Relationship between body mass index and mortality among Europeans

Xin Song, Janne Pitkäniemi, Weiguo Gao, Robert Heine, Kalevi Pyörälä, S Soderberg, Coen D.A. Stehouwer, Björn Zethelius, Jaakko Tuomilehto, Qing Qiao

Relationship between body mass index and mortality among Europeans

Xin Song[1,2], Janne Pitkäniemi[1], Weiguo Gao[1,2], Robert J. Heine[3,4], Kalevi Pyörälä[5], Stefan Söderberg[6,7], Coen D.A. Stehouwer[8], Björn Zethelius[9], Jaakko Tuomilehto[1,2], Tiina Laatikainen[2], Adam G Tabák[10,11], Qing Qiao[1,2] for the DECODE Study Group

[1] Department of Public Health, Hjelt Institute, University of Helsinki, Helsinki, Finland; [2] Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland; [3] VU University of Meical Center, Amsterdam, The Netherlands; [4] Eli Lilly and Company, Indianapolis, USA; [5] Institute of Clinical Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland; [6] Department of Public Health and Clinical Medicine, Cardiology, Umeå University Hospital, Umeå, Sweden; [7] Baker IDI Heart and Diabetes Institute, Melbourne, Australia; [8] Department of Internal Medicine and Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, The Netherlands; [9] Department of Public Health/Geriatrics, Uppsala University Hospital, Uppsala, Sweden; [10] Department of Epidemiology and Public Health, University College London, London, UK; [11] Semmelweis University Faculty of Medicine, 1st Department of Medicine, Budapest, Hungary.

Correspondance to: Xin Song, Department of Public Health, Hjelt Institute, University of Helsinki, Helsinki, Finland; Mannerheimintie 172, KTTL, 6krs, PL 41, FIN-00014 Helsinki, Finland.

Tel. +358 9 19127320

Fax. +358 9 19127313

E-mail: xin.song@helsinki.fi

This study was supported by a grant from Academy Finland (129197).

Abstract

Background/Objectives: To investigate the relationship between body mass index (BMI) and mortality from various causes.

Subjects/Methods: Data of 72 947 European men and 62 798 women aged 24-99 years at baseline were collaboratively analyzed. Both absolute and relative mortality risks were estimated within each BMI categories. The hazard ratio (HR) was estimated using Cox regression analysis adjusting for age, cohort, and smoking status.

Results: Over a median follow-up of 16.8 years, 29 071 participants died, 13 502 from CVD and 8 748 from cancers of all types. All-cause and cancer mortality showed a U-shaped relationship: decreased first, leveled off, and then increased with increasing BMI with the lowest mortality risk approximately between 23.0 to 28.0 kg/m^2 of BMI in men and 21.0 to 28.0 kg/m^2 in women. The U-shaped relationship hold for all-cause mortality but disappeared for cancer mortality among non-smokers. The CVD mortality was constant until a BMI of approximately 28.0 kg/m^2 and then increased gradually in both men and women, which was independent of age, cohort and smoking status.

Conclusions: A U-shaped relationship of BMI with all-cause mortality but a graded relationship with CVD mortality at BMI greater than 28.0 kg/m^2 was detected. The relationship between cancer mortality and BMI largely depended on smoking status, and need to be further investigated with site-specific cancers.

Keywords: body mass index, cause of death, mortality, obesity

Introduction

Obesity had become the sixth most important risk factor contributing to the overall burden of various diseases worldwide (Ezzati *et al.*,2002) according to the World Health Organization (WHO) 2002 report. It has been well recognized that obesity defined as having a body mass index (BMI) equal or higher than 30 kg/m^2 is associated with many diseases that contribute to premature death, such as cardiovascular disease (CVD), diabetes and certain types of cancers (Hubert *et al.*,1983; Kurth *et al.*,2002; Nyamdorj *et al.*,2009; Colditz *et al.*,1990; Batty *et al.*,2005; Calle *et al.*,2003). However, the association of BMI with mortality of various causes is controversial: a positive(Lee *et al.*,1993), a J-shaped(Manson *et al.*,1995; Calle *et al.*,1999; Moore *et al.*,2008) or U-shaped(Seidell *et al.*,1996; Shaper *et al.*,1997; Rosengren *et al.*,1999; Baik *et al.*,2000; Flegal *et al.*,2005; Breeze *et al.*,2006; Pischon *et al.*,2008; Klenk *et al.*,2009) relation with all-cause mortality; a positive(Lee *et al.*,1993; Seidell *et al.*,1996; Kivimaki *et al.*,2008; Flegal *et al.*,2007), or a J-shaped(Jonsson *et al.*,2002) relation with CVD mortality; a positive(Calle *et al.*,1999; Calle *et al.*,2003; Hu et al.,2004; Berrington de Gonzalez et al., 2010), a J-shaped(Reeves *et al.*,2007) relation, and no association(Baik *et al.*,2000; Meyer et al.,2002; Batty et al.,2005; Flegal *et al.*,2007) with cancer mortality have all been reported.

Recently, the WHO definition for overweight has been questioned by several studies which showed that overweight (BMI between 25.0 and 30 kg/m^2) was not associated with increased risk of death (Flegal *et al.*,2005; Lenz *et al.*,2009; McGee & Diverse Populations Collaboration,2005). The controversy between previous studies may be due to differences in study design and study populations. To clarify shape of the relationship of BMI with mortality of various causes may extend our understanding on the role of underweight, overweight and obesity in relation to the development of diseases and mortality of various causes, and could help to improve the definition of underweight and obesity. This is important considering the increase in the prevalence of obesity and its adverse health consequences worldwide. In the current study, the BMI-mortality relationship is investigated based on the data of the large Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study.

Subjects and methods

Study population

Data were collected from 33 prospective studies in 11 European countries and the study population comprised 142 885 Europeans including 76 226 men and 66 659 women aged 24-99 at baseline. This involved the completion of a self-reported questionnaire on smoking and participation in a medical examination to measure body weight and height, described in detail in previous DECODE publications (DECODE, 2001). Participants with missing data on body weight and height (n=2 588), and on smoking status (n=4 490) were excluded. Subjects who had emigrated but the dates of the emigration were recorded were treated as censored cases. Individuals without exact date of emigration or completely lost to follow-up were also excluded (n=50). Thus the final sample for this analysis included a total of 135 745 participants (72 947 men and 62 798 women) with a median follow-up of 16.8 years.

Individual participant data from each cohort was sent to the Diabetes Prevention Unit of the National Institute for Health and Welfare in Helsinki, Finland for collaborative data analyses. Each study was approved by the local ethics committees and the analysis plan was approved by the ethics committee of the National Institute for Health and Welfare.

Definition of covariates

BMI at baseline was calculated as body weight in kilograms divided by the square of height in meters. Smoking status at baseline was classified based on responses to the questionnaire into three categories of never smokers, current smokers and former smokers in most of the studies but not in all. The mortality risk of former smokers was checked against never- and current- smokers within each BMI category, and the results showed that the mortality risk among former smokers was similar to that of never smokers within each BMI category. In addition, the mean BMI of former smokers was similar to that of never smokers, both higher than that of current smokers. Thus in the final data analysis we combined never smokers with former smokers to form a currently non-smoking category to increase statistical power and to harmonize and standardize the smoking variables received from different studies.

Definition of fatal events

Vital status and cause of deaths were recorded in all of the studies included. CVD mortality was defined according to the International Classification of Disease (ICD) codes 331, 420 (7^{th} revision), 401-448 (8^{th} or 9^{th} revision), and codes I10-I79 (10^{th} revision). Cancer mortality was defined as cancers of all types by ICD codes 158, 162, 181, 193, 199, 200, 204 (7^{th} revision), 140-239 (8^{th} or 9^{th} revision) and codes C00-C97, D00-D09 (10^{th} revision).

Statistical analysis

Participants were classified into the following 18 BMI categories of <19.0, 19.0-19.9, 20.0-20.9, 21.0-21.9, 22.0-22.9, 23.0-23.9, 24.0-24.9, 25.0-25.9, 26.0-26.9, 27.0-27.9, 28.0-28.9, 29.0-29.9, 30.0-30.9, 31.0-31.9, 32.0-32.9, 33.0-33.9, 34.0-34.9, and ≥35.0 kg/m^2. Crude mortality was calculated and plotted for each BMI category. The category with the lowest mortality rate was chosen as the reference category to estimate the relative risk or hazard ratio (HR) using Cox proportional hazards models adjusting for age, cohort, and smoking status. A sensitivity analysis by excluding the participants who died in the first five-year follow-up was performed to assess the reverse causation. Because current smokers were leaner and had increased mortality compared to current non-smokers in this study, a further analysis was performed stratified by currrent smoking status using nine BMI categories of <19.0, 19.0-21.0, 21.0-23.0, 23.0-25.0, 25.0-27.0, 27.0-29.0, 29.0-31.0, 31.0-33.0 and ≥33.0 kg/m^2 to explore to what extent smoking has contributed to the increased mortality in the low BMI categories. The formal interaction between smoking status and the BMI categories was also tested. In addition, we performed analyses for competing risks using STATA 11.0 to estimate the probability of the CVD mortality in the presence of competing risk of cancer mortality, or vice versa.

Results

Baseline characteristics of the cohorts are presented in table 1. Over a median follow-up of 16.8 years, 29 071 participants died, 13 502 from CVD and 8 748 from cancers. Old age was associated with both CVD and cancer mortality (table 2). Current smoking was associated with cancer mortality in both genders and with CVD mortality in men but not in women. Mean BMI was significantly higher in individuals who died of CVD but not in those who died of cancers compared with those who were still alive.

Crude mortality rates per 1000 person-years and HRs (95% confidence intervals) for mortality from various causes adjusted for age, cohort and further adjusted for smoking status are shown in figure 1 and online tables 1-2. All-cause and cancer mortality decreased first, leveled off, and then increased with increasing BMI levels (kg/m^2), a U-shaped relationship with the lowest all-cause mortality in the BMI interval of 23.0 to 28.0 kg/m^2 in men and 21.0 to 28.0 kg/m^2 in women approximately. The mortality from CVD was approximately constant up to a BMI of 28 kg/m^2 and then increased gradually in both men and women. The relationship between BMI and mortality from various causes did not change substantially after exclusion of deaths occurring during the first five-year follow-up (online tables 1-2).

Adjustment for smoking status lowered the HRs in the lower BMI categories but increased the HRs associated with higher BMI levels (figure 1). Smokers tended to have low BMI (table 3). The smoking-BMI interaction was significant for mortality from various causes in both men and women. Our analysis stratified by smoking status showed that among non-smokers the U-shaped relationship between BMI and all-cause mortality held, but it disappeared for cancer mortality. CVD mortality increased gradually at the upper BMI distribution among non-smokers. Among current smokers the HRs for mortality of various causes were constantly higher across the entire range of BMI than non-smokers within the same BMI category. Because the deaths from CVD and cancers are mutually exclusive, a competing risk analysis was also performed which did not alter the observed relationship between BMI and mortality of CVD and cancers (online tables 1-2).

Discussion

In this European population, a U-shaped relationship between BMI and mortality from all-cause and from all cancers was observed, however the increased risk associated with low BMI disappeared for cancer mortality among non-smokers. Mortality from CVD increased positively with increasing BMI levels at the upper BMI distribution, which was independent of smoking status.

Almost all studies investigating all-cause mortality have found significantly increased risk at both the lower and the upper ends of the BMI distributions, with constant lower risk of mortality in the middle of the BMI distribution(Manson *et al.*,1995; Calle *et al.*,1999; Moore *et al.*,2008; Seidell *et al.*,1996; Rosengren *et al.*,1999; Flegal *et al.*,2005; Breeze *et al.*,2006; Kivimaki *et al.*,2008; Klenk *et al.*,2009; Prospective Studies Collaboration *et al.*,2009). Thus, these studies claimed a J- or a U-shaped relationship of BMI with all-cause mortality, but the ideal BMI range where the mortality risk was low has not been consistently defined partly due to differences in BMI classifications, methods used to estimate mortality risk and partly by diffenret smoking rates within different populations. There was, however, one study reporting a positive relationship between all-cause mortality and BMI in men(Lee *et al.*,1993), without any excess mortality among lean individuals (BMI< 22.5kg/m^2). It worths to mention that the BMI cut-off to define "lean" was set higher in this study compared with ours that might obscure a risk increase at low BMI levels. As shown in the table 3, more current smokers than non-smokers had a low BMI category, and smoking has largely contributed to the high mortality risk observed in the lean individuals. This is consistent with a previous study by Lawlor et al. (Lawlor *et al.*,2006).

For CVD mortality, most studies have consistently reported a positive relationship at the upper BMI levels, with varying cutoff values from 22.5 to 30.0 kg/m^2(Lee *et al.*,1993; Seidell *et al.*,1996; Kivimaki *et al.*,2008; Prospective Studies Collaboration,2009; Flegal *et al.*,2007). There were two studies, however, showing a U-shaped relationship with the lowest CVD mortality at the BMI interval of 20.0 to 29.9 kg/m^2 in Swedish men(Jonsson *et al.*,2002), and 22.5 to 24.9 kg/m^2 in Austrian adults(Klenk *et al.*,2009). Our study with a large sample size showed a strong positive relationship between CVD mortality and BMI among non-smokers at BMI levels above approximately 28.0 kg/m^2 in both men and women.

A limited number of studies have reported a linear(Calle *et al.*,1999; Calle *et al.*,2003; Hu et al.,2004; Berrington de Gonzalez et al., 2010), or no relationship(Seidell *et al.*,1996; Baik *et al.*,2000; Meyer et al.,2002; Batty et al.,2005; Flegal *et al.*,2007) between BMI and cancer mortality. We found a vague U-shaped relationship between BMI and cancer mortality which confirmed the findings of Reeves GK et al.(Reeves *et al.*,2007). Stratified analysis by smoking status, however, revealed that the high cancer mortality in lean individuals was mainly attributable to smoking. As shown in our study, current smokers were more commonly found in the low BMI categories compared to non-smokers in both genders. Further investigations are required to study site-specific cancer mortality in men and women.

This study was based on data from large European population- or occupational-based studies and should be representative of the general population. Thus, a large number of middle-aged and elderly European men and women followed for a median 16.8 years led to a relatively large number of deaths from all causes, CVD and cancers that gave power to investigate the association between BMI and risk of mortality with small BMI intervals.

A relative limitation of the study is the lack of information on weight changes before the study, that makes it impossible to exclude the "reverse causation" possibility which is inherently existing in any study of mortality(Willett *et al.*,1999) because the weight changes before the baseline examination could be a consequence of underlying diseases before enrolment rather than a cause of deaths. However, after excluding the deaths arisen within the first 5-year follow-up the results were not changed substantially. Another limitation of the study is that no information on physical activity (a potential confounder in our analysis) at baseline is available, furthermore physical activity and fitness is an independent predictor of death and the effect of obesity on morbidity and mortality could be largely diminished by higher levels of physical fitness(Hu *et al.*,2004). Nevertheless, the effect of physical activity on longevity is still controvesial and needs further investigation. Other potential confounders were also unavailable such as menopuse status at baseline and body composition that could be very different between men and women and changes with menopause(Poehlman *et al.*,1995; Hoover et al.,2000).

In spite of a decrease in mortality, BMI has increased slightly during the last three decades in Europe(Flegal et al.,2002; Hedley *et al.*,2004; Vartiainen *et al.*,2010) that might suggest that cohort effects may play a role in our findings, however the increase in BMI in the current study is too small to substantially affect the results (mean BMI 25.6 kg/m^2 in the 1970s, 25.6 kg/m^2 in the 1980s and 26.3 kg/m^2 in the 1990s). The shift of the BMI distribution towards the right in the general population can increase the risk of obesity-related disorders such as diabetes and CVD, but its direct impact on mortality is not straight forward, since mortality is a complex outcome of many factors including occurrence of a disease and its treatment. Therefore, obesity defined by BMI maybe a useful indicator for intervention for diabetes and CVD, but a poor measure of mortality from all-causes and certain cancers. Considering the complex underlying causes of cancer deaths and the vague relationship found in our study, further investigations are required to study site-specific cancer mortality.

In conclusion, a U-shaped relationship between BMI and mortality from all-cause and from cancer was observed, but the relationship disappeared for cancer mortality among non-smokers. Mortality from CVD increased positively with increasing BMI levels at the upper BMI distribution, which was independent of smoking status.

Conflict of interest

There are no conflicts of interest.

Studies and investigators included in this collaborative study are:

Denmark Glostrups Study: T. Jørgensen[1,2], K. Borch-Johnson[3]. 1. Research Centre for Prevention and Health, Glostrup University Hospital; 2. Faculty of Health Science, University of Copenhagen; 3. Steno Diabetes Center, Gentofte.

Finland East-West Study: A. Nissinen,[1] J. Pekkanen,[1] J. Tuomilehto[1,2,3]. 1. Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland; 2. Department of Public Health, University of Helsinki, Helsinki, Finland; 3. South Ostrobothnia Central Hospital, Seinäjoki.

Helsinki Policemen Study: M. Pyörälä, K. Pyörälä. Institute of Clinical Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio.

National FINRISK 1972-1997 Cohorts: J. Tuomilehto[1,2,3], P. Jousilahti[2], J. Lindström[2]. 1. Department of Public Health, University of Helsinki, Helsinki; 2. Department of Chronic

Disease Prevention, National Institute for Health and Welfare, Helsinki; 3. South Ostrobothnia Central Hospital, Seinäjoki.

National FINRISK 2002 Study: J. Tuomilehto[1,2], T. Laatikainen[2], M. Peltonen[2], J. Lindström[2]. 1. Department of Public Health, University of Helsinki, Helsinki; 2. Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki.

Oulu Study: S Keinänen-Kiukaanniemi[1,2,3], U. Rajala[1], M. Laakso[1,3].1. The Institute of Health Sciences, University of Oulu, Oulu; 2. Oulu Health Centre; 3. Oulu University Hospital, Unit of General practice.

Vantaa Study: R. Tilvis[1], J. Tuomilehto[2,3]. 1. Division of geriatrics, Department of medicine, University of Helsinki, Helsinki; 2. Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki; 3. Department of Public Health, University of Helsinki, Helsinki.

Iceland Reykjavik Study: G. Sigurdsson[1,2]. 1. University of Iceland, Reykjavik, Iceland; Icelandic Heart Association, Kopavogur; 2. Landspitali-Univerisity Hospital, Reykjavik.

Israel GOH-I Study: R. Dankner[1,2]. 1. Unit for Cardiovascular Epidemiology, The Gertner Institute, Sheba Medical Center, Tel Hashomer, Israel; 2. Division of Epidemiology and Prevention, School of Public Health, Sackler School of Medicine, Tel Aviv University, Israel.

Italy Cremona Study: M.P. Garancini[1], G. Calori[1], G. Ruotolo[1,2], S. Mannino[3], M. Villa[3]. 1. Division of Metabolic and Cardiovascular Diseases, San Raffaele Scientific Institute, Milan; 2. AstraZeneca R&D Mölndal, Sweden; 3. ASL Provincia di Cremona, Cremona.

Poland POLMONICA: A. Pajak, E. Kawalec. Department of Epidemiology and Population Studies, Institute of Public Health, Unit of Health Care, Collegium Medicum Jagiellonian University, Krakow.

Spain Catalonia Study: C. Castell. Division of Public Health, Department of Health, Generalitat of Catalonia, Barcelona.

Sweden Northern Sweden MONICA Survey: S. Söderberg[1,2], M. Eliasson[1]. 1. Department of Public Health and Clinical Medicine, Cardiology, Umeå University Hospital, Umeå; 2. Baker IDI Heart and Diabetes Institute, Melbourne, Australia.

The Uppsala Longitudinal Study of Adult Men (ULSAM): B. Zethelius, Department of Public Health/Geriatrics, Uppsala University Hospital, Uppsala.

Malmo Preventive Project: PM. Nilsson and G. Berglund. Department of Clinical Sciences, Lund University, University Hospital, Malmö.

The Netherlands Hoorn Study: J.M. Dekker[1], G. Nijpels[1], C.D.A. Stehouwer[2]. 1. Department of Epidemiology and Biostatistics and the EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam; 2. Department of Internal Medicine and Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht.

Zutphen Study: Ed. Feskens. Department of Chronic Disease and Environmental Epidemiology, National Institute of Public Health and Environmental Protection, Bilthoven.

Turkey Turkish Adult Risk Factor Study: A. Onat[1,2]. 1.Turkish Society of Cardiology, Istanbul; 2. Department of Cardiology, Cerrahpasa Medical Faculty, Istanbul University,

Istanbul.

United Kingdom Isle of Ely Diabetes Project: N.J. Wareham, MRC Epidemiology Unit, Strangeways Research Labs, Cambridge.

Newcastle Heart Project: N. Unwin[1], N. Ahmad[1], K.G.M.M. Alberti[2], L. Hayes[1]. 1. Department of Medicine and Epidemiology and Public Health, University of Newcastle, Newcastle; 2. Imperial College, St Mary's Campus, St Mary's Hospital, London.

Goodinge Study: R. W. Morris, J. S. Yudkin, M. Gould, A. Haines, Department of Primary Care & Population Sciences, Royal Free and University College Medical School, London.

Whitehall II Study: M.G.Marmot[1], A.G. Tabák[1,2], M. Kivimäki[1,3], E.J. Brunner[1], D.R. Witte[1,4]. 1. Department of Epidemiology and Public Health, University College London, London; 2. Semmelweis University Faculty of Medicine, 1st Department of Medicine, Budapest; 3. Finnish Institute of Occupational Health, Helsinki; 4. Steno Diabetes Center, Gentofte.

Sources of funding

This study was supported by a grant from Academy Finland (129197).

References

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

Batty GD, Shipley MJ, Jarrett RJ, Breeze E, Marmot MG,Smith GD,(2005). Obesity and overweight in relation to organ-specific cancer mortality in london (UK): Findings from the original whitehall study. *Int J Obes (Lond)* **29,**1267-1274.

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

Breeze E, Clarke R, Shipley MJ, Marmot MG,Fletcher AE(2006). 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* **35,**169-178.

Calle EE, Thun MJ, Petrelli JM, Rodriguez C,Heath CJ(1999). Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* **341,**1097-1105.

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

Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA *et al.*,(1990). Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* **132,**501-513.

DECODE Study Group, the European Diabetes Epidemiology Group (2001). Glucose tolerance and cardiovascular mortality: Comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* **161,**397-405.

Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ,Comparative Risk Assessment Collaborating Group (2002). Selected major risk factors and global and regional burden of disease. *Lancet* **360,**1347-1360.

Flegal KM, Carroll MD, Ogden CL,Johnson CL,(2002). Prevalence and trends in obesity among US adults, 1999-2000. *JAMA* **288,**1723-1727.

Flegal KM, Graubard BI, Williamson DF,Gail MH (2005). Excess deaths associated with underweight, overweight, and obesity. *JAMA* **293,**1861-1867.

Flegal KM, Graubard BI, Williamson DF,Gail MH (2007). Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA* **298,**2028-2037.

Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR,Flegal KM,(2004). Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *JAMA* **291,**2847-2850.

Hoover LW and Boote EJ,(2000). Longitudinal assessment of intra-abdominal fat in postmenopausal women. *Ann N Y Acad Sci* **904,**520-525.

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

Hubert HB, Feinleib M, McNamara PM,Castelli WP,(1983). Obesity as an independent risk factor for cardiovascular disease: A 26-year follow-up of participants in the framingham heart study. *Circulation* **67,**968-977.

Jonsson S, Hedblad B, Engstrom G, Nilsson P, Berglund G,Janzon L(2002). 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* **26,**1046-1053.

Kivimaki M, Ferrie JE, Batty GD, Davey Smith G, Elovainio M, Marmot MG *et al.*(2008). Optimal form of operationalizing BMI in relation to all-cause and cause-specific mortality: The original whitehall study. *Obesity (Silver Spring)* **16,**1926-1932.

Klenk J, Nagel G, Ulmer H, Strasak A, Concin H, Diem G *et al.*(2009). Body mass index and mortality: Results of a cohort of 184,697 adults in austria. *Eur J Epidemiol* **24,**83-91.

Kurth T, Gaziano JM, Berger K, Kase CS, Rexrode KM, Cook NR *et al.*,(2002). Body mass index and the risk of stroke in men. *Arch Intern Med* **162,**2557-2562.

Lawlor DA, Hart CL, Hole DJ,Davey Smith G (2006). Reverse causality and confounding and the associations of overweight and obesity with mortality. *Obesity (Silver Spring)* **14,**2294-2304.

Lee IM, Manson JE, Hennekens CH,Paffenbarger RJ(1993). Body weight and mortality. A 27-year follow-up of middle-aged men. *JAMA* **270,**2823-2828.

Lenz M, Richter T,Muhlhauser I (2009). The morbidity and mortality associated with overweight and obesity in adulthood: A systematic review. *Dtsch Arztebl Int* **106,**641-648.

Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE *et al.*(1995). Body weight and mortality among women. *N Engl J Med* **333,**677-685.

McGee DL and Diverse Populations Collaboration (2005). Body mass index and mortality: A meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol* **15,**87-97.

Meyer HE, Sogaard AJ, Tverdal A,Selmer RM,(2002). Body mass index and mortality: The influence of physical activity and smoking. *Med Sci Sports Exerc* **34,**1065-1070.

Moore SC, Mayne ST, Graubard BI, Schatzkin A, Albanes D, Schairer C *et al.*(2008). Past body mass index and risk of mortality among women. *Int J Obes (Lond)* **32,**730-739.

Nyamdorj R, Qiao Q, Soderberg S, Pitkaniemi JM, Zimmet PZ, Shaw JE *et al.*,(2009). BMI compared with central obesity indicators as a predictor of diabetes incidence in mauritius. *Obesity (Silver Spring)* **17,**342-348.

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

Poehlman ET, Toth MJ,Gardner AW,(1995). Changes in energy balance and body composition at menopause: A controlled longitudinal study. *Ann Intern Med* **123,**673-675.

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

Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D *et al.*(2007). Cancer incidence and mortality in relation to body mass index in the million women study: Cohort study. *BMJ* **335,**1134.

Rosengren A, Wedel H,Wilhelmsen L (1999). 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* **20,**269-277.

Seidell JC, Verschuren WM, van Leer EM,Kromhout D (1996). Overweight, underweight, and mortality. A prospective study of 48,287 men and women. *Arch Intern Med* **156,**958-963.

Shaper AG, Wannamethee SG,Walker M (1997). Body weight: Implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men. *BMJ* **314,**1311-1317.

Vartiainen E, Laatikainen T, Peltonen M, Juolevi A, Mannisto S, Sundvall J *et al.*,(2010). Thirty-five-year trends in cardiovascular risk factors in finland. *Int J Epidemiol* **39,**504-518.

Willett WC, Dietz WH,Colditz GA (1999). Guidelines for healthy weight. *N Engl J Med* **341,**427-434.

-

Figure legends

Figure 1 Crude mortality rate per 1000 PY (person-years) (open circles), age- and cohort-adjusted hazard ratios (open triangles), and age-, cohort- and smoking- adjusted hazard ratios (solid circles) with their 95% confidence intervals (vertical bars) for mortality corresponding to a one unit increase in body mass index (BMI, kg/m^2). In men, the BMI reference category was 23.0-23.9 kg/m^2 for all-cause mortality, 20.0-20.9 kg/m^2 for CVD mortality and 25.0-25.9 kg/m^2 for cancer mortality. In women, the BMI reference category for all these three was 20.0-20.9 kg/m^2.

Table 1 Baseline characteristics of the cohorts and the data of follow-up

Study	Number		Age (years)	Body mass index(kg/m^2)		Current smokers (%)	Non-smokers (%)	Median of follow-up (maximum)	Number of deaths		
	Men	Women		Men	Women				CVD	Cancer	All-cause
Denmark,											
Glostrup-1897	229	208	70.0(-)	24.5(3.4)	23.7(4.9)	58.1	41.9	12.5(27.0)	212	101	424
Glostrup-1914	360	306	60.2(0.4)	24.6(3.4)	23.6(4.7)	60.5	39.5	19.0(19.8)	132	89	290
Glostrup-1936	504	548	40.4(0.4)	25.4(3.3)	24.1(3.8)	54.8	45.2	17.1(17.7)	17	29	71
Finland,											
East-west men	437	0	76.4(4.6)	24.8(3.9)	-	14.0	86.0	7.8(17.1)	172	73	390
FINRISK-1972	5341	5616	41.3(9.9)	26.0(3.3)	27.0(4.6)	31.4	68.6	36.7(36.9)	2630	1242	4903
FINRISK-1977	5376	5763	44.0(11.0)	26.2(3.5)	26.7(4.7)	27.4	72.6	31.8(32)	2409	1048	4359
FINRISK-1982	4179	4326	43.9(11.4)	26.5(3.7)	26.4(4.7)	28.8	71.2	26.8(27)	1158	709	2344
FINRISK-1987	2638	2936	44.0(11.4)	26.9(3.8)	26.8(5.0)	26.7	73.3	21.8(22)	458	288	955
FINRISK-1992	2578	2831	44.2(11.4)	26.8(3.9)	26.3(4.9)	28.4	71.6	16.9(17)	208	182	531
FINRISK-1997	3848	3902	47.6(13.3)	26.9(3.9)	26.5(5.0)	24.1	75.9	11.8(12)	292	233	634
FINRISK-2002	3891	4518	47.4(13.1)	27.3(4.1)	26.7(5.1)	26.5	73.5	6.8(7.0)	96	84	239
Helsinki Policemen	1136	0	44.7(8.0)	25.9(2.8)	-	48.6	51.4	32.8(36.8)	327	178	668
Oulu-55	328	415	55.0(-)	26.4(3.4)	25.7(4.3)	23.4	76.6	16.8(17.3)	42	39	115
Vantaa	272	339	65.1(0.4)	26.0(3.7)	25.3(4.6)	16.5	83.5	17.2(17.9)	105	41	204
Iceland,											
Reykjavik	8975	9437	52.5(8.5)	25.6(3.5)	24.5(4.2)	47.0	53.0	17.7(27.1)	1941	1482	4274
Israel,											
GOH-I	2324	2370	43.6(8.4)	25.1(3.7)	26.1(4.7)	35.6	64.4	27.9(27.9)	474	283	1331
Italy,											
Cremona	909	1153	58.7(10.8)	26.2(3.8)	24.9(4.8)	22.2	77.8	15.0(15.8)	203	204	511
The Netherlands,											
Hoorn study	1137	1340	61.7(7.4)	25.5(3.0)	25.1(4.0)	33.5	66.5	8.9(10.2)	114	117	330
Zutphen study	480	0	75.8(4.6)	24.1(3.1)	-	22.9	77.1	4.7(4.8)	53	21	119

Poland,											
MONICA-Krakow	166	192	58.0(8.4)	25.8(4.0)	28.2(4.9)	25.1	74.9	6.5(6.6)	16	6	29
Spain,											
Catalonia	912	1184	55.3(13.9)	25.9(3.4)	25.4(4.4)	21.3	78.7	5.0(5.0)	31	29	91
Sweden,											
Northern Swedish-MONICA 1986	815	789	45.2(11.2)	25.8(3.5)	25.5(4.4)	24.4	75.6	20.5(20.6)	80	70	256
Northern Swedish-MONICA 1990	767	799	45.3(11.4)	26.0(3.3)	25.5(4.4)	24.5	75.5	16.5(16.6)	45	33	134
Northern Swedish MONICA 1994	924	954	49.9(14.0)	26.1(3.6)	25.6(4.6)	21.2	78.8	12.5(14.5)	60	59	207
Northern Swedish MONICA 1999	1070	1104	50.8(13.9)	26.7(3.5)	26.1(4.7)	16.7	83.3	7.4(13.5)	22	27	99
Northern Swedish MONICA 2004	882	923	50.8(14.1)	27.1(4.0)	26.4(5.1)	13.9	86.1	2.5(2.6)	0	0	13
MPP	13016	5277	49.5(4.9)	25.1(3.3)	24.5(4.4)	44.2	55.8	23.9(30.3)	1816	1739	4582
Uppsala study	1181	0	71.0(0.6)	25.1(3.4)	-	20.7	79.3	10.0(12.4)	142	127	333
Turkey,											
TARFS	1588	1630	53.0(12.4)	26.2(4.0)	28.3(5.6)	11.8	88.2	7.9(8.0)	91	NA	167
UK,											
Ely	451	624	54.0(7.8)	25.8(3.2)	25.3(5.0)	17.2	82.8	14.5(15.7)	28	49	99
Goodinge	452	582	54.7(10.3)	25.2(4.1)	25.1(5.2)	37.4	62.6	8.7(9.7)	42	47	114
Newcastle	402	378	54.9(12.5)	26.0(3.9)	25.7(5.0)	27.7	72.3	8.9(10.6)	36	34	97
Whitehall II	5379	2354	49.6(6.1)	25.1(3.2)	25.5(4.7)	13.8	86.2	5.9(7.9)	50	85	158
Total	72947	62798	48.6(11.5)	25.6(3.6)	25.9(4.8)	31.5	68.5	16.8(36.9)	13502	8748	29071

CVD, cardiovascular diseases; NA, not available.

Data are means (standard deviation) or as noted.

Table 2 Baseline characteristics of participants by mortality from all-cause, cardiovascular diseases and cancer

	Men						Women					
	All-cause		Cardiovascular diseases		Cancer		All-cause		Cardiovascular diseases		Cancer	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Number (%)	19170	53777	9175	63772	5536	65823	9901	52897	4327	58471	3212	57956
	(26.3)	(73.7)	(12.6)	(87.4)	(7.8)	(92.2)	(15.8)	(84.2)	(6.9)	(93.1)	(5.3)	(94.7)
Age (years)	53	47	54	48	53	48	54	48	56	48	53	48
	(0.08)[a]	(0.05)	(0.11)[a]	(0.05)	(0.13)[a]	(0.04)	(0.10)[a]	(0.05)	(0.13)[a]	(0.05)	(0.17)[a]	(0.05)
Current smokers (%)	10222	18170	4793	23599	3104	24968	2613	11782	978	13417	985	13349
	(53.3)[a]	(33.8)	(52.2)[a]	(37.0)	(56.1)[a]	(37.9)	(26.4)[a]	(22.3)	(22.6)	(22.9)[a]	(30.7)[a]	(23.0)
Non-smokers (%)	8948	35607	4382	40173	2432	40855	7288	41115	3349	45054	2227	44607
	(46.7)	(66.2)	(47.8)	(63.0)	(43.9)	(62.1)	(73.6)	(77.7)	(77.4)	(77.1)	(69.3)	(77.0)
Body mass index	25.8	25.9	26.2	25.8	25.2	25.8	25.6	25.8	26.4	25.7	25.5	25.6
(kg/m^2)	(0.07)	(0.03)	(0.09)[a]	(0.03)	(0.12)	(0.03)[a]	(0.13)	(0.05)	(0.23)[a]	(0.03)	(0.18)	(0.04)

[a]P<0.05 for differences between Yes and No.

Data are cohort- and age- adjusted mean (standard error) or as noted.

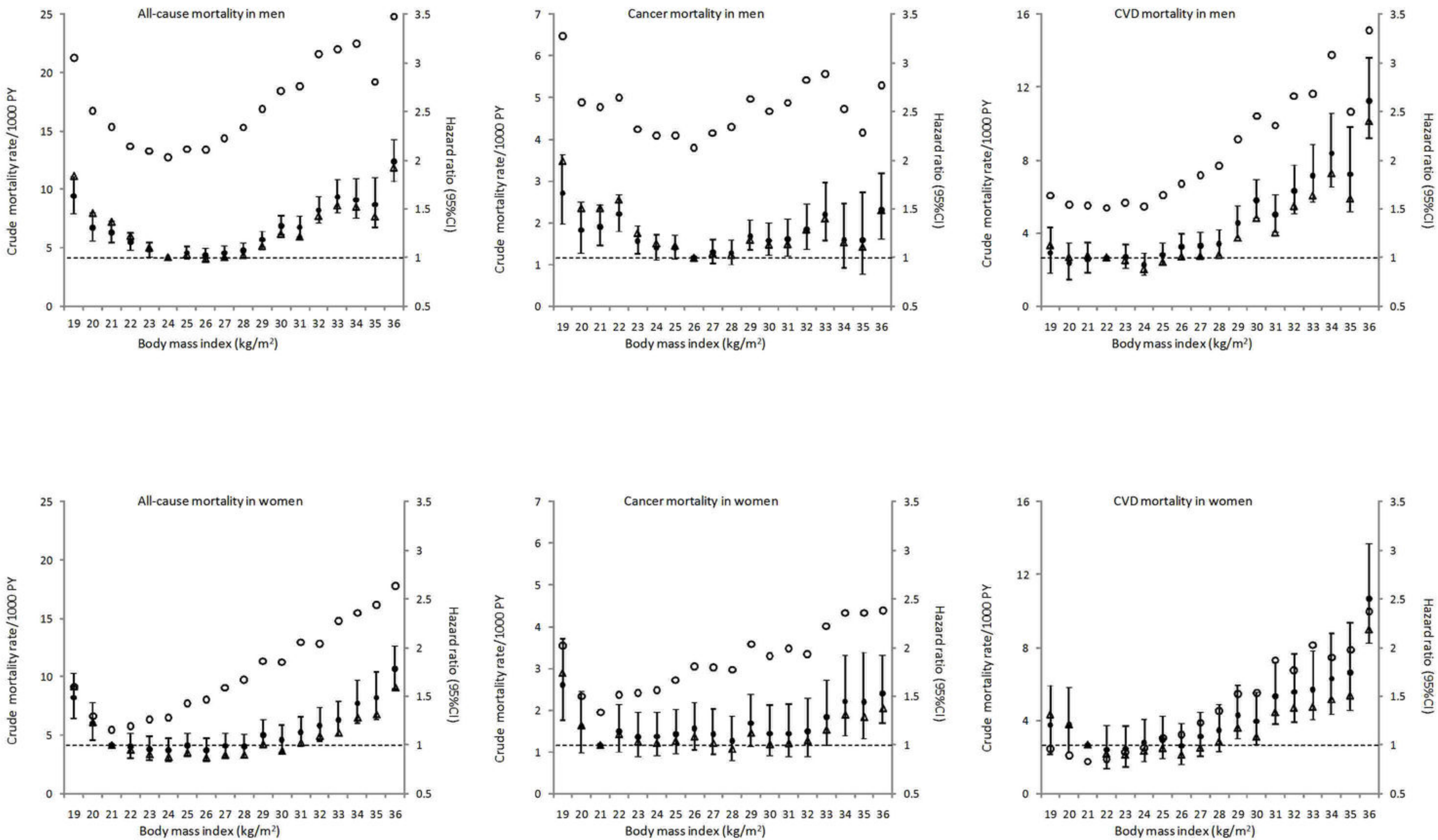
Table 3 Hazard ratios (95% confidence interval) of mortality of various causes in relation to body mass index categories in non-smokers (NS) and current smokers (CS)*

	Body mass index (kg/m^2)									
	<19.0	**19.0-20.9**	**21.0-22.9**	**23.0-24.9**	**25.0-26.9**	**27.0-28.9**	**29.0-30.9**	**31.0-32.9**	**≥33.0**	**P value for interaction**
Men										
Number (%)										
NS	365 (39.4)	1785 (46.4)	5385 (53.3)	10080 (60.1)	10694 (63.6)	7772 (65.4)	4572 (67.4)	2121 (66.1)	1781 (68.5)	
CS	562 (60.6)	2062 (53.6)	4713 (46.7)	6684 (39.9)	6129 (36.4)	4117 (34.6)	2215 (32.6)	1090 (33.9)	820 (31.5)	
Cardiovascular disease										
No. of deaths (NS/CS)	17/79	101/283	332/705	749/998	1007/1041	877/803	653/467	345/214	301/203	
Hazard ratios (95% CI)										
NS	0.85 (0.51-1.43)	1.00 (Reference)	0.95 (0.76-1.18)	1.02 (0.83-1.25)	1.15 (0.94-1.42)	1.25 (1.02-1.54)	1.60 (1.30-1.98)	2.05 (1.64-2.57)	2.56 (2.04-3.20)	
CS	2.27 (1.69-3.05)	1.97 (1.57-2.47)	2.11 (1.71-2.60)	1.97 (1.61-2.42)	2.27 (1.85-2.78)	2.59 (2.10-3.18)	3.09 (2.49-3.84)	2.98 (2.35-3.78)	4.18 (3.29-5.31)	P<0.001
Cancer										
No. of deaths (NS/CS)	17/84	73/258	261/581	511/718	554/609	477/441	287/228	152/109	100/76	
Hazard ratios (95% CI)										
NS	1.17 (0.69-1.98)	1.00 (Reference)	1.09 (0.79-1.34)	0.98 (0.76-1.25)	0.91 (0.71-1.16)	1.00 (0.78-1.28)	1.05 (0.81-1.36)	1.32 (0.99-1.74)	1.21 (0.90-1.64)	
CS	3.26 (2.38-4.47)	2.53 (1.95-3.28)	2.48 (1.94-3.16)	2.03 (1.59-2.59)	1.90 (1.49-2.42)	2.08 (1.62-2.66)	2.21 (1.69-2.87)	2.23 (1.66-3.00)	2.35 (1.70-3.24)	P<0.001
All-cause										
No. of deaths (NS/CS)	75/262	301/796	827/1683	1691/2270	2010/2086	1724/1512	1183/859	634/418	503/336	
Hazard ratios (95% CI)										

NS	1.52 (1.20-1.93)	1.25 (1.09-1.42)	1.00 (Reference)	0.99 (0.91-1.08)	1.01 (0.93-1.09)	1.09 (1.01-1.19)	1.30 (1.19-1.42)	1.66 (1.49-1.84)	1.86 (1.67-2.08)	
CS	3.09 (2.69-3.55)	2.37 (2.15-2.61)	2.16 (1.99-2.35)	1.93 (1.78-2.09)	1.96 (1.80-2.12)	2.12 (1.95-2.31)	2.47 (2.25-2.72)	2.54 (2.25-2.72)	3.00 (2.64-3.41)	P<0.001
Women										
Number (%)										
NS	966 (58.3)	3967 (67.5)	7969 (72.0)	9515 (76.5)	8142 (78.7)	6206 (81.5)	4381 (83.2)	2930 (84.7)	4327 (85.3)	
CS	692 (41.7)	1910 (32.5)	3095 (28.0)	2922 (23.5)	2210 (21.3)	1405 (18.5)	885 (16.8)	529 (15.3)	747 (14.7)	
Cardiovascular disease										
No. of deaths (NS/CS)	29/44	104/106	264/162	433/194	503/147	532/116	482/88	376/49	626/72	
Hazard ratios (95% CI)										
NS	1.15 (0.77-1.74)	1.00 (Reference)	0.88 (0.70-1.11)	0.97 (0.79-1.21)	1.00 (0.81-1.24)	1.23 (1.00-1.52)	1.32 (1.06-1.63)	1.58 (1.27-1.96)	2.16 (1.75-2.66)	
CS	2.57 (1.81-3.67)	2.39 (1.82-3.13)	2.23 (1.74-2.86)	2.43 (1.91-3.09)	2.26 (1.76-2.91)	2.26 (1.74-2.95)	3.04 (2.29-4.04)	2.56 (1.82-3.60)	3.55 (2.63-4.80)	P<0.001
Cancer										
No. of deaths (NS/CS)	30/75	115/116	264/222	398/186	403/151	325/94	232/67	178/27	282/47	
Hazard ratios (95% CI)										
NS	1.14 (0.77-1.71)	1.00 (Reference)	0.95 (0.76-1.18)	1.06 (0.86-1.30)	1.09 (0.88-1.34)	1.10 (0.89-1.36)	1.02 (0.81-1.28)	1.23 (0.97-1.56)	1.47 (1.18-1.83)	
CS	3.29 (2.46-4.41)	1.90 (1.47-2.47)	2.24 (1.79-2.81)	1.87 (1.48-2.36)	1.96 (1.54-2.50)	1.77 (1.35-2.33)	2.25 (1.66-3.04)	1.48 (0.97-2.25)	2.15 (1.53-3.01)	P<0.001
All-cause										
No. of deaths (NS/CS)	102/171	330/324	739/507	1114/494	1180/387	1097/277	887/195	691/97	1154/161	
Hazard ratios (95% CI)										

NS	1.30	1.00	0.86	0.91	0.91	1.01	1.02	1.23	1.61	
	(1.04-1.63)	(Reference)	(0.76-0.98)	(0.80-1.03)	(0.81-1.03)	(0.89-1.15)	(0.89-1.16)	(1.08-1.41)	(1.42-1.82)	
CS	2.91	2.10	2.02	1.88	1.82	1.78	2.21	1.73	2.50	P<0.001
	(2.42-3.51)	(1.80-2.45)	(1.75-2.32)	(1.63-2.16)	(1.57-2.11)	(1.51-2.08)	(1.85-2.64)	(1.38-2.17)	(2.07-3.03)	

*Adjusted for age and cohort.



All-cause mortality in men
Cancer mortality in men
CVD mortality in men
All-cause mortality in women
Cancer mortality in women
CVD mortality in women
Crude mortality rate/1000 PY
Hazard ratio (95%CI)
Body mass index (kg/m²)