	2.6 (1.6–4.1) ♂, 2.2 (1.3–3.8) ♀
				Relative risk (95%CI) associated with level of abdominal obesity
		WC continuous (cm)	All-cause mortality	1.03 (1.00–1.07) ♂, 1.06 (0.97–1.15) ♀
		WC continuous (cm)	CVD mortality	1.11 (0.99–1.26) ♂, 1.28 (0.92–1.77) ♀
				WC level associated with a twofold increased risk
		WC continuous (cm)	All-cause mortality	132 cm ♂, 116 cm ♀
		WC continuous (cm)	CVD mortality	123 cm ♂, 105 cm ♀
5†	SENECA study; n = 516 ♂, 545 ♀; 70–77 years			**Hazard ratio (95%CI)**
		ΔWeight (kg): ≥ -3.2	All-cause mortality	1.48 (0.99–2.20)
		ΔWC (cm): ≥ -3.1	All-cause mortality	1.52 (1.01–2.31)
		ΔMUAC (cm):		
		≥ -1.6 cm, -0.6 to -1.6,	All-cause mortality	1.81 (1.17–2.79), 1.66 (1.10–2.49)
		≥ + 1.3	All-cause mortality	1.52 (1.00–2.31)
		≥ + 1.3	CVD mortality	1.94 (1.00–3.75)
6†a	DCS; n = 2,005 ♂, 2,130 ♀; 26–70 years			**Statistically significant difference in ΔQoL compared to a stable weight (+/- <2 kg)**
		Δweight (kg):		
		≥ -2kg	ΔQoL scores	-1.6 to -2.8 (3 of 8 dimensions) ♂, -1.1 to -4.0 (3 of 8 dimensions) ♀
		+2 – ≤ +4 kg	ΔQoL scores	-1.5 to -1.6 (3 of 8 dimensions) ♀
		+4 – ≤ +6 kg	ΔQoL scores	-1.5 to -2.8 (4 of 8 dimensions) ♂, -2.1 to -4.6 (3 of 8 dimensions) ♀
		> +6 kg	ΔQoL scores	-2.2 to -3.9 (4 of 8 dimensions) ♂, -2.0 to -5.9 (5 of 8 dimensions) ♀

Table 8.1 continues on next page

Table 8.1 *Continued*

Ch	Population	Exposure	Outcome measure	Main results
7[†a]	DCS; n = 1,677 ♂, 1,731 ♀; 20–66 years	*Long-term BMI patterns*		**Statistically significant difference in QoL compared to a persistent healthy weight**
		Developing overweight	QoL scores	-1.8 to -3.3 (2 of 8 dimensions) ♂, -2.4 to -3.9 (4 of 8 dimensions) ♀
		Persistent overweight	QoL scores	-3.2 (1 of 8 dimensions) ♀
		Developing obesity	QoL scores	-3.2 to -3.5 (2 of 8 dimensions) ♂, -3.2 to -6.3 (5 of 8 dimensions) ♀
		Persistent obesity	QoL scores	-5.0 (1 of 8 dimensions) ♂, -6.2 to -11.6 (5 of 8 dimensions) ♀
		Switching between BMI categories	QoL scores	-3.6 to -9.8 (4 of 8 dimensions) ♀

BMI: body mass index, CHD: coronary heart disease, CI: confidence interval, CVD: cardiovascular disease, DCS: *Doetinchem Cohort Study*, MUAC: mid-upper arm circumference, SENECA: *Survey in Europe on Nutrition and the Elderly: a concerted action study*, QoL: quality of life, WC: waist circumference. [†] Sensitivity analyses were performed by excluding deaths during the first two years of follow-up, and excluding persons with chronic diseases at baseline; this did not change our main findings. [a] The sensitivity analysis only involves excluding persons with chronic diseases.

Table 8.2 WC-BMI classification

	WC (cm) categories (men/women)		
BMI (kg/m^2) categories	Small: <94/<80	Medium: 94–101/80–87	Large: ≥102/≥88
Underweight: <20	Underweight	n.a.	n.a.
Healthy weight: 20–24.9	Reference	Medium WC-Healthy weight	Large WC-Healthy weight
Overweight: 25–29.9	Small WC-Overweight	Medium WC-Overweight	Large WC-Overweight
Obesity: ≥30	n.a.	Medium WC-Obesity	Large WC-Obesity

BMI: body mass index, WC: waist circumference. n.a.: not applicable. In our study, we did not find enough individuals with this body composition to calculate a relative risk of mortality for this classification.

Body mass index as a single predictor of mortality

When we examined the standard BMI classifications, i.e. underweight, overweight, and obesity, as a predictor of all-cause and cause-specific mortality in the elderly, we found associations for underweight and obesity with all-cause and cause-specific mortality.

With respect to underweight, we found high increased all-cause and cause-specific mortality risks; this is supported by previous studies.[6,8,15,16]

For overweight, we found no association with all-cause and cause-specific mortality; this is in line with previous studies among the elderly.[6,7,15,16] However, a meta-analysis including 18 studies in old age (≥65 years) found an inverse association between overweight and all-cause mortality;[17] this led to a discussion about whether overweight is protective for mortality or not.[18]

Overweight might not be protective, but might be the wrong labelling for a high BMI associated with an increased mortality risk due to the above-described mechanisms. When we look at our results of a U-shaped association between BMI and all-cause mortality, and cause-specific mortality, the definition of cut-off points of the reference category seem very important. We observed the lowest all-cause and cause-specific mortality risks at higher BMI levels than the WHO reference category, i.e. between 25.6 and 27.4 kg/m^2. This finding is supported not only by our results of the WC-BMI classifications, where we observed the lowest all-cause mortality risk within the overweight category across WC categories, but also by other studies among the elderly.[19-21] Moreover, a 10% increased mortality risk can be considered as relevant since the absolute mortality is much higher among the elderly than in younger adults. In our study, ≥10% increased all-cause and

cause-specific mortality risks were observed at ≤24.2 and ≥30.1 kg/m^2, respectively; this is similar to other studies among the elderly.[7,19-21] Given this BMI range (24 kg/m^2–30 kg/m^2), elderly individuals within the lower ranges of BMI at increased risk of mortality are included in the standard reference category (18.5–24.9 kg/m^2, or 20–24.9 kg/m^2). With respect to obesity, the definition of the reference category might also explain why findings of an association with mortality are inconsistent.[6,7,15-17] Since we observed a 10% increased risk at the standard cut-off point for obesity (30 kg/m^2), this might be an alternative for the current cut-off point of overweight.

Overall, we conclude that both high and low BMI levels are associated with all-cause and cause-specific mortality among the elderly. However, the WHO cut-off points to indicate underweight and overweight are too low and need to be reconsidered for the elderly.

WC as a single predictor of mortality

For the WC classification, the cut-off points might also be different for the elderly than for younger adults. The association between a high WC and all-cause and CVD mortality is stronger among general adult populations (20–74 years)[10,22,23] than among specifically elderly populations.[24,25,26] In a Canadian elderly population, an inverse association was even observed with all-cause mortality.[27] Our results for WC as a continuous variable showed strong J-shaped associations with all-cause mortality and CVD mortality. At the level of abdominal obesity (102 cm in men, 88 cm in women), the risks of all-cause and CVD mortality were only modestly increased, or the risks were not statistically significantly increased. At higher levels of WC, we observed significantly increased risks; this is in line with other studies for mortality and other health outcomes among elderly individuals.[20,28] To be specific, we observed a two-fold increased all-cause and CVD mortality risk at 132 cm and 123 cm, respectively, in men and at 116 cm and 105 cm, respectively, in women. From exploratory analyses, the prevalence of these levels was found to be about 1–2%, and the prevalence of abdominal obesity was about 12–48% among populations. So, to target a large part of the population that is at risk, a WC level between 102 cm and 123 cm in men, and between 88 cm and 105 cm in women, might be more appropriate for clinical guidelines.

We conclude that WC is associated with all-cause and cause-specific mortality, but the cut-off points for WC should be reconsidered for the elderly for the prediction of health risks.

The combination of waist circumference and body mass index in the association with mortality

A combination of WC and BMI might be a better proxy for body composition. By using WC as a single predictor, underweight is not considered. We found a J-shaped association for continuous WC with all-cause, CVD, and cancer mortality, and a U-shaped association with respiratory disease mortality ($p<0.05$). In our study, as well as in other studies, the association of WC with mortality became stronger after adjustment for BMI.[10,23,29] In previous studies including elderly populations, the association changed from inverse or no association to an adverse association with mortality.[24,27] This might be explained by body fat composition, in particular the proportion of hazardous visceral abdominal fat.[30] In addition, the adjustment for BMI might attenuate the influence of underweight in the association between WC and mortality. This suggests that WC and BMI, although highly correlated, have a different role in the association with mortality.[31]

The importance of a combination of WC and BMI manifested itself in our results of the WC-BMI classification and all-cause and CVD mortality. We observed that a large WC was associated with an increased all-cause and CVD mortality risk across BMI categories; this is in line with previous literature.[10,22,23,29] For *large WC-healthy weight*, we observed the highest risk of all-cause and CVD mortality (about 2.0) of all BMI categories. This is not in line with the findings of two studies including younger American (30–55 years) and Canadian (18–74 years) populations, in which the highest risk was found for *large WC-obesity*.[22,23] However, these two studies included in general younger individuals who have a different body composition than elderly individuals.[22,23]

The WHO guidelines[14] indicate the highest disease risk for *large WC-obesity* and do not rigorously consider the health risk for persons with *large WC-healthy weight*. In the WHO guidelines, the following note is made: 'Increased waist circumference can also be a marker for increased risk even in persons of normal weight.' Although the prevalence for this specific elderly group may not be high, this group may need more attention because of the increased all-cause and CVD mortality risk.

> *We conclude that, in elderly populations, a combination of WC and BMI can be recommended, since they complement each other in predicting mortality risks.*

Developments in weight status are important for mortality and QoL in old age and in an ageing population

Mid-upper arm circumference as an anthropometric measure of changes in body composition in the elderly

Among the elderly (70–77 years, Chapter 5), we found that a **decrease** in three out of eight anthropometric measures, i.e. weight, WC, and mid-upper arm circumference (MUAC), over an approximately four-year period was associated with increased all-cause mortality risks. For only one measure, i.e. MUAC, an **increase** was also associated with an increased all-cause and CVD mortality risk.

Our findings for weight loss are consistent with previous literature.[32-35] For changes in WC, we found an association for a decrease, but not for an increase, in WC. The latter finding is in line with a previous study.[36] Adjustment for changes in BMI resulted in an increased mortality risk for an increment in WC.[36] During exploratory analysis, we observed the same, which again suggests that a combination of WC and BMI would provide more information than WC or BMI alone.

For MUAC, which to our knowledge has not been observed before, we found associations with all-cause and CVD mortality for both decreases (≥1.6 cm and 0.6–1.6 cm) and an increase of ≥1.3 cm. Decreases in MUAC probably reflect a loss of subcutaneous fat and muscle mass. A decrease in muscle mass might be a result of sarcopenia, which is a common problem among the elderly leading to frailty, functional disabilities, and mortality.[37,38] Even when in exploratory analyses MUAC was adjusted for changes in weight, BMI, or WC, the associations of decreases in MUAC with all-cause mortality remained, as well as the association between an increase in MUAC and all-cause and CVD mortality. When we further explored the association between an increase in MUAC and CVD mortality, we observed that this association was attenuated after excluding persons with ischemic heart disease and diabetes at baseline rather than persons with cancer and respiratory diseases. The results from the exploratory analyses may indicate that the increase in MUAC reflects an increase in oedema.

> *On the basis of our findings, we conclude that MUAC as a single anthropometric measure and that WC and BMI, or WC and weight, as combined measures seem good body compositional predictors of mortality among the elderly.*

Stable weight, provided it is not within the extreme ranges, is best for health maintenance among all ages

Among the elderly (70–77 years), we found clear evidence that weight loss was associated with an increased mortality risk (Chapter 5). Among adults of 26–70 years of age (Chapter 6), we observed that persons who lost weight were at a disadvantage in relation to changes in QoL compared with those who had a stable weight. This was most pronounced among men aged ≥60 years. These findings are in line with other longitudinal studies reporting associations between weight loss and adverse outcomes on mortality and QoL.[32-34,39,40] However, some studies have found a beneficial impact of weight loss on all-cause mortality risk and improvement in physical performance and bodily pain score of QoL for individuals. These studies included persons with a high or extremely high BMI and hypertension, in which substantial weight losses (3–5 BMI units/2 years, 1.6 kg/year, ≥9 kg/4 years) could be observed[41-43] in contrast to our weight loss categories (Chapter 5: ≥3.1 kg/4 years; Chapter 6: ≥2kg/5 years). This relates to the intentionality of weight loss, which has been shown to influence the association between weight loss and mortality specifically in unhealthy obese individuals.[44,45] Thus, information on the intentionality of weight loss might influence the association between weight loss (among obese adults) and health. Our studies did not include many individuals with extreme levels of BMI and weight loss and thus could not detect a beneficial impact of weight loss among the obese, and no data were available on the intentionality of weight loss. In general, we conclude that weight loss, especially among the elderly, is associated with adverse health outcomes.

With regard to weight gain, we observed among the elderly no clear evidence for an association between weight gain and mortality (Chapter 5). In adults, previous studies observed an association with increased mortality risk and reduced odds of healthy survival only in cases of large weight gains over the long term (≥15 kg/20 years and ≥20 kg/32 years).[46,47] With regard to QoL, we observed consistent associations between weight gain and a decline in QoL (Chapter 6). Moreover, we found associations between developing overweight and developing obesity and a lower QoL compared with those who persistently had a healthy weight (Chapter 7). These findings are in line with other studies.[33-35,40,41,48-52] The lack of a consistent association between weight gain and mortality but a clear association between weight gain and QoL might be explained by the difference between an objective measure (mortality) and a subjective measure (QoL). More time is required to expose the detrimental impact of weight gain on mortality, whereas the impact on QoL can be more directly detected as it is measured from the individual's perspective. Therefore, we conclude that weight gain is adversely associated with mortality and quality of life.

Since weight loss and weight gain are associated with adverse health outcomes, it seems that a stable weight is the best prognosis for good health. However, this prognosis is less straightforward than it seems, as it appears to depend on the level of weight. In additional analyses, we found that women with a stable weight in the obese range had larger declines on the physical dimensions of QoL than those in the healthy weight range (Chapter 6). Furthermore, we found that persistently obese women and men had the lowest QoL scores on most dimensions of QoL of the six BMI patterns, i.e. persistent healthy weight, developing overweight, persistent overweight, developing obesity, persistent obesity, and switching between BMI categories. Moreover, women who switched between BMI categories had lower scores on all four mental dimensions of QoL (Chapter 7). Given all of our findings, a stable weight contributes to health maintenance, but a too low or too high body weight should be avoided. The exact ranges within which a stable weight should be maintained cannot be provided by our results.

We conclude that a stable weight, provided it does not fall within the extreme ranges, over a person's life course is important for health maintenance.

Representativeness of the cohort studies

The representativeness of the cohort studies examined in this thesis is important for the translation of the findings to general populations. Therefore, we compared important study characteristics of the selected elderly individuals (70–77 years) from the *Survey in Europe on Nutrition and the Elderly: a concerted action* (SENECA study) at baseline, and the adults (20–66 years) from the *Doetinchem Cohort Study* (DCS) during the first round (1989–1994) with statistics gathered by the Eurostat,[53-56] Statistics Netherlands (CBS),[57-59] and the foundation for public health and smoking (STIVORO).[60] For the SENECA study, in some cases, the prevalence of study characteristics was compared with Eurostat data of 65–84-year olds from the 11 individual European countries included in the SENECA study, hereafter called the Eurostat countries.

Survey in Europe on Nutrition and the Elderly: a concerted action

The prevalence of underweight, overweight, and obesity in the SENECA study was 4%, 44%, and 21%, respectively. This seems comparable with the prevalence of underweight, overweight, and obesity for the Eurostat countries, i.e. 0.4–4%, 40–56%, 12–29% in 2002.[53] However, as BMI was self-reported, the prevalence of overweight and obesity in the general

European population is probably higher. The SENECA population included fewer current smokers (18%) as compared to the Eurostat countries (19–37%) in 2002.[54] In addition, in the SENECA study, 58% of the population perceived their health as good or very good. In nine Eurostat countries, the population that perceived their health as good, or very good was lower (9–58%), whereas in two countries it was higher (65–78%) in 2002.[55] Finally, more persons in the SENECA study were highly educated (8%) compared to 25–64-year olds in the European Union in 2011 (27%).[56] Given that the proportion of highly educated persons increased over time and that it declines with increasing age,[56] the proportion of highly educated persons in the SENECA study might be an underrepresentation for the current situation, but it is probably an overrepresentation for the time when the SENECA study started, i.e. in 1989.

Doetinchem Cohort Study

The prevalence of overweight and obesity in the DCS was 35% and 6%, respectively; this prevalence of overweight is somewhat higher than the prevalence in 1991 given by the CBS among persons aged 20 years and over (overweight: 29%, obese: 6%).[57] However, BMI given by the CBS is self-reported, which means that the prevalence of overweight and obesity is an underestimation. The prevalence of current smokers in the DCS was lower (27%) than the prevalence reported by STIVORO in 1991 (34%).[60] More people in the DCS perceived their health as good or very good (90%) than reported by the CBS among 20–64-year olds (70–90%).[58] The prevalence of highly educated persons is 27% in the DCS, which is similar to the prevalence of highly educated people according to the CBS data (28%).[59] Given that the prevalence of highly educated people has increased over the past decade (20% in 2001 to 28% in 2011),[59] the prevalence among the DCS is higher than among the general Dutch population.

> *Thus, the populations used in this thesis seem healthier and have a higher education than the general European and Dutch population; this is due to a selective loss to follow-up, mostly of individuals with an unfavourable lifestyle, or due to diseases.[61,62] Given that the results of this thesis are based on a relatively healthy population, the associations may be underestimated, and the public health implications of our findings may be even larger.*

Implications for clinical practice and public health

In an ageing population, weight status is an important factor to reach old age in good health. In this thesis, we found clear associations between weight status, measured with several anthropometrics, and health among all ages; this has implications for public health as well as clinical practice.

Public health implications

The prevalence of obesity and abdominal obesity has increased worldwide among all ages.[63] Although the relative risks of mortality as a result of high BMI levels are lower among elderly individuals than among younger adults, the absolute mortality rates are much higher among the elderly. In 2008, among European 70–79-year olds, the number of all-cause and CVD deaths was 2,376,995 and 1,324,979, respectively, whereas among 30–44-year olds the number of deaths was 451,725 and 94,312, respectively.[64] This indicates that the public health implications of obesity among the elderly remain high.

To gain insight into how many deaths among elderly individuals could have been prevented by proper weight management, i.e. by preventing obesity, the *Population Attributable Risk% (PAR%)* needs to be calculated. The PAR indicates the proportion of cases that would not occur if obesity were eliminated, on the assumption of a causal relationship. The PAR% is calculated using the prevalence of persons at risk, i.e. persons with obesity, and the relative risk of CVD mortality because of obesity. Since we observed evidence for an increased risk of mortality at a BMI level of 30 kg/m^2, we use the RR of CVD mortality of 1.39 from our categorical analysis.

If we consider a European elderly population with 21% obese individuals and a 39% increased CVD mortality risk based on our results, then the PAR% is 7.6%. This means that, yearly, 100,698 CVD deaths among 70–79-year olds could have been prevented Europe-wide.

With regard to public health interventions, the results presented in this thesis underpin the importance across all ages of a stable weight, provided it is not within the extreme ranges. We know from intervention studies that weight loss among obese and high risk populations can have beneficial effects on QoL,[65] the progression from IGT to type 2 diabetes, and CVD risk factors,[66] thereby potentially reducing the chance of mortality. Since sarcopenia, i.e. loss in muscle mass and an age-related decrease in muscle function, and specifically sarcopenic obesity, could be present among the elderly,[38,67,68] it is of great importance that weight loss programmes targeting these groups pay attention to exercise in order to maintain muscle

mass, more specifically resistance training, in addition to a healthy diet, including e.g. sufficient protein.[67,69] Such an approach is in line with current recommendations aiming at a stable healthy weight by means of a healthy diet and physical activity.[70]

Clinical implications

This thesis underlines the need to reconsider the current WHO cut-off points for BMI and WC classifications for the elderly, so that treatment becomes tailored rather than generic or even misguided. Our results, as well as previous literature,[19-21,28] showed that the current labelling of the categories 'overweight' and 'abdominal obesity' is not in agreement with the mortality risks among the elderly. The current labelling might tempt general practitioners to prescribe treatments that are not needed and may even result in disadvantageous effects.

Furthermore, in this thesis we found specific groups among the elderly who are at a high all-cause or CVD mortality risk, i.e. a relative risk of 2.0. These groups, with different underlying conditions, were individuals with a WC of 123 cm in men and 105 cm in women, individuals with underweight (<20.0 kg/m^2), and individuals with *large WC-healthy weight*, which can be identified by using a combination of WC and BMI. Clinicians need to have a raised awareness about these groups.

A combination of WC and BMI can also be used to detect changes in body composition, but as a single measure, MUAC might be a good alternative. MUAC of eight different anthropometric measures was the most sensitive in detecting hazardous changes in body composition of which increased mortality risks approaching 2.0 were observed. These findings of MUAC need further confirmation prior to clinical practice use.

Conclusion

BMI and WC can be used as single predictors of mortality for the elderly, but higher cut-off points for BMI and WC to indicate underweight and excess fat should be considered. Moreover, a combination of these two anthropometric measures can be recommended, as that would provide more information on body composition than one anthropometric measure alone. With regard to assessing changes in body composition, MUAC might be a good alternative for the elderly. Furthermore, a stable weight is best for health maintenance among all ages provided it is not within the extreme values of weight. In all, our results underscore the value of anthropometric measures in the management of weight and the importance of maintaining a stable weight during ageing.

References

1. Zamboni M, Mazzali G, Zoico E, Harris TB, Meigs JB, Di Francesco V, et al. Health consequences of obesity in the elderly: a review of four unresolved questions. *Int J Obes (Lond)*. 2005;29(9):1011–1029.
2. Lemieux S, Prud'homme D, Bouchard C, Tremblay A, Despres JP. A single threshold value of waist girth identifies normal-weight and overweight subjects with excess visceral adipose tissue. *Am J Clin Nutr.* 1996;64(5):685–693.
3. Hughes VA, Roubenoff R, Wood M, Frontera WR, Evans WJ, Fiatarone Singh MA. Anthropometric assessment of 10-y changes in body composition in the elderly. *Am J Clin Nutr.* 2004;80(2):475–482.
4. Cartwright MJ, Tchkonia T, Kirkland JL. Aging in adipocytes: potential impact of inherent, depot-specific mechanisms. *Exp Gerontol.* 2007;42(6):463–471.
5. Calle EE, Teras LR, Thun MJ. Obesity and mortality. *N Engl J Med.* 2005;353(20):2197–2199.
6. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. *Jama.* 2005;293(15):1861–1867.
7. Janssen I, Mark AE. Elevated body mass index and mortality risk in the elderly. *Obes Rev.* 2007;8(1):41–59.
8. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med.* 2010;363(23):2211–2219.
9. Kuk JL, Ardern CI. Influence of age on the association between various measures of obesity and all-cause mortality. *J Am Geriatr Soc.* 2009;57(11):2077–2084.
10. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med.* 2008;359(20):2105–2120.
11. van Dis I, Kromhout D, Geleijnse JM, Boer JM, Verschuren WM. Body mass index and waist circumference predict both 10-year nonfatal and fatal cardiovascular disease risk: study conducted in 20,000 Dutch men and women aged 20–65 years. *Eur J Cardiovasc Prev Rehabil.* 2009;16(6):729–734.
12. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet.* 2009;373(9669):1083–1096.
13. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, et al. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet.* 2006;368(9536):666–678.
14. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res.* 1998;6 Suppl 2:51S–209S.
15. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA.* 2007;298(17):2028–2037.

16. Wannamethee SG, Shaper AG, Lennon L, Whincup PH. Decreased muscle mass and increased central adiposity are independently related to mortality in older men. *Am J Clin Nutr.* 2007;86(5):1339–1346.

17. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *Jama.* 2013;309(1):71–82.

18. Hughes V. The big fat truth. *Nature.* 2013;497(7450):428–430.

19. Flicker L, McCaul KA, Hankey GJ, Jamrozik K, Brown WJ, Byles JE, et al. Body mass index and survival in men and women aged 70 to 75. *J Am Geriatr Soc.* 2010;58(2):234–241.

20. Kvamme JM, Holmen J, Wilsgaard T, Florholmen J, Midthjell K, Jacobsen BK. Body mass index and mortality in elderly men and women: the Tromso and HUNT studies. *J Epidemiol Community Health.* 2012;66(7):611–617.

21. Zunzunegui MV, Sanchez MT, Garcia A, Casado JM, Otero A. Body mass index and long-term mortality in an elderly Mediterranean population. *J Aging Health.* 2012;24(1):29–47.

22. Staiano AE, Reeder BA, Elliott S, Joffres MR, Pahwa P, Kirkland SA, et al. Body mass index versus waist circumference as predictors of mortality in Canadian adults. *Int J Obes (Lond).* 2012;36(11):1450–1454.

23. Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in US women. *Circulation.* 2008;117(13):1658–1667.

24. Guallar-Castillon P, Balboa-Castillo T, Lopez-Garcia E, Leon-Munoz LM, Gutierrez-Fisac JL, Banegas JR, et al. BMI, waist circumference, and mortality according to health status in the older adult population of Spain. *Obesity (Silver Spring).* 2009;17(12):2232–2238.

25. Price GM, Uauy R, Breeze E, Bulpitt CJ, Fletcher AE. Weight, shape, and mortality risk in older persons: elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. *Am J Clin Nutr.* 2006;84(2):449–460.

26. Baik I, Ascherio A, Rimm EB, Giovannucci E, Spiegelman D, Stampfer MJ, et al. Adiposity and mortality in men. *Am J Epidemiol.* 2000;152(3):264–271.

27. Janssen I, Katzmarzyk PT, Ross R. Body mass index is inversely related to mortality in older people after adjustment for waist circumference. *J Am Geriatr Soc.* 2005;53(12):2112–2118.

28. Heim N, Snijder MB, Heymans MW, Deeg DJ, Seidell JC, Visser M. Optimal cutoff values for high-risk waist circumference in older adults based on related health outcomes. *Am J Epidemiol.* 2011;174(4):479–489.

29. Jacobs EJ, Newton CC, Wang Y, Patel AV, McCullough ML, Campbell PT, et al. Waist circumference and all-cause mortality in a large US cohort. *Arch Intern Med.* 2010;170(15):1293–1301.

30. Janssen I, Heymsfield SB, Allison DB, Kotler DP, Ross R. Body mass index and waist circumference independently contribute to the prediction of nonabdominal, abdominal subcutaneous, and visceral fat. *Am J Clin Nutr.* 2002;75(4):683–688.

31. *Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8–11 December 2008. Geneva:* World Health Organization, 2011.

32. Bamia C, Halkjaer J, Lagiou P, Trichopoulos D, Tjonneland A, Berentzen TL, et al. Weight change in later life and risk of death amongst the elderly: the European Prospective Investigation into Cancer and Nutrition-Elderly Network on Ageing and Health study. *J Intern Med.* 2010;268(2):133–144.

33. Lee CG, Boyko EJ, Nielson CM, Stefanick ML, Bauer DC, Hoffman AR, et al. Mortality risk in older men associated with changes in weight, lean mass, and fat mass. *J Am Geriatr Soc.* 2011;59(2):233–240.

34. Yaari S, Goldbourt U. Voluntary and involuntary weight loss: associations with long term mortality in 9,228 middle-aged and elderly men. *Am J Epidemiol.* 1998;148(6):546–555.

35. Newman AB, Yanez D, Harris T, Duxbury A, Enright PL, Fried LP. Weight change in old age and its association with mortality. *J Am Geriatr Soc.* 2001;49(10):1309–1318.

36. Berentzen TL, Jakobsen MU, Halkjaer J, Tjonneland A, Overvad K, Sorensen TI. Changes in waist circumference and mortality in middle-aged men and women. *PLoS One.* 2010;5(9).

37. Roubenoff R. Sarcopenia and its implications for the elderly. *Eur J Clin Nutr.* 2000;54 Suppl 3:S40–47.

38. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc.* 2011;12(4):249–256.

39. Burns CM, Tijhuis MA, Seidell JC. The relationship between quality of life and perceived body weight and dieting history in Dutch men and women. *Int J Obes Relat Metab Disord.* 2001;25(9):1386–1392.

40. Leon-Munoz LM, Guallar-Castillon P, Banegas JR, Gutierrez-Fisac JL, Lopez-Garcia E, Jimenez FJ, et al. Changes in body weight and health-related quality-of-life in the older adult population. *Int J Obes (Lond).* 2005;29(11):1385–1391.

41. Fine JT, Colditz GA, Coakley EH, Moseley G, Manson JE, Willett WC, et al. A prospective study of weight change and health-related quality of life in women. *Jama.* 1999;282(22):2136–2142.

42. Myrskyla M, Chang VW. Weight change, initial BMI, and mortality among middle- and older-aged adults. *Epidemiology.* 2009;20(6):840–848.

43. Somes GW, Kritchevsky SB, Shorr RI, Pahor M, Applegate WB. Body mass index, weight change, and death in older adults: the systolic hypertension in the elderly program. *Am J Epidemiol.* 2002;156(2):132–138.

44. Wannamethee SG, Shaper AG, Lennon L. Reasons for intentional weight loss, unintentional weight loss, and mortality in older men. *Arch Intern Med.* 2005;165(9):1035–1040.

45. Harrington M, Gibson S, Cottrell RC. A review and meta-analysis of the effect of weight loss on all-cause mortality risk. *Nutr Res Rev.* 2009;22(1):93–108.

46. Strandberg TE, Strandberg A, Salomaa VV, Pitkala K, Miettinen TA. Impact of midlife weight change on mortality and quality of life in old age. Prospective cohort study. *Int J Obes Relat Metab Disord.* 2003;27(8):950–954.

47. Sun Q, Townsend MK, Okereke OI, Franco OH, Hu FB, Grodstein F. Adiposity and weight change in mid-life in relation to healthy survival after age 70 in women: prospective cohort study. *Bmj.* 2009;339:b3796.

48. Kozak AT, Daviglus ML, Chan C, Kiefe CI, Jacobs DR, Jr., Liu K. Relationship of body mass index in young adulthood and health-related quality of life two decades later: the Coronary Artery Risk Development in Young Adults study. *Int J Obes (Lond).* 2011;35(1):134–141.

49. Sorkin JD, Muller DC, Andres R. Longitudinal change in height of men and women: implications for interpretation of the body mass index: the Baltimore Longitudinal Study of Aging. *Am J Epidemiol.* 1999;150(9):969–977.

50. Spaaij CJ, van Raaij JM, de Groot LC, van der Heijden LJ, Boekholt HA, Hautvast JG. No changes during pregnancy in the net cost of cycling exercise. *Eur J Clin Nutr* Jul 1994;48(7):513–521.

51. Srikanthan P, Seeman TE, Karlamangla AS. Waist-hip-ratio as a predictor of all-cause mortality in high-functioning older adults. *Ann Epidemiol* Oct 2009;19(10):724–731.

52. Verkleij SP, Adriaanse MC, Wendel-Vos GC, Schuit AJ. Longitudinal relation between weight change and quality of life in a community-based population: a prospective cohort study. *European journal of public health.* 2013;23(2):285–290.

53. Eurostat. Body mass index (BMI) by sex, age and educational level (%) - collection round 2002. 2002; http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_ls_bmie&lang=en. Accessed 06-06-2013, 2013.

54. Eurostat. Smokers by sex, age and educational level (%) - collection round 2002. 2002; http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_ls_smke&lang=en. Accessed 16-06-2013, 2013.

55. Eurostat. Self-perceived health by sex, age and educational level (%) - collection round 2002. 2002; http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_ls_spe&lang=en. Accessed 18-06-2013, 2013.

56. Eurostat. Persons aged 25-64 with tertiary education attainment by sex and NUTS 2 regions (from 2000 onwards) - %. 2012; http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=edat_lfse_11&lang=en. Accessed 18-06-2013, 2013.

57. CBS. Lengte en gewicht van personen, ondergewicht en overgewicht vanaf 1981. . 2012; http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=81565NED&D1=a&D2=0&D3=5-12&D4=0&D5=0,10,20,30&HDR=T&STB=G1,G2,G3,G4&VW=T, 2012.

58. CBS. Gezondheid aandoeningen beperkingen; persoonskenmerken. 2011; http://statline.cbs.nl/StatWeb/publication/?VW=T&DM=SLNL&PA=81173NED&D1=0-1&D2=a&D3=0&D4=l&HD=110829-0959&HDR=G3,G2,T&STB=G1. Accessed 17-06-2013, 2013.

59. CBS. Beroepsbevolking; behaalde onderwijs naar herkomst geslacht en leeftijd. 2011; http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=71822NED&D1=0-1&D2=0&D3=0&D4=0&D5=a&D6=0&D7=a&HDR=T,G2,G1,G5,G6&STB=G4,G3&VW=T. Accessed 17-06-2013, 2013.

60. *Trendpublicatie percentage rokers. Percentage rokers in de Nederlandse bevolking 1958 – 2011*. Den Haag, the Netherlands: STIVORO, 2012.

61. Blokstra A, Picavet HSJ, Verschuren WMM. *De Doetinchem Cohort Studie 4e ronde 2003–2007 Onderzoek naar volksgezondheid en veroudering (in Dutch)*. Bilthoven, the Netherlands: National Institute for Public Health and the Environment (RIVM), 2010.

62. van't Hof MA, Burema J. Assessment of bias in the SENECA study. *Eur J Clin Nutr.* 1996;50 Suppl 2:S4–8.

63. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. *Lancet.* 2011;377(9765):557–567.

64. WHO. Cause-specific mortality, 2008: WHO region by country. 2008; http://apps.who.int/gho/data/node.main.887?lang=en. Accessed 10-06-2013, 2013.

65. Fontaine KR, Barofsky I. Obesity and health-related quality of life. *Obes Rev.* 2001;2(3):173–182.

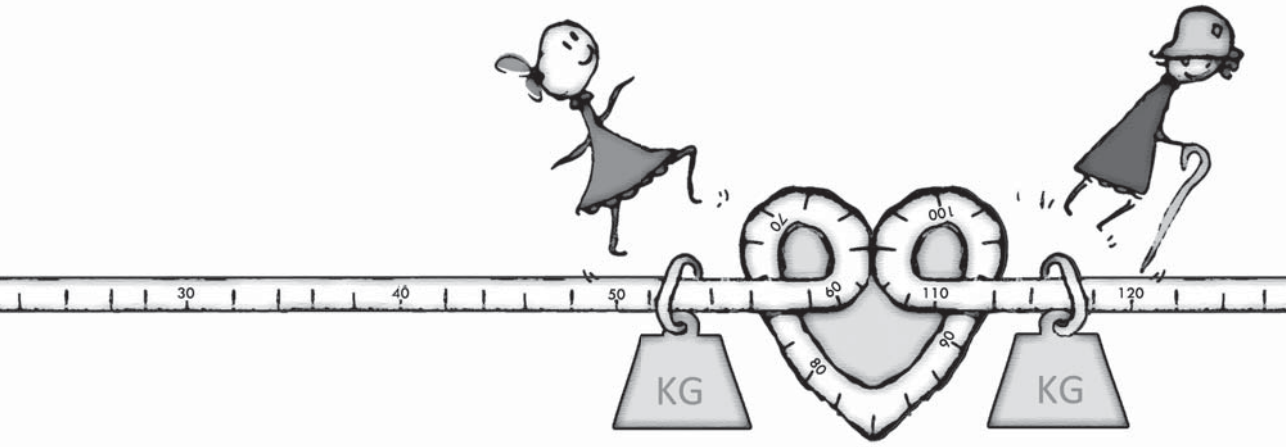
66. Horton ES. Effects of lifestyle changes to reduce risks of diabetes and associated cardiovascular risks: results from large scale efficacy trials. *Obesity (Silver Spring).* 2009;17 Suppl 3:S43–48.

67. Li Z, Heber D. Sarcopenic obesity in the elderly and strategies for weight management. *Nutrition reviews.* 2012;70(1):57–64.

68. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. Sarcopenic obesity: a new category of obesity in the elderly. *Nutr Metab Cardiovasc Dis.* 2008;18(5):388–395.

69. Tieland M, van de Rest O, Dirks ML, van der Zwaluw N, Mensink M, van Loon LJ, et al. Protein supplementation improves physical performance in frail elderly people: a randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc.* 2012;13(8):720–726.

70. Branca F, Nikogosian H, Lobstein T. *The challenge of obesity in the WHO European Region and the strategies for response.* Copenhagen, Denmark: World Health Organization, 2007.



Samenvatting
(Summary in Dutch)

De vergrijzing van de Westerse bevolking is toegenomen in de laatste decennia, en zal verder toenemen in de toekomst. Daarom is het van belang factoren te bestuderen die het 'gezond ouder worden' kunnen beïnvloeden. Dergelijke factoren zijn het gewicht van een persoon en de ontwikkeling daarvan in de loop der jaren (gewichtstoestand). De gewichtstoestand wordt vaak gemeten met antropometrische maten zoals de body mass index (BMI) en de middelomtrek. In de klinische praktijk en in het onderzoek wordt de BMI gebruikt om personen in te delen: ondergewicht (<18.5 kg/m^2, of <20.0 kg/m^2), normaal gewicht (18.5–24.9 kg/m^2, of 20.0–24.9 kg/m^2), overgewicht (25.0–29.9 kg/m^2) en obesitas (≥30.0 kg/m^2). Daarnaast wordt de middelomtrek gebruikt om personen in te delen: kleine middelomtrek (<94 cm ♂, 80 cm ♀), middelmatige middelomtrek (94–101 cm ♂, 80–87 cm ♀), en een grote middelomtrek ofwel abdominale obesitas (≥102 cm ♂, ≥88 cm ♀). Deze categorieën geven aan of iemand te veel buikvet heeft. Bij volwassenen is het verband tussen overgewicht, of obesitas en gezondheidsrisico's duidelijk, maar bij ouderen (65 jaar en ouder) is dit niet het geval. Een onderliggende factor die hierbij een rol kan spelen is de verandering van de lichaamssamenstelling bij het ouder worden. Ouderen hebben ten opzichte van jongvolwassenen met eenzelfde BMI of middelomtrek een grotere vetmassa door het verlies van spiermassa; zij hebben meer inwendig vet doordat het vet zich herverdeelt en zij hebben een afname in lengte doordat de wervels slijten en de tussenwervelschijven inzakken. Gezien deze verandering van de lichaamssamenstelling is het de vraag of de huidige afkappunten voor ondergewicht, overgewicht, en (abdominale) obesitas wel toepasbaar zijn bij ouderen.

Het doel van dit proefschrift is dan ook om de betekenis van de gewichtstoestand, gemeten met verschillende antropometrische maten, voor verschillende gezondheidsmaten op latere leeftijd en in een ouder wordende populatie te onderzoeken. Deze gezondheidsmaten zijn ziekten aan het hart waarbij de kransslagaders zijn vernauwd (coronaire hartziekten), sterfte en kwaliteit van leven.

Om dit te onderzoeken is er gebruik gemaakt van databestanden van grote internationale en nationale studies. In het bijzonder zijn de *Survey in Europe on Nutrition and the Elderly: a concerted action* (*SENECA*) studie en de *Doetinchem Cohort Studie* (*DCS*) gebruikt. De SENECA populatie bestaat uit ouderen van 70–77 jaar en de DCS populatie uit volwassenen van 20–66 jaar. Binnen beide studies zijn antropometrische maten zoals de BMI, middelomtrek en armomtrek om de 5 jaar gemeten over een periode van 5–15 jaar. Daarnaast zijn ziekten, sterfte en doodsoorzaak, en kwaliteit van leven vastgesteld, alsmede het moment van intreden van een ziekte of overlijden. Hierna wordt onderscheid gemaakt in totaal overlijden (overlijden aan allerlei doodsoorzaken), en overlijden aan een specifieke ziekte. Kwaliteit

van leven is gemeten met vragen over hoe men het handelen in het dagelijks leven ervaart, waarbij onderscheid gemaakt kan worden naar fysieke en mentale aspecten van kwaliteit van leven. Deze informatie is gebruikt om het verband tussen een antropometrische maat (gewicht, BMI, middelomtrek en armomtrek) en een gezondheidsmaat (coronaire hartziekten, overlijden, en kwaliteit van leven) te onderzoeken.

Omdat de gezondheidszorg in de afgelopen decennia is verbeterd, is onderzocht of het risico op het krijgen van coronaire hartziekten en het overlijden aan coronaire hartziekten dat samenhangt met obesitas verschillend zou zijn voor en na 1985 (**hoofdstuk 2**), en of leeftijd van invloed zou zijn op dit risico. Voor het eerste is geen overtuigend bewijs gevonden. Leeftijd, echter, beïnvloedt dit risico sterk. Een toename van 10 jaar in leeftijd geeft een daling van 31% van het risico. Een 65-jarige heeft bijvoorbeeld ten opzichte van een 55-jarige met obesitas een 31% lager risico op het krijgen van coronaire hartziekten of het overlijden aan coronaire hartzieken.

In **hoofdstuk 3 en 4** is het verband bij ouderen tussen BMI en het overlijden, en tussen middelomtrek en het overlijden beschreven. In **hoofdstuk 3** is een verband gevonden tussen BMI en het totaal overlijden, tussen BMI en het overlijden aan hart- en vaatziekten (HVZ), en tussen BMI en het overlijden aan een andere oorzaak dan HVZ, kanker en ziekten aan de luchtwegen. Personen met een BMI lager dan 24 kg/m^2 en hoger dan 30 kg/m^2 hadden een verhoogd overlijdensrisico van 10%. In **hoofdstuk 4** is ook een sterk verband gevonden tussen middelomtrek en het totaal overlijden, en tussen middelomtrek en het overlijden aan HVZ, kanker, en ziekten aan de luchtwegen. Het overlijdensrisico bij een middelomtrek van 102 cm bij oudere mannen en 88 cm bij oudere vrouwen (het afkappunt voor abdominale obesitas) was desondanks niet substantieel verhoogd. Bij hogere waarden van de middelomtrek was het overlijdensrisico wel verhoogd en bleek dat een tweevoudig risico op het totale overlijdensrisico en het overlijdensrisico aan HVZ gepaard ging met een middelomtrek van 132 en 123 cm bij mannen, respectievelijk 116 en 105 cm bij vrouwen. In **hoofdstuk 4** is tevens de combinatie van standaard BMI- en middelomtrekcategorieën, zoals gebruikt in de praktijk, en het verband met overlijden onderzocht. Ouderen met ondergewicht in combinatie met een kleine middelomtrek, en ouderen met normaal gewicht in combinatie met abdominale obesitas hadden een twee keer zo hoog totaal overlijdensrisico en overlijdensrisico aan HVZ ten opzichte van ouderen met een normaal gewicht en een kleine middelomtrek.

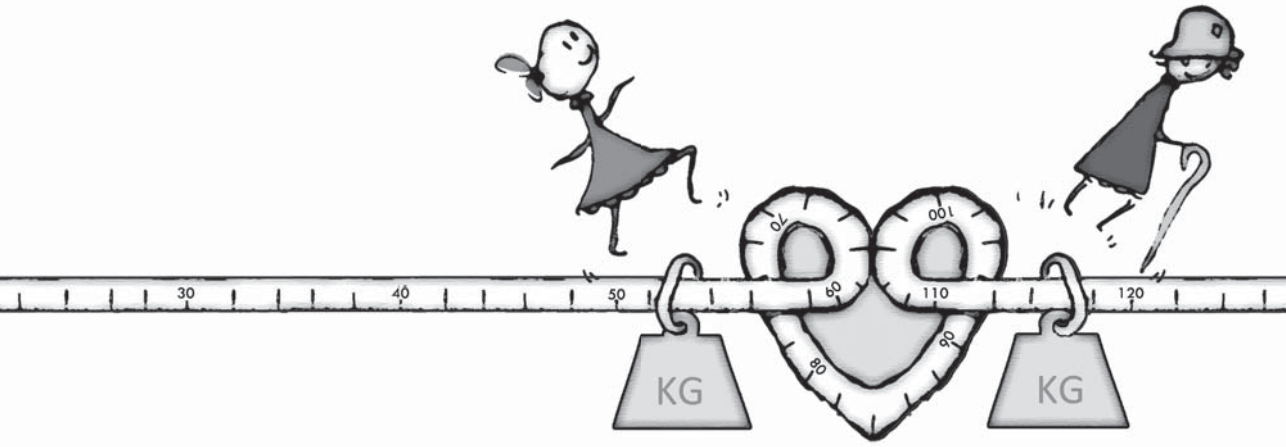
In **hoofdstuk 5** is het verband tussen veranderingen in antropometrische maten over een periode van ongeveer 4 jaar en het overlijdensrisico bij ouderen beschreven. Veranderingen

in BMI toonden geen verband met het overlijdensrisico. Voor veranderingen in hun middelomtrek en gewicht werd alleen bij een afname van deze maten een verband gevonden met het totaal overlijdensrisico. De resultaten voor deze twee maten waren vergelijkbaar. Zo hadden ouderen met een afname in middelomtrek van ≥3.1 cm een 52% hoger totaal overlijdensrisico dan ouderen met een stabiele middelomtrek, en hadden ouderen met een afname van ≥3.2 kg in gewicht een 48% hoger totaal overlijdensrisico dan ouderen met een stabiel gewicht. Voor één antropometrische maat, de armomtrek, werd bij zowel een toename als een afname een verband met het totaal overlijdensrisico en het overlijdensrisico aan HVZ gevonden. Ouderen die een afname van ≥1.6 cm en tussen de 0.6 en 1.6 cm in armomtrek lieten zien, hadden een 81% en 66% hoger totaal overlijdensrisico dan ouderen met een stabiele armomtrek. Ouderen met een toename van ≥1.3 cm in armomtrek hadden een 52% hoger totaal overlijdensrisico, en een 94% hoger overlijdensrisico aan HVZ dan ouderen met een stabiele armomtrek.

In **hoofdstuk 6 en 7** zijn de veranderingen in gewicht en BMI van een ouder wordende populatie in een tijdsbestek van 10–15 jaar bestudeerd. Daaruit bleek dat onder volwassenen met een gewichtstoename van >2 kg —met name onder volwassenen met een toename van >6 kg— de kwaliteit van leven voor wat betreft de fysieke aspecten verminderde in de loop van de jaren. Bij volwassenen met een gewichtsafname van >2 kg veranderde de kwaliteit van leven niet of nauwelijks. Ten opzichte van volwassenen met een stabiel gewicht trad er desondanks een ongunstige verandering op in kwaliteit van leven voor wat betreft de mentale aspecten. Dat komt doordat de kwaliteit van leven van volwassenen met een stabiel gewicht verbeterde in de loop van de jaren. Wanneer de BMI-patronen van volwassenen werden geanalyseerd over een periode van 15 jaar bleek dat volwassenen met stabiele obesitas de slechtste kwaliteit van leven hadden. Ten opzichte van volwassenen met een stabiel normaal gewicht hadden volwassenen die overgewicht ontwikkelden, volwassenen die obesitas ontwikkelden, en volwassenen die stabiel obees waren een slechtere kwaliteit van leven voor wat betreft de fysieke aspecten aan het einde van de periode van 15 jaar. Vrouwen die wisselden tussen BMI-categorieën hadden een slechtere kwaliteit van leven voor wat betreft de mentale aspecten, ten opzichte van vrouwen met een stabiel normaal gewicht. Als enige groep, verschilden volwassenen met stabiel overgewicht weinig van volwassenen met een stabiel 'gezond gewicht'. De resultaten uit deze hoofdstukken waren consistent voor verschillende leeftijdsgroepen.

Tenslotte zijn de belangrijkste bevindingen bediscussieerd en zijn de implicaties voor de volksgezondheid en de klinische praktijk besproken in **hoofdstuk 8**. Ondanks dat het risico op coronaire hartziekten of overlijden in samenhang met obesitas lager is bij ouderen dan

bij jongvolwassenen, werden er sterke verbanden gevonden tussen een hoge BMI en het overlijdensrisico en tussen middelomtrek en het overlijdensrisico. De absolute aantallen van overlijdensgevallen in samenhang met een hoge BMI onder de oudere bevolking zijn aanzienlijk. Het voorkomen van een hoge BMI door middel van preventieve interventies bij ouderen zou daarom een positief effect kunnen hebben op de volksgezondheid. Daarnaast blijkt uit dit proefschrift dat het behouden van een stabiel gewicht, mits dit niet in de extremen valt, van belang blijft om een goede gezondheid te behouden. Voor de klinische praktijk is het van belang dat de afkappunten voor ondergewicht, overgewicht, en abdominale obesitas worden heroverwogen en worden opgehoogd om ouderen met een verhoogd gezondheidsrisico te kunnen identificeren. Daarnaast kan een combinatie van BMI en middelomtrek worden aanbevolen zodat de specifieke groep met een zeer hoog (tweevoudig) risico kan worden geïdentificeerd. Een combinatie van antropometrische maten geeft mogelijk meer informatie over de lichaamssamenstelling dan elke maat afzonderlijk. Om veranderingen in gewichtstoestand bij ouderen te meten zou de armomtrek naast gewicht en middelomtrek overwogen kunnen worden. De resultaten van dit proefschrift onderschrijven de waarde van antropometrische maten in het bepalen van de gewichtstoestand en het belang van een stabiel gewicht gedurende het leven.



Dankwoord
(Acknowledgements)

Yes!!! Mijn boekje is klaar! Na een periode van hard werken met de bekende ups and downs is het dan helemaal af. Gelukkig kreeg ik daarbij steun van vele vrienden, familie en collega's. Daarnaast heb ik ontzettend veel geleerd tijdens deze periode, en is het tijd om iedereen daarvoor te bedanken.

Wanda, bedankt dat je mij hebt aangedragen voor dit project. Je bent een kei in het er uit pikken van de grote lijnen en de belangrijkste bevindingen. Dat heeft mij geholpen bij het structureren van de artikelen, en heeft tot mooie resultaten geleid. Lisette, ondanks je drukke agenda wist je toch altijd de tijd te nemen met zoveel rust dat ik met een goed gevoel uit onze afspraken kwam. Ik heb daar bewondering voor. Met jouw kritische vragen, zeker tijdens de laatste fase van mijn promotietraject, zette jij mij goed en dieper aan het denken. Moniek bedankt dat ik het stokje van je over mocht nemen.

Beste opponenten, Daan Kromhout, Jantine Schuit, Marjolein Visser, en Paul Deurenberg. Ik wil jullie hartelijk bedanken voor het beoordelen van mijn proefschrift en het opponeren.

Lieve paranimfen, wat ben ik blij dat jullie met mij op het podium staan! Emmy, we hebben elkaar leren kennen tijdens een onderzoeksproject waar we samen aan werkten. Ik ben blij dat we, ondanks dat het project was afgerond, het contact hebben voortgezet. Je bent een heel fijne vriendin die altijd voor me klaar staat, en waar ik ontzettend om moet lachen als je weer zo direct uit de hoek komt. Eline, jij kwam in 2011 werken als AIO bij het RIVM en werd mijn kamergenoot. Ik ben blij dat we 2 jaartjes de kamer hebben mogen delen, ook al is het ondanks het @nders werken niet heel anders geworden… Je bent een kei in het zoeken naar oplossingen voor welk probleem dan ook. Op naar jouw promotie! Meiden, ontzettend bedankt voor jullie steun!

In dit proefschrift heb ik met veel co-auteurs mogen schrijven, met name door de twee meta-analyses. Dit is een ontzettend leerzaam traject geweest. Daarom wil ik hen bedanken voor hun inhoudelijke kennis en de collaborators voor het beschikbaar stellen van hun data. Thus, Annika Rosengren, Martin Shipley, Paul Knekt, Pierre Ducimetiere, Alessandro Menotti, the BMI-CHD collaboration investigators, Nele Friedrich, Henri Wallaschofski, Pilar Guallar-Castillón, Stefan Walter, Carola Zillikens, Lauren Lissner, Julie Bassett, Graham Giles, Nicola Orsini, Noor Heim, Marjolein Visser and the WC elderly collaborators; thank you for your support and knowledge. It was a pleasure working with you! In het bijzonder wil ik hierbij Rik bedanken. Door jouw kennis en ervaring was het voor mij makkelijker om deze 'best' lastige exercitie uit te voeren. Hendriek, jij was bij beide publicaties een rots in de branding. Jouw uitleg en advisering op het gebied van de statistiek maakte dat ik zeker was van mijn resultaten.

Ivon, Susan, en Monique, heel veel dank voor jullie kritische inhoudelijk blik op de Doetinchem stukken, en de gesprekken daarnaast. Wien bedankt voor het helpen bij het zetten van de puntjes op de i van het Doetinchem stuk en de stellingen.

Joyce en Rosemarie, ik vond het leuk om jullie te begeleiden tijdens een stage of afstudeervak. Veel succes met jullie verdere carrière!

Een proefschrift wordt niet gemaakt zonder het mooi vorm te geven en te editen. Catherine, thank you for your fast and accurate work. Renate en Kitty, bedankt! Het proefschrift is heel mooi geworden dankzij jullie.

Op het RIVM bij de oude afdeling PZO zat ik in het begin van mijn AIO-periode op de gezelligste kamer van de afdeling, kamer 227. Bedankt voor de leuke tijd!!! En zeker jij Jeroen, de 'die hard' van kamer 227, en standaard reismaatje bij congressen. Je was bijna altijd de enige man tussen al die kwekkende dames… Maar, met jouw gevatte en rake opmerkingen hield je je goed staande. Jammer dat je ons hebt verlaten, maar wat ga jij een leuk AIO-project doen!!! Ik ben heel benieuwd naar jouw boekje over 4 jaar! Marga, ook jij was vaak van de partij op congressen. Ik ben blij dat ik bij jou terecht kon voor adviezen of alleen voor een luisterend oor als mede-AIO bij PZO. Om even het werk te onderbreken waren daar de dagelijkse boswandelingen. Jorien, Simone, Sandra, Laura, Claudia, Iris, Gerben en Mattijs, bedankt voor de gezellig praatjes. Lidwien, bedankt voor de tips in de laatste fase van mijn promotie. De dames van het secretariaat, bedankt voor jullie betrokkenheid. Alle andere oud-PZO- en de nieuwe VPZ-collega's, bedankt voor de fijne sfeer en het altijd binnen kunnen lopen voor vragen!

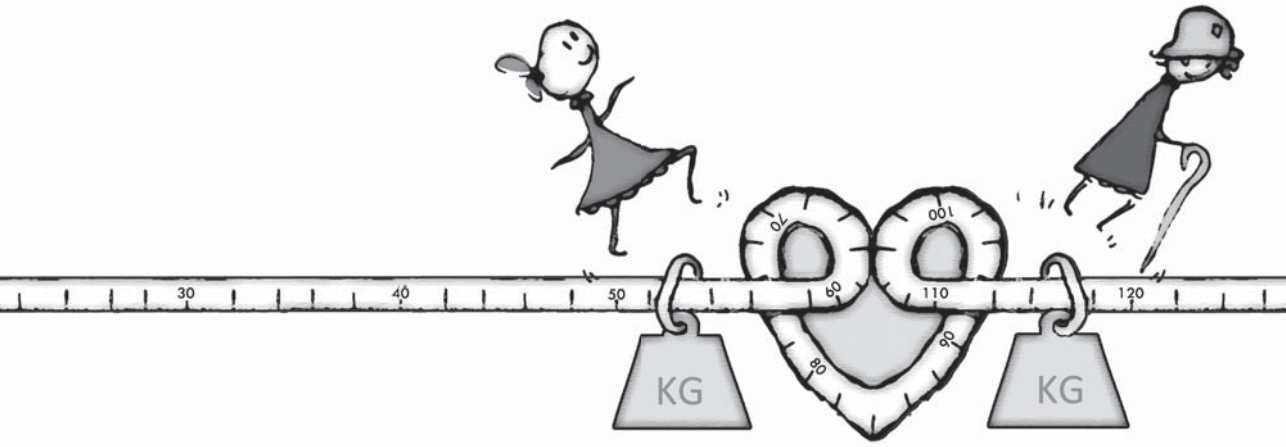
Op de WUR ben ik weinig geweest, maar ik heb daar wel een leuke tijd gehad. Karen, wat ben jij toch behulpzaam en snel! Bedankt voor het inplannen van de afspraken met Lisette en het zoeken van een werkplekje. De PhD tour in 2011 in Mexico en West Amerika was ontzettend gezellig door de leuke club mede-PhD-studenten. De vele U-turns die we hebben gemaakt zullen mij zeker bijblijven…. Sandra, laten we onze koffiemomentjes op een andere manier voortzetten!

Bij het promoveren hoort ook de nodige ontspanning. Gelukkig had ik voordat ik wist dat ik ging promoveren mijn eigen paard, Sien, gekocht, waardoor ik elke dag mijn dosis ontspanning kreeg. Maar, ik zou ik niet zijn als ik niet ook in het paardrijden wilde presteren. Met de goede coaching van Jeroen kan ik zeggen dat dat aardig lukt. Door de relativerende lessen heb ik ook impliciet tips gekregen die ik tijdens mijn promotietraject kon gebruiken. Bedankt! Josse, Astrid, Ad en Nel, bedankt voor jullie interesse en goede zorgen.

Lieve Oma, bedankt voor de lieve kaartjes, en Ton bedankt voor alle interesse die je in mijn promotie hebt getoond.

Lieve vriendinnen, Chantal en Kristel, naast de fijne gesprekken, waren daar ook onze leuke 'uitjes'. Wat een onnozele hilariteit!! Laten we dat vooral voortzetten. Noor, wat ben jij toch altijd enthousiast over het onderzoek. Dat werkt aanstekelijk! Ga je misschien toch ook promoveren? Dat zou zo leuk zijn!

Lieve mam en Keesje, bedankt voor jullie steun op echt alle vlakken. Zonder jullie had ik nooit kunnen doen wat ik allemaal in de afgelopen tijd heb gedaan. Ook al was die wetenschapswereld jullie misschien soms wat vreemd en taai, jullie waren wel betrokken. Bedankt daarvoor!



About the author

Curriculum vitae

Ellen Lisette de Hollander was born on 24th of September,1984 in Muntendam, the Netherlands. In 2002, she completed secondary school (VWO) at the St. Bonifatius College in Utrecht. In 2006 and 2007, she received her Bachelor's followed by her Master's degree in Human Movement Sciences with the specialization in "Rehabilitation and Physical Therapy" at the VU University, Amsterdam.

In February 2008, she started working as a junior researcher at the Centre for Prevention and Health Services Research at the National Institute for Public Health and the Environment (RIVM). The subjects of research included validation of physical activity questionnaires, lifestyle interventions, overweight and prevention. Then, in 2010, the opportunity came along to start her PhD project of which the results are described in this thesis. This project was conducted at the RIVM in collaboration with the Division of Human Nutrition of the Wageningen University. In 2013, she continued working at the reorganised Centre for Nutrition, Prevention and Health Services (RIVM) on health-related subjects.

Peer reviewed scientific publications

Bogers RP, Barte JC, Schipper CM, Vijgen SM, **de Hollander EL**, Tariq L, Milder IE, Bemelmans WJ. Relationship between costs of lifestyle interventions and weight loss in overweight adults. *Obes Rev*. 2010;11(1):51-61.

de Hollander EL, Zwart L, de Vries SI, Wendel-Vos W. The SQUASH was a more valid tool than the OBiN for categorizing adults according to the Dutch physical activity and the combined guideline. *J Clin Epidemiol*. 2012;65(1):73-81.

de Hollander EL, Van Zutphen M, Bogers RP, Bemelmans WJ, De Groot LC. The impact of body mass index in old age on cause-specific mortality. *J Nutr Health Aging*. 2012;16(1):100-106.

de Hollander EL, Bemelmans WJ, Boshuizen HC, Friedrich N, Wallaschofski H, Guallar-Castillon P, Walter S, Zillikens MC, Rosengren A, Lissner L, Bassett JK, Giles GG, Orsini N, Heim N, Visser M, de Groot LC. The association between waist circumference and risk of mortality considering body mass index in 65- to 74-year-olds: a meta-analysis of 29 cohorts involving more than 58 000 elderly persons. *Int J Epidemiol*. 2012;41(3):805-817.

de Hollander EL, Bemelmans WJ, de Groot LC. Associations between changes in anthropometric measures and mortality in old age: a role for mid-upper arm circumference? *J Am Med Dir Assoc*. 2013;14(3):187-193.

de Hollander EL, Bogers RP, Boshuizen HC, Rosengren A, Shipley MJ, Knekt P, Ducimetiere P, Menotti A, de Groot LC, Bemelmans WJ. Influence of calendar period on the association between BMI and coronary heart disease: A meta-analysis of 31 cohorts. *Obesity (Silver Spring)*. 2013;21(5):865-880.

de Hollander EL, Picavet HSJ, Milder IE, Verschuren WMM, Bemelmans WJE, de Groot LCPGM. The Impact of Long-Term Body Mass Index Patterns on Health-Related Quality of Life: The Doetinchem Cohort Study. *Am J Epidemiol*. 2013; doi: 10.1093/aje/kwt053.

Wientzek A, Díaz MJ, Castaño JM, Amiano P, Arriola L, Overvad K, Ostergaard JN, Charles MA, Fagherazzi G, Palli D, Bendinelli B, Skeie G, Borch KB, Wendel-Vos W, **de Hollander E**, May AM, den Ouden ME, Trichopoulou A, Valanou E, Söderberg S, Franks PW, Brage S, Vigl M, Boeing H, Ekelund U. Cross-sectional associations of objectively measured physical activity, cardiorespiratory fitness and anthropometry in European adults. *Obesity (Silver Spring)*. 2013, doi: 10.1002/oby.20530.

The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (BMI Mediated Effect), Yuan Lu, Kaveh, Majid Ezzati, Mark Woodward, Eric B Rimm, Goodarz Danaei. Metabolic mediators of the effect of body mass index on coronary heart disease and stroke: Pooled analysis of 97 prospective cohorts with 1.8 million participants. (Revision submitted to the Lancet) Note: EL de Hollander is part of the The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration.

RIVM reports

Kosteneffectiviteit beweeg- en dieetadvisering bij mensen met (hoog risico op) diabetes mellitus type 2. Literatuuronderzoek en modelsimulaties rondom de Beweegkuur. W.J.E. Bemelmans (red.), G.C.W. Wendel-Vos,R.P. Bogers, I.E.J. Milder, **E.L. de Hollander**, J.C.M. Barte, L. Tariq, M.A.M. Jacobs-van der Bruggen (RIVM rapport: 260401005). Bilthoven: Rijksinstituut voor Volksgezond-heid en Milieu (RIVM), 2008.

Effecten van preventie, Deelrapport van de VTV 2010 'Van gezond naar beter'. P.W. Achterberg, E.W. de Bekker-Grob, M. van den Berg, S.R. de Bruin, M.C.M. Busch, R. Gijsen, H.H. Hamberg-van Reenen, **E.L. de Hollander**, S. Kooijker, H.J. van Kranen, L.C. Lemmens, S.A. Meijer, N.A.M. Post, M. Savelkoul, C.G. Schoemaker, A.J. Schuit, L.C.J. Slobbe, H. Verkleij, M. Verschuuren, S. van Wieren. (RIVM rapport: 270061007). Bilthoven: Rijksinstituuut Gezondheid en milieu (RIVM), 2008.

Leefstijlinterventies in GGD-regio's: inventarisatie via GGD'en. **E.L. de Hollander**, R.P. Bogers. CGL-rapportage 09-02 Bilthoven: RIVM Centrum Gezond Leven, 2009.

De seniorenkeuring voor het rijbewijs: effecten en alternatieven, **E.L. de Hollander**, C.C.M. Molema, J.A. Ferreira, P.M.Engelfriet. (RIVM rapport: 280001001) Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu (RIVM), 2013.

Overview of completed training activities Graduate School VLAG

Name: Ellen L. de Hollander

Supervisors: Dr. ir. W.J.E. Bemelmans,
Prof. dr. ir. L.C.P.G.M. de Groot

Discipline specific activities	Place/Institute	Year(s)
17th, 18th, 19th European and 11th International Congress on Obesity (ECO/ICO)	Amsterdam, Istanbul, Lyon and Stockholm	2009-2012
2010 European Public Health Conference	Amsterdam	2010
VII IAGG European Congress	Bologna	2011
Annual Meeting of the Netherlands Epidemiology Society	Nijmegen, IJmuiden	2010-2011
11th and 12th Dutch National Gerontology Congress	Ede	2010, 2012
Annual NASO meeting	Utrecht	2010, 2012
Annual Meeting for Diabetes Research	Arnhem	2010
EPIC-NL symposium	Utrecht	2012
NCHA International Congress	The Hague	2013
Summer course 'Why and how we age'	Leyden Academy	2011
Exposure Assessment in Nutrition Research	VLAG	2012
General courses		
Scientific writing in English	Hogeschool Utrecht	2009
Meta-Analysis	University Utrecht	2010
Master class Linear and Logistic regression	VLAG	2010
Survival Analysis	NIHES	2010
PhD Retreat	VLAG	2010
Workshop 'Zakelijk flirten' (professional interaction)	RIVM	2010
Workshop "how to present"	WUR	2011
PhD Competence Assessment	VLAG	2011
Master class Multilevel Analysis	VLAG	2011
Career Perspectives	VLAG	2012
Masterclass 'wetenschappelijke dillema's voor jonge promovendi"	Proneri, RIVM	2012
Optional courses and activities		
Monday Morning Lectures of the Centre for Nutrition, Prevention and Health Services	RIVM	2009-2013
Methodology meetings	RIVM	2009-2013
Lunch Lectures on Public Health	RIVM	2009-2013
Obesity meetings	RIVM	2009-2013
General Medicine	WUR	2011
PhD Tour 2011	VLAG	2011
Symposium 'Calculating with knowledge'	WUR	2012
Doetinchem Cohort Study research meetings	RIVM	2012-2013

The PhD project described in this thesis was financially supported by the Strategic Research RIVM (SOR), program 'Chronic diseases Intervention and Lifestyle'.

The financial support for the publication of this thesis by Wageningen University and the National Institute for Public Health and the Environment (RIVM) is gratefully acknowledged. Additional financial support was provided by the Netherlands Association for the Study of Obesity (NASO).

Cover design Kitty van der Veer
Layout Renate Siebes [Proefschrift.nu]
Printed by Ridderprint, Ridderkerk