Anthropometric measurements of obesity in relation to mortality and cancer incidence among European adults

DECODE and FINRISK Studies

Xin Song

Department of Public Health, Clinicum, Faculty of Medicine, University of Helsinki and Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland

2015

ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in Lecture Room 2, the Institute of Dentistry, Kytösuontie 9, Helsinki, on May 29th 2015, at 12 noon.
Supervised by:
Adjunct professor Qing Qiao, MD, PhD
Department of Public Health, University of Helsinki, Helsinki, Finland
and
Professor Jaakko Tuomilehto, MD, MA (sociol), PhD
Department of Public Health, University of Helsinki,
Diabetes Prevention Unit, Department of Chronic Disease Prevention, National
Institute for Health and Welfare, Helsinki, Finland

Reviewed by:
Adjunct professor Tea Lallukka, PhD
Finnish Institute of Occupational Health, Helsinki, Finland
Adjunct professor Kai Savonen, MD, PhD, MSc, MA
Kuopio Research Institute of Exercise Medicine, Kuopio, Finland

Opponent:
Professor Per Wändell, MD, PhD
Karolinska Institutet, Huddinge, Sweden
“Corpulence is not only a disease itself, but the harbinger of others.”

-Hippocrates

To my family and my friends
CONTENTS

LIST OF ORIGINAL PUBLICATIONS..........................................................7
ABBREVIATIONS.................................................................................8
ABSTRACT..........................................................................................10
TIIVISTELMÄ.....................................................................................13
1 INTRODUCTION..............................................................................16
2 REVIEW OF THE LITERATURE.........................................................19
  2.1 Obesity..................................................................................19
  2.2 Anthropometric measures of obesity and health outcomes............20
  2.3 Comparison of strengths of different anthropometric measures of obesity in relation to CVD mortality.........................................................22
  2.4 Sex differences in CVD risk......................................................23
  2.5 Confounding factors in study of obesity and health outcomes........24
  2.6 A summary of the literature.....................................................26
3 AIMS OF THE STUDY.....................................................................27
4 STUDY POPULATION AND METHODS.............................................28
  4.1 Study population.....................................................................28
  4.2 Measurements.........................................................................30
  4.3 Definition of end-points..........................................................31
  4.4 Ethical considerations............................................................32
  4.5 Statistical analyses..................................................................32
5 RESULTS........................................................................................34
  5.1 Natural relationship between anthropometric measures of obesity and all-cause mortality (Studies I and III).........................................................34
  5.2 Natural relationship between anthropometric measures of obesity and CVD mortality (Studies I and III)..........................................................41
  5.3 Natural relationship between BMI and cancer mortality (Study I).....46
5.4 Natural relationship between BMI and incidence of cancer (Study II)……….49
5.5 Comparison of strengths of different anthropometric measures of obesity in relation to CVD mortality (Study IV)………………………………………………………53
5.6 Sex differences in CVD mortality in relation to obesity (Study V)…………54
6 DISCUSSION…………………………………………………………………………………55
6.1 Summary of main findings………………………………………………………………55
6.2 Fat accumulation and distribution in relation to CVD mortality………………56
6.3 Sex differences in relationship between obesity and CVD mortality…………58
6.4 Association between BMI and cancer outcomes…………………………………61
6.5 Methodological considerations………………………………………………………63
7 CONCLUSIONS AND FUTURE DIRECTIONS……………………………......65
8 ACKNOWLEDGEMENTS……………………………………………………………….66
9 REFERENCES………………………………………………………………………………68
APPENDIX………………………………………………………………………………….91
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on following original publications that have been reprinted with permission of the copyright holders. They are referred to in the text by their Roman numerals (I-V).


### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSI</td>
<td>a body shape index</td>
</tr>
<tr>
<td>AIC</td>
<td>Akaike’s information criterion</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DECODE</td>
<td>Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe study</td>
</tr>
<tr>
<td>FCR</td>
<td>Finnish Cancer Registry</td>
</tr>
<tr>
<td>FPG</td>
<td>fasting plasma glucose</td>
</tr>
<tr>
<td>HDL-C</td>
<td>high-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Disease</td>
</tr>
<tr>
<td>LDL-C</td>
<td>low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>LRT</td>
<td>likelihood ratio test</td>
</tr>
<tr>
<td>MCP-1</td>
<td>monocyte chemoattractant protein-1</td>
</tr>
<tr>
<td>OGTT</td>
<td>oral glucose tolerance test</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SHBG</td>
<td>sex hormone-binding globulin</td>
</tr>
<tr>
<td>Total-C</td>
<td>total cholesterol</td>
</tr>
<tr>
<td>TG</td>
<td>triglyceride</td>
</tr>
<tr>
<td>VAT</td>
<td>visceral adipose tissue</td>
</tr>
<tr>
<td>WC</td>
<td>waist circumference</td>
</tr>
<tr>
<td>WHHR</td>
<td>waist-to-hip-to-height ratio</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WHR</td>
<td>waist-to-hip ratio</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>WHtR</td>
<td>waist-to-height ratio</td>
</tr>
<tr>
<td>WSR</td>
<td>waist-to-stature ratio</td>
</tr>
<tr>
<td>2hPG</td>
<td>2-hour plasma glucose</td>
</tr>
</tbody>
</table>
ABSTRACT

Background and aims: Obesity has become the sixth most important risk factor contributing to the overall burden of a variety of diseases worldwide. The association of anthropometric measures of obesity with mortality from various causes and incidence of cancers of various sites has been investigated, but it remains controversial. The aims of this study were to: 1) evaluate the epidemiological nature of the association of anthropometric measures of obesity with mortality from various causes, and to detect a potential threshold in this association; 2) study the epidemiological nature of the association between body mass index and incidence of cancer of different sites, and to detect a potential threshold in the association; 3) compare the strengths of different anthropometric measures of obesity in relation to cardiovascular disease (CVD) mortality; 4) assess the risk of CVD mortality in relation to obesity and sex in the general population, and also separately for those with or without diabetes at baseline.

Study population and Methods: This study was based on data subsets of the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study and the National FINRISK study, including 72 947 European men and 62 798 women (I), 26 636 Finnish men and 28 089 women (II), 24 686 European men and 21 965 women (III/IV), and 23 629 European men and 21 965 women (V) aged 24 years or above at baseline. Hazard ratios (HRs) corresponding to categorical or continuous body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR) or waist-to-stature ratio (WSR), a body shape index (ABSI) and waist-to-hip-to-height ratio (WHHR) were estimated by the Cox proportional hazards model adjusting for several potential confounding factors measured at baseline. The non-parametric smooth functions of several anthropometric measures of obesity were fitted to health outcomes in order to explore the potential curvilinear relationship using the spline regression model,
with a threshold detected by a piecewise regression model (II/III). HR per standard deviation increment of each anthropometric measure of obesity in relation to CVD mortality was compared using the paired homogeneity test (IV).

**Results:** BMI, WC and WHtR had a U- or J-shaped relationship with all-cause mortality (I/III), whereas WHR, ABSI and WHHR had a linear positive relationship with all-cause mortality (III). BMI had a J-shaped relationship with CVD mortality (I/III), whereas anthropometric measures of abdominal obesity (WC, WHR, WHtR and ABSI) had a linear positive relationship with CVD mortality (III). BMI had a U-shaped relationship with cancer mortality in both men and women but disappeared among non-smokers, which showed no association (I). BMI had a linear positive association with incidence of cancers of the colon, liver, kidney, bladder and all sites combined in men, and of cancers of the stomach, colon, gallbladder and ovary in women, an inverse association with incidence of cancers of the lung in men and the lung and breast in women, and a J-shaped association with incidence of all cancers combined in women (II).

A one-standard-deviation increase in all obesity indicators were significantly associated with a more than 19% increase of CVD mortality risk in both men and women, and the prediction for CVD mortality was stronger with anthropometric measures of abdominal obesity than that with BMI and ABSI, and most strongly with the WHtR/WSR (IV). Men had higher CVD mortality rates and higher HRs across BMI categories, and categories of abdominal obesity than women (V). The sex difference in CVD mortality was slightly smaller in obese than in non-obese individuals; the negative interactions were statistically significant between sex and WC (p =0.02), and sex and WHtR (p =0.01). None of the interaction terms was significant when the analyses were carried out among non-diabetic or diabetic individuals separately (V).
**Conclusions:** This study confirmed the deleterious effect of obesity on mortality from various causes and incidence of cancers of certain sites. The prediction for CVD mortality with anthropometric measures of abdominal obesity was stronger than that with BMI, which may imply a more important role of fat distribution than fat accumulation and suggest that an effective obesity prevention strategy should emphasize the importance of abdominal obesity. Men had higher CVD mortality than women across all categories of anthropometric measures of obesity, which further supports the view of higher intra-abdominal fat accumulation in men than in women, even in non-obese individuals. Obesity seems slightly to diminish the female advantage in CVD mortality, irrespective of diabetes status. This may indicate that women may gradually lose their cardiovascular advantage when they are obese, probably due to a more pronounced clustering of CVD risk factors among obese women.
TIIVISTELMÄ

Tutkimuksen tausta ja tavoitteet: Lihavuudesta on tullut kuudenneksi tärkein riskitekijä, joka lisää useiden eri sairauksien aiheuttamaa tautitaakkaa maailmanlaajuisesti. Lihavuuden antropometristen mittareiden yhteyttä kuolleisuuteen ja eri syöpätyyppien ilmaantuvuuteen on tutkittu useissa tutkimuksissa, mutta tämä yhteys on edelleen kiistanalainen. Tämän tutkimuksen tavoitteena oli 1) arvioida lihavuuden antropometristen mittareiden epidemiologista yhteyttä kuolleisuuteen ja määrittää siihen mahdollinen raja-arvo; 2) tutkia kehon painoindeksin (BMI) epidemiologista yhteyttä eri syöpätyyppien ilmaantuvuuteen ja määrittää siihen mahdollinen raja-arvo; 3) verrata lihavuuden eri antropometrisiä indikaattoreita suhteessa sydän- ja verisuonitautilukuille; 4) arvioida sydän-jä verisuonitautilukuille suhteessa lihavuuteen ja sukupuoleen väestössä, ja myös erityisesti diabeetikoilla ja e-diabeetikoilla.

Aineisto ja menetelmät: Tutkimus perustuu DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) ja FINRISKI – tutkimuksissa kerättyyn aineistoon sisältäen 72 947 eurooppalaista miestä ja 62 798 naista (I), 26 636 suomalaista miestä ja 28 089 naista (II), 24 686 eurooppalaista miestä ja 21 965 naista (III/IV), ja 23 629 eurooppalaista miestä ja 21 965 naista (V) iältään 24 vuotta tai enemmän lähtötilanteessa. Painoindeksin (BMI), vyötärömpäryksen (WC), vyötärömpäryys-lantion –suhteen (WHR), vyötärömpäryys-pituus –suhteen (WHtR) tai vyötärömpäryys - koko –suhteen (waist-to-stature ratio) (WSR), vartalotyyppi-indeksin (a body shape index ABSI) ja vyötärömpäryys-lantio-pituus –suhteen (WHHR) vaarasuhteita (Hazard ratios, HRs) laskettiin käyttäen Coxin vaarasuhdemallia vakoimalla useilla mahdollisilla sekoittavilla tekijöillä lähtötilanteessa. Mahdollisen kurvilineaarisen yhteyden selvittämiseksi, lihavuuden eri antropometristen mittareiden ei-parametrisiä tasoittavia funktioita mallinnettiin yhdessä terveyttä kuvaavien mittareiden kanssa.


Jokaisen lihavuusindikaattorin yhden keskihajontayksikön nousulla oli merkitsevää yhteys, yli 19 prosentin kasvu, sekä miesten että naisten sydän- ja verisuonitautikouleisuurskiin. Keskivartalolihavuutta kuvaavat antropometriset mittarit ennustivat vahvemmin sydän- ja verisuonitautikouleisuutta kuin kehon painoindeksi tai ABSI. Vahvin ennustevoina oli WHtR/WSR:llä (IV). Miehillä oli suurempi sydän- ja verisuonitautikouleisuus ja korkeampi HR kaikissa kehon painoindeksi - ja keskivartalolihavuuskategorioissa kuin naisilla (V); sukupuolten välillä erot olivat hieman pienemmät lihavilla kuin normaalipainoisilla. Negatiivinen yhdysvaikutus oli tilastollisesti merkitsevää sukupuolen ja vyötärönpäätöksen välillä (p=0.02) ja sukupuolen ja vyötärön pituus –
suhteen (WHtR) (p=0.01) välillä. Mikään yhdysvaikutusmuuttuja ei ollut merkitsevää tutkittaessa sitä erikseen ei-diabeetikoilla ja diabeetikoilla.

1 INTRODUCTION

The prevalence of obesity has dramatically increased for decades worldwide. Obesity is a major risk factor for development of chronic diseases and metabolic abnormalities that have high morbidity and mortality (1,2), and may also have an adverse effect on psychosocial health and well-being (3). Most studies have found that a high level of anthropometric measures of obesity is associated with an increased risk of mortality from various causes among adult Caucasians (2,4-13). However, the association of anthropometric measures of obesity with mortality from various causes remains controversial: a J-shaped, a U-shaped, a positive or no association (2,4-31). Moreover, it has been consistently shown that high Body mass index (BMI) is associated with an increased risk of incidence of cancers of the colon (32-37), pancreas (11,33,38-41), kidney (11,36,42-44) and ovary (11,45-48), but with a decreased risk of incidence of cancer of the lung (11,36,49-51). No association is evident for BMI with incidence of cancers of the prostate (52-58) and rectum (34,35,59-62). The relationship between BMI and incidence of cancers of other sites, however, remains inconsistent: a positive, an inverse or no association (11,33,63-76).

BMI is the most common measure for contemporary diagnosis of general obesity in both clinical practice and epidemiological studies (77). In 1995, the World Health Organization (WHO) proposed to define Caucasian individuals as underweight (BMI <18.5 kg/m$^2$), normal weight (BMI 18.5-24.9 kg/m$^2$), overweight (BMI 25.0-29.9 kg/m$^2$) and obese (BMI $\geq$30.0 kg/m$^2$) (78). Waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) or waist-to-stature ratio (WSR) are used as surrogate anthropometric measures of abdominal obesity (79-81). Currently, the most often used definitions for central obesity among adult Caucasians are WC of 102 cm and 88 cm (82), or of 94 cm and 80 cm (83), or WHR of 0.95 and 0.80 (82) in men and in women, respectively.
These existing cut-off values have, however, been determined arbitrarily based on analysis of the trade-offs between sensitivity and specificity for discrimination of diabetes or metabolic syndrome (84). Most of these previous studies were cross-sectional (82). Less is known about whether thresholds for anthropometric measures of obesity exist in predicting cardiovascular disease (CVD) mortality risk.

BMI does not distinguish between muscle and fat accumulation, or between fat locations, hence it is recognized as a crude surrogate for general obesity. WC or WHtR appears to be a better indicator of abdominal obesity than BMI inasmuch as the correlation of cardiometabolic risk factors with intra-abdominal fat content is higher than the corresponding correlation with BMI (85-92). Several studies have reported that relative risks for CVD mortality corresponding to a one-standard-deviation increment in anthropometric measures of abdominal obesity are higher than that of BMI (14,19,93-95), but none of these studies have performed a formal statistical test.

Further, middle-aged women are known to have a much lower CVD mortality than men. Epidemiological studies have shown that men tend to have a higher prevalence of abnormal levels of conventional CVD risk factors than women, such as hypertension, smoking, lipid abnormalities and obesity (96,97). However, this female advantage is abrogated with diabetes and aging (96,98-105). The prevalence of obesity is rising worldwide, leading to increased risks of diabetes and CVD (106,107). It is unclear, however, whether the sex difference in CVD mortality remains with the development of obesity.

The purpose of this study was to examine the association of anthropometric measurements of obesity with mortality and cancer incidence among European adults, to explore a better anthropometric measure of obesity in relation to CVD mortality and sex differences in these associations. The results give evidence on detrimental effect of obesity on mortality and cancer incidence and a better
anthropometric measure of obesity in relation to CVD mortality with threshold values detected, which could be used to direct a more effective obesity prevention strategy.
2 REVIEW OF THE LITERATURE

2.1 Obesity

Definition of obesity based on anthropometric measures

Obesity is associated with both increased fat cell size and number within adipose tissue (108,109). Even though the gold-standard definition of obesity by the WHO is an excess in body fatness (>25% in men and >35% in women) (77), BMI is the most common measure for contemporary diagnosis of general obesity in both clinical practice and epidemiological studies (77). In 1995, the WHO proposed to define Caucasian individuals as underweight (BMI <18.5 kg/m\(^2\)), normal weight (BMI 18.5-24.9 kg/m\(^2\)), overweight (BMI 25.0-29.9 kg/m\(^2\)) and obese (BMI ≥30.0 kg/m\(^2\)) (78). WC, WHR and WHtR/WSR are used as surrogate anthropometric measures of abdominal obesity (79-81). Currently, the most often used definitions for central obesity among Caucasians are WC of 102 cm and 88 cm (82), or of 94 cm and 80 cm (83), or WHR of 0.95 and 0.80 (82) in men and in women, respectively.

Causes of obesity

The causes of obesity are multifactorial: environmental, behavioral, and genetic factors can all contribute to its development. There is a common agreement among experts that the environment, rather than biology, is driving the obesity epidemic through discouraging expenditure of energy, leading to an imbalance between the energy ingested in food and the energy expended (110), although the relative contributions of factors to obesity are not properly known. It is challenging and of considerable interest to identify the biological initiating and driving forces for this energy imbalance, by increased food intake and/or decreased energy expenditure, as well as disturbed fat accumulation in adipose tissue (111). Low socioeconomic
status and genetic variations might play a role in the development of obesity as well (112-117).

2.2 Anthropometric measures of obesity and health outcomes

2.2.1 Anthropometric measures of obesity and all-cause mortality

**BMI and all-cause mortality**

Most studies have found that BMI has a J- (4,21,118-120) or U-shaped (2,5,6,16,19,22-26,121-123) association with all-cause mortality adjusting for a variety of confounding variables. Katzmarzyk et al found that BMI had a positive relationship with all-cause mortality in Canadian women adjusting for age, smoking status and alcohol consumption (15). Lahmann et al also found that BMI had a non-significant positive association with all-cause mortality in Swedish women adjusting for age, smoking status and alcohol consumption, perhaps due to a limited duration of follow-up (27).

**WC and all-cause mortality**

Several studies have found that WC has a U- or J-shaped (2,12,15-19), or a linear positive (8,13-16) association with all-cause mortality. Cameron et al found a non-significant association between WC and all-cause mortality adjusting for age, smoking status and self-reported history of CVD or cancer (31).

**WHR and all-cause mortality**

Most studies have found that WHR has a linear positive association with all-cause mortality (2,8,13,14,16,27,124). Hotchkiss et al found a U-shaped association between WHR and all-cause mortality in Scottish women adjusting for age,
smoking status, alcohol consumption and year of survey (18). Simpson et al found a U-shaped relationship between WHR and all-cause mortality in Australian women adjusting for age, country of birth, physical activity, alcohol intake, education, and smoking status (16). Cameron et al found a non-significant association between WHR and all-cause mortality adjusting for age, smoking status and self-reported history of CVD or cancer (31).

**WHtR and all-cause mortality**

Two studies have found that WHtR has a linear positive relationship with all-cause mortality (94,125), whereas Petursson et al found a linear positive relationship in Norwegian men in contrast to a J-shaped relation in women (14).

**A body shape index (ABSI) and all-cause mortality**

A new measure, ABSI has been proposed to have a linear positive association with all-cause mortality (19).

**2.2.2 Anthropometric measures of obesity and CVD mortality**

Several studies have found that BMI has a linear positive (6,7,21-23,25,26,28), a J- or U-shaped (5,8,14,28,29,126,127) association with CVD mortality, whereas most anthropometric measures of abdominal obesity show a linear positive relationship with CVD mortality (2,8,12-14,128).

**2.2.3 BMI and incidence of cancer**

Most studies have found that BMI has a positive association with incidence of colon cancer (32-37), pancreatic cancer (11,33,38-41), ovarian cancer (11,45-48), kidney cancer (11,36,42-44) and breast cancer among postmenopausal women (11,33,63,66-70,129), and an inverse association with incidence of lung cancer (11,36,49-51) or with breast cancer among premenopausal women
(63, 66, 69, 70, 129, 130), but no association with incidence of rectal cancer (34, 35, 59-62) or prostate cancer (52-58). The relationship between BMI and incidence of cancer of other sites is still inconsistent: an inverse relationship (36) or no association (11, 72) with stomach cancer, a non-significant positive association with liver cancer (33, 36, 73, 74), a linear positive (71, 131) relationship or no association (36) with gallbladder cancer, a linear relationship (11, 73) or no association (33) with cervical cancer, a linear positive relationship (75) or no association (11, 33, 36, 76) with bladder cancer, and a non-significant positive association with all cancers combined (11, 33, 36).

2.2.4 BMI and cancer mortality

The relationship between BMI and cancer mortality is still inconsistent: a positive (4, 9, 10, 20), a U- or J-shaped (11, 25) relationship or no association (7, 21, 22, 24, 29, 30).

2.3 Comparison of strengths of different anthropometric measures of obesity in relation to CVD mortality

BMI does not distinguish between muscle and fat accumulation, or between fat locations, hence it is recognized as a crude surrogate for general obesity. WC or WHtR appears to be a better indicator of abdominal obesity than BMI inasmuch as the correlation of cardiometabolic risk factors with intra-abdominal fat content is higher than the corresponding correlation with BMI (85-92). Several studies have reported that relative risks for CVD mortality corresponding to a one-standard-deviation increment in anthropometric measures of abdominal obesity are higher than that of BMI (14, 19, 93-95), but none of these studies have performed a formal statistical test.
2.4 Sex differences in CVD risk

**Female cardiovascular advantage**

Middle-aged women are known to have a much lower CVD mortality than men. Epidemiological studies have shown that men tend to have a higher prevalence of abnormal levels of conventional CVD risk factors than women, such as hypertension, smoking, lipid abnormalities and obesity (96,97). There is substantial evidence of a sex difference in cardiac autonomic modulation (132-135), lipid and glucose metabolism (136-139), sex hormones (134,140-144) and cytokines (145-149). On average, women have augmented sympathetic inhibition, higher cardiac vagal tone, higher heart rate variability, lower susceptibility to arrhythmias, and decreased myocardial contractility than men (132,133,150), leading to a preponderance of vagal over sympathetic control of cardiac function (132-135).

**Influence of menopause status on cardiovascular risk factors**

Before menopause, middle-aged women generally have lower levels of serum total and low-density lipoprotein cholesterol (Total-C and LDL-C), triglycerides (TG) and apolipoprotein B and higher levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I than their male counterparts (136,151-153), although Total-C and LDL-C increase in women after menopause (151,152).

**Influence of diabetes on sex differences of cardiovascular mortality**

Female cardiovascular advantage is abrogated with diabetes and aging (96,98-105), perhaps as a consequence of diabetes inducing higher levels of inflammatory markers and impairment of higher rates of nitric oxide release in women compared with men, resulting in reduced protective effects of estrogen on body fat
distribution and insulin action, or a more impaired endothelial function in women than in men (140,154).

2.5 Confounding factors in study of obesity and health outcomes

Age

Fat tissue mass increases through middle age and declines in old age (155,156). Fat is redistributed among different fat depots over time, especially during and after middle age from subcutaneous to intra-abdominal visceral depots (156-161). Visceral adipose tissue (VAT) accumulation increases more rapidly in women with aging, especially after menopause (141,162), despite the higher VAT accumulation in men than in women throughout the life span (162,163).

Smoking status

Even though smoking is known to decrease body weight, it is associated with an increase in abdominal obesity (164-168), perhaps through simultaneously affecting lipoprotein lipase activity and increasing cortisol levels (167,168). One study found a reduced visceral fat accumulation in Turkish female smokers (169). Smoking has been well known to be associated with increased risks of CVD (170), type 2 diabetes (171-175) and mortality (16,176-178).

Leisure-time physical activity

A sedentary lifestyle is an independent risk factor for all-cause and CVD mortality, and also contributes to obesity (179,180). Physical activity has been reported to attenuate or eliminate the relation between BMI and the risk of incidence of cancers of the colon, rectum and pancreas (35,38), perhaps through improving insulin resistance and increasing adiponectin levels (181-185). Limited evidence
indicates that leisure-time physical inactivity might play an intermediate role between the relationship of anthropometric measures of abdominal obesity and mortality (186), and weaken, but not eliminate, the risk associated with excess weight (176).

Reverse causality

‘Reverse causality’, which refers to illness-associated weight loss and higher mortality (106,187), may bias observed associations between anthropometric measures of obesity and mortality or incidence.
2.6 A summary of the literature

This literature review focused on epidemiological studies on the association between anthropometric measures of obesity and mortality from various causes and cancer incidence, and sex differences in prevalence of abnormal levels of conventional CVD risk factors.

Evidence of the association between a high level of anthropometric measures of obesity and an increased risk of mortality from various causes among adult Caucasians is very strong, however, the association of anthropometric measures of obesity with mortality from various causes remains controversial, and there is very little evidence of a threshold detected. Several studies have reported that relative risks for CVD mortality corresponding to a one-standard-deviation increment in anthropometric measures of abdominal obesity are higher than that of BMI, but none of these studies have performed a formal statistical test. Studies concerning the association between BMI and incidence of cancers of various sites are scarce and the evidence is less convincing, especially for some rare types of cancer. Inconsistent findings could be partially attributed to confounding factors, reverse causality or methodological issues, for instance, statistical models or time-scale used that may bias associations.

The prevalence of obesity is rising worldwide, leading to increased risks of diabetes and CVD. Despite the fact that middle-aged women are known to have a much lower CVD mortality than men, this female advantage is abrogated with diabetes and aging. Several epidemiological studies have shown that middle-aged men tend to have a higher prevalence of abnormal levels of conventional CVD risk factors than women, such as hypertension, smoking, lipid abnormalities and obesity. It is unclear whether the sex difference in CVD mortality remains with the development of obesity.
3 AIMS OF THE STUDY

The general aims of this thesis were to examine the association of anthropometric measurements of obesity with mortality and cancer incidence among European adults, to identify the potential threshold, to explore a better anthropometric measure of obesity in relation to CVD mortality and sex differences in these associations.

The specific aims of the study were:

1) To evaluate the epidemiological nature of the association of anthropometric measures of obesity with mortality from various causes, and to detect a potential threshold (Studies I and III)
2) To study the epidemiological nature of body mass index and incidence of cancer of different sites, and to detect a potential threshold (Study II)
3) To compare the strengths of various anthropometric measures of obesity in relation to CVD mortality (Study IV)
4) To assess the risk of CVD mortality in relation to obesity and sex in the general population, and separately for those with or without diabetes at baseline (Study V)
4 STUDY POPULATION AND METHODS

4.1 Study population

The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (the DECODE) study is one of the largest epidemiological studies on hyperglycemia and other metabolic disorders in the world, comprising almost 40 mainly population- or occupation-based cohorts from 14 countries in Europe, with about 84 000 Europeans included in the collaboration (188). All survey participants included in the data analysis are Caucasians (Appendix). The study populations varied according to inclusion/exclusion criteria (Table 1), and comprised 135 745 Europeans (72 947 men and 62 798 women) from 33 individual studies (Study I), 46 651 Europeans (24 686 men and 21 965 women) from 12 individual studies (Studies III/IV), and 45 594 Europeans (23 629 men and 21 965 women) from 11 individual studies (Study V), respectively.

Population-based surveys on CVD and other non-communicable disease risk factors have been conducted in selected areas of Finland every 5 years since 1972 (189). Seven FINRISK cohort studies of 1972, 1977, 1982, 1987, 1992, 1997 and 2002 were included in the current data analysis (Table 1). All seven surveys included people who were 24-64 years of age, and the 1997 and 2002 surveys also included people aged 65-74 years. A total of 54 725 Finns (21 148 men and 18 437 women) were included in the data analysis (Study II).
<table>
<thead>
<tr>
<th>Study</th>
<th>Data source</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>DECODE</td>
<td>1) Population- or occupation-based cohort study with data on cause-specific mortality; 2) Participants aged 24–99 at baseline; 3) The availability of sex, baseline body weight, height and smoking status.</td>
<td>1) Individuals without exact date of emigration or completely lost to follow-up.</td>
</tr>
<tr>
<td>II</td>
<td>FINRISK</td>
<td>1) Population-based cohort study with valid data on diagnosis of incident cancer of various sites and dates; 2) Participants aged 24-74 years; 3) The availability of sex, baseline body weight, height, smoking status, leisure-time physical activity and schooling years.</td>
<td>1) Individuals completely lost to follow-up; 2) Individuals with cancer at enrolment.</td>
</tr>
<tr>
<td>III-V</td>
<td>DECODE</td>
<td>1) Population- or occupation-based cohort study with data on CVD mortality; 2) Participants aged 24-99 at baseline; 3) The availability of sex, baseline body weight, height, waist circumference and hip circumference, smoking status and leisure-time physical activity.</td>
<td>1) Individuals without exact date of emigration or completely lost to follow-up.</td>
</tr>
</tbody>
</table>
4.2 Measurements

An anthropometric measure of obesity

Height and weight were measured without shoes and with light clothing. WC was measured midway between the lower rib margin and iliac crest. Hip circumference was measured at the level of the widest circumference over the greater trochanters. BMI was calculated as weight in kilograms divided by the square of height in meters. WHR, WHtR/WSR, or WHHR was calculated as WC divided by hip circumference, height, or both in meters, respectively. The calculation of ABSI was based on WC adjusted for weight and height, which was defined as follows: ABSI=WC height$^{5/6}$ weight$^{-2/3}$ (19). General obesity was defined as a BMI level of $\geq 30.0$ kg/m$^2$ in both sexes, whereas abdominal obesity based on the sex-specific top quartile of WC, WHR or WHtR (WC $\geq 99$ cm, WHR $\geq 0.97$, and WHtR $\geq 0.57$ for men; WC $\geq 90$ cm, WHR $\geq 0.85$, and WHtR $\geq 0.56$ for women, respectively) for comparison purposes (Study V).

Assessment of smoking status, leisure-time physical activity and education status

Based on responses to the questionnaire, smoking status at baseline was classified into three categories of never, former and current smokers (Studies I-V). Reading, watching TV, housework, sewing and walking $\leq 1$ km daily were defined as physically inactive; all those engaging in higher levels of physical activity were defined as physically active (Studies II-V). Education was classified into three categories ($\leq 9$, 10-12, $> 13$ schooling years) (Study II).

Laboratory measurements and assays

Diabetes was defined as either a self-reported history of diabetes at baseline or a fasting plasma glucose (FPG) level of $\geq 7.0$ mmol/L and/or a 2-hour plasma glucose (2hPG) level of $\geq 11.1$ mmol/L (79) (Study V).
4.3 Definition of end-points

CVD mortality was defined according to the International Classification of Disease (ICD) codes 331, 420 (7th revision), 401–448 (8th or 9th revision) and codes I10–I79 (10th revision) (Studies I, III-V). Cancer mortality was defined as cancers of all types by the ICD codes 158, 162, 181, 193, 199, 200, 204 (7th revision), 140–239 (8th or 9th revision) and codes C00–C97, D00–D09 (10th revision) (Study I).

Information on incidence of cancers was obtained from the Finnish Cancer Registry (FCR) and the dates of death from the cause-of-death register of Statistics Finland by computer-based record linkage using the unique personal identity codes assigned to every resident of Finland (Study II). The data coverage in the FCR is virtually complete, 99% for solid tumours, and the data accuracy is high as previously validated by different researchers (190).

The FCR uses International Classification of Diseases for Oncology, 3rd (ICD-O-3) in classification of the cancer cases. For the current study, cancers were categorised into following sites: any site (C000–C809), stomach (C16), colon (C18–C19), rectum (C20), liver (C220), gallbladder and extrahepatic bile ducts (C23-C24), pancreas (C25), lung (C34), breast (C50), cervix uteri (C53), ovary (C56), prostate (C61), kidney (C649) and bladder (C67). Only the first occurrence of cancer after the baseline examination was included in the analysis, subsequent cancers of the same site or not were excluded and people with a cancer diagnosed before the baseline survey were excluded from the cohort (n =1173, 1.9%). Follow-up of each cohort member started from the date of baseline survey and continued until the date of first cancer diagnosis, date of death, or 31 December, 2008, whichever was the earliest.
4.4 Ethical considerations

Individual participant data from each cohort was sent to 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, Helsinki, Finland.

4.5 Statistical analyses

Hazard ratios (HR) and their 95% confidence intervals (CI) were estimated by the Cox proportional hazards model using follow-up time (Study I) or age (Studies II-V) as the time-scale, adjusting for baseline risk factors. The proportional hazards assumptions were tested and met for all studies. Because the death from CVD and cancers are mutually exclusive, the probability of the CVD mortality was estimated in the presence of competing risk of cancer mortality or vice versa (Study I), in order to evaluate a possible overestimate of the cumulative mortality (191). Interactions between anthropometric measure of obesity and factors were checked in the Cox models, using a chi-squared log-likelihood ratio test. Non-parametric smooth functions of anthropometric measures of obesity in relation to mortality were fitted to explore the curvilinear relationship using a linear or restricted cubic spline regression model, with threshold detected by a piecewise regression model (Studies II/III). Akaike’s information criterion (AIC) was used to judge the model fitness between their conventional linear model and polynomial models (including quadratic, cubic or fractional polynomial model), the lower the AIC value the better the model fitness, with reduction of AIC evaluated by the likelihood ratio test (LRT) or a deviance difference test (192,193) (Studies II-IV). AIC difference ≥4 was considered to be considerably less supported relative to the lowest AIC value between non-nested models (194) (Study III). HR per standard deviation increase
of each anthropometric measure of obesity in relation to CVD mortality was formally compared by paired homogeneity test, which is a Wald test of the linear hypothesis of the Cox model regression coefficients, performed to test the null hypothesis of equality of the effect sizes (Study IV).
5 RESULTS

5.1 Natural relationship between anthropometric measures of obesity and all-cause mortality (Studies I and III)

Baseline characteristics of the cohorts and the follow-up data are shown in Table 1 in Study I and Table 2. Over a median follow-up of 16.8 years, 29 071 participants died, 13 502 (46%) from CVD and 8 748 (30%) from cancers of all types (see Table 1 in Study I). Over a median follow-up of 7.9 years, 2381 men and 1055 women died, 1071 men (45%) and 339 women (32%) from CVD (Table 2). Table 3 shows that old age, high distribution of anthropometric measures of obesity, smoking and leisure-time physical inactivity were significantly associated with all-cause mortality.

Relationship between categorical BMI and all-cause mortality (Study I)

Crude mortality rates per 1000 person-years and HRs (95% CI) for mortality from various causes corresponding to a one-unit increase in BMI adjusted for age, cohort and smoking status are shown in Figure 1 and online Tables 1-2 in Study I. All-cause mortality decreased first, leveled off, and then increased with increasing BMI levels (kg/m²), which indicates a U-shaped relationship with the lowest all-cause mortality in the BMI interval of 23.0 to 28.0 kg/m² in men and 21.0 to 28.0 kg/m² in women approximately. Further, the U-shaped relationship did not change substantially after exclusion of deaths occurring during the first five-year follow-up. The smoking-BMI interaction was significant for all-cause mortality in both men and women and the U-shaped relationship held after a data analysis stratified by smoking status (see Table 3 in Study I). For most studies, study-specific HRs were within 10% of the pooled estimate, although there was evidence of
Table 2 Baseline characteristics and the follow-up data of the survey (Studies III-V)

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of participants</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
<th>WC (cm)</th>
<th>WHtR</th>
<th>WHR</th>
<th>ABSI (m² kg⁻²)</th>
<th>Median follow-up (years)</th>
<th>No. of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FINRISK (1987)</td>
<td>2541</td>
<td>43.8</td>
<td>26.7 (3.7)</td>
<td>92.2</td>
<td>0.53</td>
<td>0.90</td>
<td>0.0784 (0.0041)</td>
<td>21.8 (0.04)</td>
<td>293 (52)</td>
</tr>
<tr>
<td>FINRISK (1992)</td>
<td>2570</td>
<td>44.3</td>
<td>26.6 (3.9)</td>
<td>93.9</td>
<td>0.53</td>
<td>0.92</td>
<td>0.0796 (0.0040)</td>
<td>16.8 (0.05)</td>
<td>152 (45)</td>
</tr>
<tr>
<td>FINRISK (1997)</td>
<td>3788</td>
<td>48.6</td>
<td>26.9 (3.9)</td>
<td>94.5</td>
<td>0.54</td>
<td>0.93</td>
<td>0.0796 (0.0040)</td>
<td>11.8 (0.05)</td>
<td>205 (49)</td>
</tr>
<tr>
<td>FINRISK (2002)</td>
<td>3808</td>
<td>48.0</td>
<td>27.2 (4.1)</td>
<td>95.4</td>
<td>0.54</td>
<td>0.97</td>
<td>0.0796 (0.0041)</td>
<td>6.8 (0.05)</td>
<td>69 (43)</td>
</tr>
<tr>
<td><strong>Sweden</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uppsala (1991-1995)*</td>
<td>1057</td>
<td>71.0</td>
<td>26.2 (3.4)</td>
<td>94.4</td>
<td>0.54</td>
<td>0.94</td>
<td>0.0811 (0.0037)</td>
<td>10.0 (0.04)</td>
<td>126 (46)</td>
</tr>
<tr>
<td>Northern Sweden MONICA (1986)</td>
<td>671</td>
<td>46.0</td>
<td>25.4 (3.4)</td>
<td>92.4</td>
<td>0.52</td>
<td>0.94</td>
<td>0.0806 (0.0032)</td>
<td>20.5 (0.04)</td>
<td>49 (37)</td>
</tr>
<tr>
<td>Northern Sweden MONICA (1990)</td>
<td>761</td>
<td>45.0</td>
<td>25.8 (3.4)</td>
<td>91.4</td>
<td>0.52</td>
<td>0.93</td>
<td>0.0789 (0.0036)</td>
<td>16.5 (0.04)</td>
<td>30 (38)</td>
</tr>
<tr>
<td>Northern Sweden MONICA (1994)</td>
<td>877</td>
<td>49.6</td>
<td>26.2 (3.7)</td>
<td>93.4</td>
<td>0.53</td>
<td>0.94</td>
<td>0.0799 (0.0040)</td>
<td>12.5 (0.04)</td>
<td>37 (29)</td>
</tr>
<tr>
<td>Northern Sweden MONICA (1999)</td>
<td>869</td>
<td>50.6</td>
<td>26.7 (3.5)</td>
<td>95.3</td>
<td>0.54</td>
<td>0.92</td>
<td>0.0805 (0.0039)</td>
<td>7.4 (0.05)</td>
<td>14 (25)</td>
</tr>
<tr>
<td>Northern Sweden MONICA (2004)</td>
<td>864</td>
<td>50.9</td>
<td>27.2 (4.0)</td>
<td>96.4</td>
<td>0.54</td>
<td>0.96</td>
<td>0.0803 (0.0036)</td>
<td>2.5 (0.04)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Turkey</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TARFS (1998-2002)</td>
<td>1580</td>
<td>53.2</td>
<td>26.4 (4.0)</td>
<td>94.3</td>
<td>0.56</td>
<td>0.93</td>
<td>0.0819 (0.0052)</td>
<td>7.9 (0.05)</td>
<td>55 (50)</td>
</tr>
<tr>
<td><strong>UK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whitehall II (1991-1993)</td>
<td>5300</td>
<td>49.3</td>
<td>25.1 (3.2)</td>
<td>87.4</td>
<td>0.50</td>
<td>0.90</td>
<td>0.0768 (0.0035)</td>
<td>5.9 (0.04)</td>
<td>41 (35)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>24 686</td>
<td>49.0</td>
<td>26.3 (3.8)</td>
<td>92.7</td>
<td>0.53</td>
<td>0.93</td>
<td>0.0792 (0.0042)</td>
<td>7.9 (0.05)</td>
<td>1071 (45)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Age</td>
<td>WC</td>
<td>BMI</td>
<td>WHR</td>
<td>WHtR</td>
<td>WHHR</td>
<td>ABSI</td>
<td>CVD</td>
</tr>
<tr>
<td>----------------</td>
<td>-------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>FINRISK (1987)</td>
<td>2812</td>
<td>43.7 (11.4)</td>
<td>26.0 (4.9)</td>
<td>79.4 (11.2)</td>
<td>0.49 (0.07)</td>
<td>0.78 (0.06)</td>
<td>0.0714 (0.0045)</td>
<td>0.48 (0.05)</td>
<td>21.8 (38)</td>
</tr>
<tr>
<td>FINRISK (1992)</td>
<td>2828</td>
<td>44.0 (11.5)</td>
<td>25.7 (4.9)</td>
<td>80.2 (11.7)</td>
<td>0.49 (0.08)</td>
<td>0.79 (0.07)</td>
<td>0.0724 (0.0043)</td>
<td>0.49 (0.05)</td>
<td>16.9 (29)</td>
</tr>
<tr>
<td>FINRISK (1997)</td>
<td>3788</td>
<td>46.1 (12.7)</td>
<td>26.1 (5.0)</td>
<td>81.3 (12.2)</td>
<td>0.50 (0.08)</td>
<td>0.80 (0.07)</td>
<td>0.0726 (0.0042)</td>
<td>0.49 (0.05)</td>
<td>11.8 (35)</td>
</tr>
<tr>
<td>FINRISK (2002)</td>
<td>4383</td>
<td>46.6 (13.0)</td>
<td>26.4 (5.1)</td>
<td>83.6 (12.6)</td>
<td>0.52 (0.08)</td>
<td>0.84 (0.06)</td>
<td>0.0742 (0.0042)</td>
<td>0.52 (0.05)</td>
<td>6.8 (24)</td>
</tr>
<tr>
<td><strong>Sweden</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northern Sweden</td>
<td>685</td>
<td>45.6 (11.1)</td>
<td>25.0 (4.4)</td>
<td>85.3 (12.2)</td>
<td>0.52 (0.08)</td>
<td>0.86 (0.07)</td>
<td>0.0783 (0.0054)</td>
<td>0.53 (0.05)</td>
<td>20.5 (24)</td>
</tr>
<tr>
<td>MONICA (1986)</td>
<td>793</td>
<td>44.8 (11.4)</td>
<td>25.0 (4.4)</td>
<td>79.4 (11.0)</td>
<td>0.49 (0.07)</td>
<td>0.81 (0.06)</td>
<td>0.0729 (0.0042)</td>
<td>0.50 (0.04)</td>
<td>16.5 (24)</td>
</tr>
<tr>
<td>Northern Sweden</td>
<td>902</td>
<td>49.4 (14.0)</td>
<td>25.8 (4.7)</td>
<td>84.2 (12.4)</td>
<td>0.52 (0.08)</td>
<td>0.83 (0.08)</td>
<td>0.0757 (0.0060)</td>
<td>0.51 (0.06)</td>
<td>12.5 (24)</td>
</tr>
<tr>
<td>MONICA (1994)</td>
<td>900</td>
<td>50.1 (14.1)</td>
<td>26.4 (4.6)</td>
<td>84.9 (11.8)</td>
<td>0.52 (0.08)</td>
<td>0.82 (0.07)</td>
<td>0.0753 (0.0047)</td>
<td>0.50 (0.05)</td>
<td>7.5 (11)</td>
</tr>
<tr>
<td>Northern Sweden</td>
<td>909</td>
<td>49.7 (13.9)</td>
<td>26.6 (5.1)</td>
<td>86.6 (12.9)</td>
<td>0.53 (0.08)</td>
<td>0.85 (0.07)</td>
<td>0.0761 (0.0045)</td>
<td>0.52 (0.05)</td>
<td>2.5 (0)</td>
</tr>
<tr>
<td><strong>Turkey</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TARFS (1998-2002)</td>
<td>1619</td>
<td>52.7 (12.3)</td>
<td>28.8 (5.7)</td>
<td>90.7 (12.7)</td>
<td>0.58 (0.09)</td>
<td>0.84 (0.08)</td>
<td>0.0778 (0.0072)</td>
<td>0.54 (0.06)</td>
<td>7.9 (63)</td>
</tr>
<tr>
<td><strong>UK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whitehall II (1991-1993)</td>
<td>2346</td>
<td>50.2 (6.1)</td>
<td>25.7 (4.7)</td>
<td>75.5 (11.7)</td>
<td>0.47 (0.07)</td>
<td>0.77 (0.07)</td>
<td>0.0683 (0.0052)</td>
<td>0.48 (0.05)</td>
<td>5.8 (15)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>21 965</td>
<td>46.9 (12.3)</td>
<td>26.2 (5.0)</td>
<td>82.0 (12.6)</td>
<td>0.51 (0.08)</td>
<td>0.81 (0.07)</td>
<td>0.0733 (0.0054)</td>
<td>0.50 (0.05)</td>
<td>11.8 (32)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WHR, waist-to-hip ratio; ABSI, A Body Shape Index; WHHR, waist-to-hip-to-height ratio; CVD, cardiovascular disease.

Data are means (standard deviations) or as noted.

*Uppsala (1991-1995) not included in Study V.
<table>
<thead>
<tr>
<th>Study I All-cause deaths</th>
<th>Study III All-cause deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No</strong></td>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>53,777</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.1 (47.0-47.2)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 (25.8-25.9)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>-</td>
</tr>
<tr>
<td>WHtR</td>
<td>-</td>
</tr>
<tr>
<td>WHR</td>
<td>-</td>
</tr>
<tr>
<td>ABSI (m¹¹/₆ kg⁻²/³)</td>
<td>-</td>
</tr>
<tr>
<td>WHHR (m⁻¹)</td>
<td>-</td>
</tr>
<tr>
<td>Leisure-time physically inactive, %</td>
<td>-</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>52,897</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.5 (47.4-47.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 (25.7-25.8)</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>-</td>
</tr>
<tr>
<td>WHtR</td>
<td>-</td>
</tr>
<tr>
<td>WHR</td>
<td>-</td>
</tr>
<tr>
<td>ABSI (m¹¹/₆ kg⁻²/³)</td>
<td>-</td>
</tr>
<tr>
<td>WHHR (m⁻¹)</td>
<td>-</td>
</tr>
<tr>
<td>Leisure-time physically inactive, %</td>
<td>-</td>
</tr>
</tbody>
</table>
| **Abbreviations:** BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WHR, waist-to-hip ratio; ABSI, A Body Shape Index; WHHR, waist-to-hip-to-height ratio.  
*Data are age-adjusted means (95% confidence intervals) or as noted.  
†P <0.05 for the difference between no and yes.
heterogeneity among studies ($I^2 = 73.8\%$, $p = 0.000$, Figure 1, unpublished results in Study I). Exclusion of any study in the analysis had little overall influence on the main results (data not shown).

**Model fitness of parametric and nonparametric modeling (Study III)**

The best-fitting conventional model was a conventional polynomial model for BMI, WC and WHtR in relation to all-cause mortality in both sexes ($p < 0.05$ for LRT and for deviance difference test against a conventional linear model), which suggests a nonlinear relationship (see online Table 1 in Study III). However, the best-fitting conventional model was observed as a conventional linear model for WHR, ABSI and WHHR in relation to all-cause mortality, of which model fitness was not significantly improved by a conventional polynomial model ($p \geq 0.05$ for LRT or for deviance difference test against a conventional linear model), which indicates a linear relationship. The relationships detected by parametric conventional modeling were further supported by nonparametric modeling without considerable difference between the best conventional and spline models (AIC difference $< 4$).

**Relationship between anthropometric measures of obesity and all-cause mortality by spline regression model (Study III)**

BMI, WC and WHtR had a U- or J-shaped association with all-cause mortality in both sexes, which indicates the existence of two potential thresholds (see Figures 2 a-c and g-i in Study III). HR for WHR, ABSI and WHHR with all-cause mortality in both sexes increased positively with increasing levels (see Figures 2 d-f and j-l in Study III).

**Threshold of anthropometric measures of obesity in relation to all-cause mortality (Study III)**

Threshold values corresponding to a steeper increase in all-cause mortality were detected at 29.88 and 29.50 kg/m$^2$ for BMI, 104.3 and 105.6 cm for WC, 0.61 and 0.67 for WHtR, 0.95 and 0.86 for WHR, 0.0807 and 0.0765 m$^{11/6}$ kg$^{-2/3}$ for ABSI in men and women, respectively, and 0.52 m$^{-1}$ for WHHR in women (see Figure 3 in Study III).
Figure 1 Forest plot (random-effects model) of individual studies assessing the hazard ratio for all-cause mortality corresponding to a one-unit increment of body mass index (BMI) in men (a) and women (b, Study I). The width of horizontal line represents 95% confidence intervals (CI) of the individual studies, and the grey boxes represents the weight of each study. The diamond represents the overall summary estimate. The unbroken vertical line was set at the null value (HR =1.0).
5.2 Natural relationship between anthropometric measures of obesity and CVD mortality (Studies I and III)

Baseline characteristics of the cohorts and the follow-up data are presented in Table 1 in Study I and Table 2. Table 4 shows that old age, high distribution of anthropometric measures of obesity and leisure-time physical inactivity were significantly associated with CVD mortality. Current smoking was associated with CVD mortality in both sexes in Study III but not in women in Study I.

Relationship between categorical BMI and CVD mortality (Study I)

Crude mortality rates per 1000 person-years and HRs (95% CI) for CVD mortality corresponding to a one-unit increase in BMI adjusted for age, cohort and smoking status are shown in Figure 1 and online Tables 1-2 in Study I. CVD mortality was approximately constant up to a BMI of 28 kg/m² and then increased gradually in both men and women. The graded relationship between BMI and CVD mortality did not change substantially after exclusion of deaths occurring during the first five-year follow-up, or after a competing risk analysis performed in the presence of competing risk of cancer mortality. The smoking-BMI interaction was significant for CVD mortality in both men and women, and CVD mortality increased gradually at the upper BMI distribution, independent of smoking status (see Table 3 in Study I). There was no substantial heterogeneity observed among these studies (Figure 2, unpublished results in Study I).
<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th></th>
<th>Studies III and IV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiovascular disease deaths</td>
<td></td>
<td>Cardiovascular disease deaths</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>63,772</td>
<td>9,175</td>
<td>23,615</td>
<td>1,071</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.0 (47.9-48.1)</td>
<td>53.5 (53.3-53.8)†</td>
<td>49.5 (49.3-49.7)</td>
<td>61.1 (60.1-62.0)†</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 (25.8-25.8)</td>
<td>26.4 (26.3-26.5)†</td>
<td>26.3 (26.3-26.4)</td>
<td>27.2 (27.0-27.5)†</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>-</td>
<td>-</td>
<td>92.6 (92.4-92.7)</td>
<td>96.0 (95.3-96.6)†</td>
</tr>
<tr>
<td>WHtR</td>
<td>-</td>
<td>-</td>
<td>0.53 (0.53-0.53)</td>
<td>0.55 (0.55-0.56)†</td>
</tr>
<tr>
<td>WHR</td>
<td>-</td>
<td>-</td>
<td>0.93 (0.93-0.93)</td>
<td>0.94 (0.94-0.94)†</td>
</tr>
<tr>
<td>ABSI (m¹¹/₆ kg⁻²/₃)</td>
<td>-</td>
<td>-</td>
<td>0.0791 (0.0790-0.0792)</td>
<td>0.0805 (0.0803-0.0808)†</td>
</tr>
<tr>
<td>WHHR (m⁻¹)</td>
<td>-</td>
<td>-</td>
<td>0.53 (0.53-0.53)</td>
<td>0.54 (0.54-0.54)†</td>
</tr>
<tr>
<td>Leisure-time physically inactive, %</td>
<td>24.1</td>
<td>24.1</td>
<td>31.2</td>
<td>31.9</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td>24.1</td>
<td>24.1</td>
<td>31.2</td>
<td>31.9</td>
</tr>
<tr>
<td>Current smokers</td>
<td>37.0</td>
<td>52.2†</td>
<td>23.9</td>
<td>37.0†</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>58,471</td>
<td>4,327</td>
<td>21,626</td>
<td>339</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48.1 (48.0-48.1)</td>
<td>56.0 (55.7-56.4)†</td>
<td>47.3 (47.1-47.5)</td>
<td>61.4 (59.3-63.6)†</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 (25.7-25.8)</td>
<td>27.4 (27.3-27.5)†</td>
<td>26.2 (26.1-26.2)</td>
<td>27.7 (27.2-28.2)†</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>-</td>
<td>-</td>
<td>81.9 (81.8-82.1)</td>
<td>86.2 (85.0-87.5)†</td>
</tr>
<tr>
<td>WHtR</td>
<td>-</td>
<td>-</td>
<td>0.51 (0.51-0.51)</td>
<td>0.54 (0.53-0.55)†</td>
</tr>
<tr>
<td>WHR</td>
<td>-</td>
<td>-</td>
<td>0.81 (0.81-0.81)</td>
<td>0.83 (0.82-0.84)†</td>
</tr>
<tr>
<td>ABSI (m¹¹/₆ kg⁻²/₃)</td>
<td>-</td>
<td>-</td>
<td>0.0732 (0.0732-0.0733)</td>
<td>0.0748 (0.0742-0.0753)†</td>
</tr>
<tr>
<td>WHHR (m⁻¹)</td>
<td>-</td>
<td>-</td>
<td>0.50 (0.50-0.50)</td>
<td>0.52 (0.51-0.52)†</td>
</tr>
<tr>
<td>Leisure-time physically inactive, %</td>
<td>-</td>
<td>-</td>
<td>23.8</td>
<td>43.7†</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td>12.8</td>
<td>5.1</td>
<td>18.2</td>
<td>11.2</td>
</tr>
<tr>
<td>Current smokers</td>
<td>22.9</td>
<td>22.6†</td>
<td>19.1</td>
<td>24.2†</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WHR, waist-to-hip ratio; ABSI, A Body Shape Index; WHHR, waist-to-hip-to-height ratio.

*Data are age-adjusted means (95% confidence intervals) or as noted.

†P < 0.05 for the difference between no and yes.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Hazard ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark, Glostrup (1897)</td>
<td>1.05 (0.98, 1.13)</td>
<td>0.32</td>
</tr>
<tr>
<td>Denmark, Glostrup (1914)</td>
<td>1.14 (1.07, 1.21)</td>
<td>0.50</td>
</tr>
<tr>
<td>Denmark, Glostrup (1930)</td>
<td>1.16 (1.05, 1.25)</td>
<td>0.70</td>
</tr>
<tr>
<td>Finland, East-West</td>
<td>0.99 (0.96, 1.03)</td>
<td>0.61</td>
</tr>
<tr>
<td>Finland, Finsrik (1972)</td>
<td>1.05 (1.00, 1.11)</td>
<td>0.70</td>
</tr>
<tr>
<td>Finland, Finsrik (1977)</td>
<td>1.07 (1.00, 1.14)</td>
<td>0.60</td>
</tr>
<tr>
<td>Finland, Finsrik (1982)</td>
<td>1.09 (1.06, 1.13)</td>
<td>0.80</td>
</tr>
<tr>
<td>Finland, Finsrik (1987)</td>
<td>1.05 (1.02, 1.09)</td>
<td>0.60</td>
</tr>
<tr>
<td>Finland, Finsrik (1992)</td>
<td>1.07 (1.03, 1.11)</td>
<td>0.58</td>
</tr>
<tr>
<td>Finland, Finsrik (1997)</td>
<td>1.04 (1.01, 1.07)</td>
<td>0.54</td>
</tr>
<tr>
<td>Finland, Finsrik (2002)</td>
<td>1.04 (1.00, 1.08)</td>
<td>0.40</td>
</tr>
<tr>
<td>Finland, Helsinki policemen</td>
<td>1.10 (1.06, 1.15)</td>
<td>1.50</td>
</tr>
<tr>
<td>Finland, Oulu-55</td>
<td>1.08 (1.01, 1.11)</td>
<td>0.46</td>
</tr>
<tr>
<td>Finland, Vantaa</td>
<td>1.02 (0.95, 1.09)</td>
<td>0.38</td>
</tr>
<tr>
<td>Iceland, Reykjavik</td>
<td>1.05 (1.04, 1.07)</td>
<td>1.25</td>
</tr>
<tr>
<td>Israel, GCHI</td>
<td>1.03 (1.00, 1.07)</td>
<td>3.22</td>
</tr>
<tr>
<td>Italy, Cremona</td>
<td>1.02 (1.01, 1.11)</td>
<td>1.26</td>
</tr>
<tr>
<td>Netherlands, Hoorn</td>
<td>1.08 (1.01, 1.12)</td>
<td>1.56</td>
</tr>
<tr>
<td>Netherlands, Zutphen</td>
<td>1.04 (1.00, 1.08)</td>
<td>0.67</td>
</tr>
<tr>
<td>Poland, Krakow</td>
<td>0.99 (0.96, 1.01)</td>
<td>0.23</td>
</tr>
<tr>
<td>Spain, Catalonia</td>
<td>1.03 (1.00, 1.06)</td>
<td>1.27</td>
</tr>
<tr>
<td>Northern Swedish, MONICA (1986)</td>
<td>1.04 (1.02, 1.11)</td>
<td>1.27</td>
</tr>
<tr>
<td>Northern Swedish, MONICA (1994)</td>
<td>1.10 (1.03, 1.01)</td>
<td>1.16</td>
</tr>
<tr>
<td>Northern Swedish, MONICA (1994)</td>
<td>1.00 (0.99, 1.01)</td>
<td>1.20</td>
</tr>
<tr>
<td>Northern Swedish, MONICA (1996)</td>
<td>1.01 (1.00, 1.02)</td>
<td>1.28</td>
</tr>
<tr>
<td>Sweden, MPP</td>
<td>1.06 (1.03, 1.10)</td>
<td>18.08</td>
</tr>
<tr>
<td>Sweden, Uppsala</td>
<td>1.08 (1.04, 1.11)</td>
<td>1.64</td>
</tr>
<tr>
<td>Turkey, TARFS</td>
<td>1.05 (1.00, 1.11)</td>
<td>2.20</td>
</tr>
<tr>
<td>UK, Ely</td>
<td>0.96 (0.94, 1.00)</td>
<td>0.63</td>
</tr>
<tr>
<td>UK, Goodinge</td>
<td>0.98 (0.96, 1.00)</td>
<td>0.63</td>
</tr>
<tr>
<td>UK, Newcastle</td>
<td>0.99 (0.98, 1.01)</td>
<td>0.56</td>
</tr>
<tr>
<td>UK, Whitehall II</td>
<td>1.02 (1.00, 1.10)</td>
<td>1.17</td>
</tr>
<tr>
<td>Northern Swedish, MONICA (2004)</td>
<td>(Excluded)</td>
<td>1.22</td>
</tr>
</tbody>
</table>

Overall (I-squared = 55.2%, p = 0.000)
Figure 2 Forest plot (random-effects model) of individual studies assessing the hazard ratio for cardiovascular disease (CVD) mortality corresponding to a one-unit increment of body mass index (BMI) in men (a) and women (b, Study I), using the same methods as shown in Figure 1.
Model fitness of parametric and nonparametric modeling (Study III)

The best-fitting conventional model was a conventional polynomial model for BMI with CVD mortality in both sexes (p <0.05 for LRT and for deviance difference test against a conventional linear model), which suggests a nonlinear relationship (see online Table 1 in Study III). However, the best-fitting conventional model was observed as a conventional linear model for anthropometric measures of abdominal obesity with CVD mortality, of which model fitness was not significantly improved by a conventional polynomial model (p ≥0.05 for LRT or for deviance difference test against a conventional linear model), which indicates a linear relationship. The relationships detected by parametric conventional modeling were further supported by nonparametric modeling without considerable difference between the best conventional and spline models (AIC difference <4).

Relationship between anthropometric measures of obesity and CVD mortality by spline regression model (Study III)

HR for BMI with CVD mortality in both sexes decreased first at the lower, then increased gradually at the middle, and increased more at the upper distributions, which indicates a J-shaped relationship with two potential thresholds (see Figures 1 a and g in Study III). HR for anthropometric measures of abdominal obesity (WC, WHtR, WHR, ABSI and WHHR) with CVD mortality in both sexes increased positively with increasing levels (see Figures 1 b-f and h-l in Study III).

Threshold of anthropometric measures of obesity in relation to CVD mortality (Study III)

Threshold values corresponding to a steeper increase in CVD mortality were detected at 29.29 and 31.98 kg/m² for BMI, 96.4 and 93.3 cm for WC, 0.57 and 0.60 for WHtR, 0.0848 and 0.0813 m¹¹/₆ kg⁻²/₃ for ABSI in men and women, respectively (see Figure 1 in Study III).
5.3 Natural relationship between BMI and cancer mortality (Study I)

Baseline characteristics of the cohorts and the follow-up data are presented in Table 1 in Study I. Old age, current smoking was associated with cancer mortality in both sexes (Table 5). Mean BMI was not significantly higher in individuals who died of cancers compared with those who were still alive.

<table>
<thead>
<tr>
<th>Table 5 Baseline characteristics of participants by cancer mortality (Study I)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
</tr>
<tr>
<td><strong>Cancer deaths</strong></td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Number (%)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Current smokers (%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)†</td>
</tr>
</tbody>
</table>

*P <0.05 for differences between cancer deaths or not (Yes and No).
†Data are age-adjusted mean (standard error).

Relationship between categorical BMI and cancer mortality (Study I)

Crude mortality rates per 1000 person-years and HRs (95% CI) for cancer mortality corresponding to a one-unit increase in BMI adjusted for age, cohort and smoking status are shown in Figure 1 and online Tables 1-2 in Study I. BMI had a U-shaped relationship with cancer mortality (see Figure 1 in Study I). The U-shaped relationship did not change substantially after exclusion of deaths occurring during the first five-year follow-up, or after a competing risk analysis performed in the presence of competing risk of CVD mortality. The smoking-BMI interaction was significant for cancer mortality in both men and women, and the U-shaped relationship disappeared among non-smokers, which showed no association (see Table 3 in Study I). There was no substantial heterogeneity observed among these studies (Figure 3, unpublished results in Study I).
Figure 3 a
Figure 3 Forest plot (random-effects model) of individual studies assessing the hazard ratio for cancer mortality corresponding to a one-unit increment of body mass index (BMI) in men (a) and women (b, Study I), using the same methods as shown in Figure 1.
5.4 Natural relationship between BMI and incidence of cancer (Study II)

Baseline characteristics of the cohorts and the follow-up data in FINRISK study is shown in Table 1 in Study II. The mean BMI was higher in older individuals, and people with a low BMI tended to be smokers (p <0.05), physically active and more educated (p <0.05 for trend test, see Table 2 in Study II). People with a low BMI tended to be more in early surveys in men but not in women. Over a mean follow-up of 20.6 years, 8429 incident cancers were recorded, 4208 (49.9%) in men.

Model fitness of parametric and nonparametric modeling

Table 6 shows that the best-fitting conventional model was a conventional linear model for BMI in relation to incidence of cancers of the colon, liver and kidney in men and the gallbladder and breast in women (all p <0.05 for LRT against their basic model), as well as the bladder and all sites combined in men and the stomach, colon, lung and ovary in women (all p ≥0.05 for LRT against their basic model), and the conventional polynomial model did not significantly improve the model fitness (p ≥0.05 for LRT or for deviance difference test against their conventional linear model), which suggests a linear relationship. To the contrary, the conventional polynomial model significantly improved the model fitness of incidence of cancers of the lung in men (all p <0.05 for LRT or deviance difference test of against the conventional linear model), the prostate in men as well as all sites combined in women (p <0.05 for LRT of quadratic polynomial model and p <0.05 for deviance difference test of second-order fractional polynomial model against their basic model), which suggests a nonlinear relationship (Table 7). Model fitness for incidence of cancers of other sites was not improved with any term of BMI added, and a sensitivity analysis that excluded the first 5 years of follow-up did not alter the main results (see online Resource 4 in Study II).
Table 6 Akaike’s information criterion (degrees of freedom) for the relationship between body mass index (BMI) and hazard risk of cancer incidence in men and women (Study II)

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Cases</th>
<th>Basic model</th>
<th>Conventional linear model</th>
<th>Conventional polynomial model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quadratic</td>
<td>Cubic</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>184</td>
<td>3305.6 (11)</td>
<td>3302.6 (12)*</td>
<td>3304.6 (13)</td>
</tr>
<tr>
<td>Liver</td>
<td>53</td>
<td>929.5 (10)</td>
<td>923.1 (11)*</td>
<td>925.0 (12)</td>
</tr>
<tr>
<td>Kidney</td>
<td>107</td>
<td>1953.6 (11)</td>
<td>1944.5 (12)*</td>
<td>1946.5 (13)</td>
</tr>
<tr>
<td>Bladder</td>
<td>192</td>
<td>3371.3 (11)</td>
<td>3369.4 (12)</td>
<td>3367.2 (13)</td>
</tr>
<tr>
<td>All sites combined</td>
<td>4208</td>
<td>74 943.5 (11)</td>
<td>74 943.9 (12)</td>
<td>74 945.3 (13)</td>
</tr>
<tr>
<td>Stomach</td>
<td>120</td>
<td>2132.5 (10)</td>
<td>2132.6 (11)</td>
<td>2131.4 (12)</td>
</tr>
<tr>
<td>Colon</td>
<td>203</td>
<td>3651.3 (10)</td>
<td>3649.9 (11)</td>
<td>3653.1 (12)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>50</td>
<td>899.6 (9)</td>
<td>896.1 (10)*</td>
<td>898.1 (11)</td>
</tr>
<tr>
<td>Lung</td>
<td>114</td>
<td>1922.0 (11)</td>
<td>1920.4 (12)</td>
<td>1919.2 (13)</td>
</tr>
<tr>
<td>Breast</td>
<td>1086</td>
<td>20 244.7 (11)</td>
<td>20 239.8 (12)*</td>
<td>20 241.2 (13)</td>
</tr>
<tr>
<td>Ovary</td>
<td>205</td>
<td>3829.5 (11)</td>
<td>3829.0 (12)</td>
<td>3830.9 (13)</td>
</tr>
</tbody>
</table>

Abbreviations: M =1 or 2, a first- or second-order of fractional polynomial; p1 or p2, power of BMI.

*P <0.05 for likelihood ratio test comparing to other models including basic model (without any term of BMI), conventional linear model (linear term of BMI), quadratic polynomial model (linear and centered quadratic term of BMI), or cubic polynomial model (linear, centered quadratic and centered cubic term of BMI) adjusting for baseline smoking status, leisure-time physical activity, education and area.
### Table 7: Akaike’s information criterion (degrees of freedom) for the relationship between body mass index (BMI) and hazard risk of cancer incidence in men and women (Study II)

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Cases</th>
<th>Basic model</th>
<th>Conventional linear model</th>
<th>Conventional polynomial model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quadratic</td>
<td>Cubic</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>626</td>
<td>10 574.2 (11)</td>
<td>10 556.9 (12)*</td>
<td>10 554.1 (13)*</td>
</tr>
<tr>
<td>Prostate</td>
<td>929</td>
<td>16 287.6 (11)</td>
<td>16 288.8 (12)</td>
<td>16 284.5 (13)*</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>4221</td>
<td>77 124.0 (11)</td>
<td>77 125.8 (12)</td>
<td>77 121.3 (13)*</td>
</tr>
</tbody>
</table>

Abbreviations: M = 1 or 2, a first- or second-order of fractional polynomial; p1 or p2, power of BMI.

*P < 0.05 for likelihood ratio test comparing to other models including basic model (without any term of BMI), conventional linear model (linear term of BMI), quadratic polynomial model (linear and centered quadratic term of BMI), or cubic polynomial model (linear, centered quadratic and centered cubic term of BMI) adjusting for baseline smoking status, leisure-time physical activity, education and area.

†P < 0.05 of deviance difference test for first- or second-order fractional polynomial model against the conventional linear model, adjusting for baseline smoking status, leisure-time physical activity and area.
**Relationship between BMI and incidence of cancer by spline regression model**

Spline regression analysis showed that BMI had a linear positive association with no threshold with incidence of cancers of the colon, liver, kidney, bladder and all sites combined in men (see Figures 1c, g, s, u and w in Study II), and of cancers of the stomach, colon, gallbladder and ovary in women (see Figures 1b, d, j and q in Study II). BMI had an inverse association with incidence of cancers of the lung in men (see Figure 1m) and the lung and breast in women (see Figures 1 n and o in Study II), whereas a J-shaped association with incidence of all cancers combined in women (Figure 1x in Study II), which indicates that there might be thresholds existing. No association was observed for BMI and incidence of cancers of prostate or other sites (see Figure 1 in Study II). The relationship between BMI and incidence of cancer was basically confirmed by the results from analyses using the Cox proportional hazards model, presented as HR (95% CI) for categorical BMI (see online Resource 2 in Study II). The interaction between linear BMI and smoking status was significant for incidence of all cancers combined in women (p =0.01). High BMI in women was associated with an increased overall cancer risk in never smokers but a reduced risk in smokers (see online Resource 3 in Study II).

**Threshold of BMI in relation to incidence of cancer**

Threshold values corresponding to a steeper increase in incidence of cancer were detected at a BMI of 25.49 kg/m² for lung cancer in men, of 24.94 kg/m² for breast cancer in women, and of 24.43 and 28.54 kg/m² for all cancers combined in women (see Figure 1 in Study II).
5.5 Comparison of strengths of different anthropometric measures of obesity in relation to CVD mortality (Study IV)

Baseline characteristics of the cohorts and the follow-up data are presented in Table 2. Table 4 shows that old age, high distribution of anthropometric measures of obesity and leisure-time physical inactivity were significantly associated with CVD mortality. When controlling for baseline age and cohort, most anthropometric measures of obesity exhibited significant correlations with each other (Pearson’s partial correlation coefficients 0.47–0.96, except for weak positive correlation between ABSI and BMI, 0.15 and 0.11 for men and women, respectively, Table 8, unpublished results in Study IV).

Table 8 Pearson’s partial correlation coefficients between anthropometric indicators adjusted for baseline age and cohort (Study IV)*

<table>
<thead>
<tr>
<th></th>
<th>BMI</th>
<th>WC</th>
<th>WHR</th>
<th>WSR</th>
<th>ABSI</th>
<th>WHHR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>1.00</td>
<td>0.88</td>
<td>0.62</td>
<td>0.89</td>
<td>0.15</td>
<td>0.56</td>
</tr>
<tr>
<td>WC</td>
<td>0.88</td>
<td>1.00</td>
<td>0.80</td>
<td>0.94</td>
<td>0.56</td>
<td>0.61</td>
</tr>
<tr>
<td>WHR</td>
<td>0.62</td>
<td>0.80</td>
<td>1.00</td>
<td>0.80</td>
<td>0.66</td>
<td>0.88</td>
</tr>
<tr>
<td>WSR</td>
<td>0.89</td>
<td>0.94</td>
<td>0.80</td>
<td>1.00</td>
<td>0.54</td>
<td>0.78</td>
</tr>
<tr>
<td>ABSI</td>
<td>0.15</td>
<td>0.56</td>
<td>0.66</td>
<td>0.54</td>
<td>1.00</td>
<td>0.55</td>
</tr>
<tr>
<td>WHHR</td>
<td>0.56</td>
<td>0.61</td>
<td>0.88</td>
<td>0.78</td>
<td>0.55</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>1.00</td>
<td>0.85</td>
<td>0.47</td>
<td>0.87</td>
<td>0.11</td>
<td>0.48</td>
</tr>
<tr>
<td>WC</td>
<td>0.85</td>
<td>1.00</td>
<td>0.78</td>
<td>0.96</td>
<td>0.59</td>
<td>0.68</td>
</tr>
<tr>
<td>WHR</td>
<td>0.47</td>
<td>0.78</td>
<td>1.00</td>
<td>0.77</td>
<td>0.78</td>
<td>0.92</td>
</tr>
<tr>
<td>WSR</td>
<td>0.87</td>
<td>0.96</td>
<td>0.77</td>
<td>1.00</td>
<td>0.57</td>
<td>0.78</td>
</tr>
<tr>
<td>ABSI</td>
<td>0.11</td>
<td>0.59</td>
<td>0.78</td>
<td>0.57</td>
<td>1.00</td>
<td>0.69</td>
</tr>
<tr>
<td>WHHR</td>
<td>0.48</td>
<td>0.68</td>
<td>0.92</td>
<td>0.78</td>
<td>0.69</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; WSR, waist-to-stature ratio; ABSI, A Body Shape Index; WHHR, waist-to-hip-to-height ratio.

*P <0.001 for all indicators.

A one-standard-deviation increase in all obesity indicators were significantly associated with a more than 19% increase in CVD mortality risk in both men ad women (see Table 3 in Study IV). The prediction for CVD mortality was stronger with anthropometric measures of abdominal obesity than with BMI or ABSI (p <0.05 for all paired homogeneity tests). WSR/WHtR appeared to be the strongest predictor among all the indicators, with a linear positive relationship with CVD mortality in both men and women. The main results remained when analyses were performed after the first 5 years of follow-up were excluded (see Table 3 in Study IV). The increased risk of CVD mortality in relation to anthropometric measures of abdominal obesity was independent of BMI levels (see Table 4 in Study IV).
5.6 Sex differences between obesity and CVD mortality (Study V)

Table 2 provides baseline characteristics of the cohorts and the follow-up data. Lean women were younger, more abnormally obese and had a low prevalence of diabetes, while obese women were older, less abnormally obese and had a higher prevalence of diabetes at baseline, compared with their male counterparts (see Table 2 in Study V). More men than women were smokers and physically active. Men tended to have higher mean values of systolic blood pressure and FPG, and a worse lipid profile than women, regardless of BMI categories. Similar sex-differences were observed among non-diabetic individuals (see online Table S1 in Study V). Diabetic men tended to be older and less physically active than diabetic women. Similar sex-differences were observed for the categories of abdominal obesity defined by sex-specific quartiles of WC, WHR and WHtR (see online Table S2 in Study V).

During the median follow-up of 7.9 years, 945 (4.0%) men and 339 (1.5%) women died from CVD. Absolute rates and age-adjusted and multivariate-adjusted HRs for CVD mortality are shown across BMI categories or sex-specific quartiles of anthropometric measures of abdominal obesity (see Table 3 in Study V). Men had higher CVD mortality rates and higher hazard ratios across BMI categories, and categories of abdominal obesity than women, but the sex difference tended to be attenuated in the obese categories. For CVD mortality, the interaction was statistically significant between sex and WC (p =0.02), and WHtR (p =0.01), but not significant with BMI and WHR. For most studies, study-specific HRs were within 10% of the pooled estimate, although there was evidence of heterogeneity among studies ($I^2 =95.5\%$, p <0.05, see online Table S3 in Study V). However, exclusion of any study from the analysis had little overall influence on the main results (see online Table S4 in Study V). The findings persisted when the analysis was restricted to individuals with the first five years of follow-up excluded, or without baseline diabetes, but the sex-obesity interaction was no longer significant (see Table 4 in Study V). The sex difference among people with baseline diabetes diminished especially in the non-obese categories.

The findings for BMI categories were not substantially altered when the analysis was repeated with additional adjusting for anthropometric measures of abdominal obesity (see online Table S5 in Study V). Multivariate adjustment for other CVD risk factors such as systolic blood pressure, FPG, TG, HDL-C and Total-C decreased the HRs in each obesity category for both men and women but the sex difference remained unchanged (see online Table S6 in Study V).
6 DISCUSSION

6.1 Summary of main findings

BMI, WC and WHtR showed J-shaped associations with all-cause mortality (Studies I and III), whereas WHR, ABSI and WHHR demonstrated positive linear associations (Study III). BMI had a J- or U-shaped relationship with CVD mortality (Studies I and III), whereas anthropometric measures of abdominal obesity (WC, WHR, WHtR and WHHR) had a linear positive association (Study III). The U-shaped association between BMI and cancer mortality was not seen among non-smokers (Study I). Elevated BMI was significantly associated with higher risk of incidence of cancer of certain sites (Study II). High BMI in women was associated with an increased overall cancer risk in never smokers but a reduced risk in smokers (Study II). Anthropometric measures of abdominal obesity (WC, WHR, WSR/WHtR and WHHR) predicted CVD mortality better than BMI did (Study IV). Men had a higher CVD mortality than women in both obese and non-obese groups, but this sex difference diminished somewhat in obese individuals (Study V).
6.2 Fat accumulation and distribution in relation to CVD mortality

This study showed that both general obesity and abdominal obesity were significantly positively associated with an increased risk of CVD mortality. In addition to excessive fat accumulation, abnormal fat distribution might also contribute to the risk of CVD mortality. The threshold values, at which a steeper increase in CVD mortality was observed, may have important clinical implications in the context of definition of obesity based on clinical outcomes of CVD mortality.

Possible explanations

Obesity might be associated with a variety of cardiometabolic risk factors including hypertension, diabetes and dyslipidemia, which subsequently leads to CVD. Obesity might be associated with hypertension, through an increment in total blood volume and cardiac output caused by increased fat mass (195), abnormal activation of the renin-angiotensin system or the renin-angiotensin-aldosterone system (196-198), or enhancement of sympathetic nervous system activity (199-206). Obesity might be associated with insulin resistance (107,207), or by increasing the level of leptin (leptin resistance) (208,209), interleukin-6 (210,211), monocyte chemoattractant protein-1 (MCP-1) (212-214), tumor necrosis factor-α (TNF-α) (210,215,216), or glucose through decreased glucose uptake or utilization but increased hepatic glucogenesis (196), or by decreasing the level of adiponectin (217,218), which subsequently results in diabetes.

Obesity might also play an important role in dyslipidemia, through enhancement of hepatic synthesis of TG, very low density lipoprotein cholesterol and LDL-C, but inhibiting synthesis of HDL-C (210,219-222), which subsequently leads to CVD (223-225). Obesity might also mediate atherosclerosis through plasminogen activator inhibitor-1 (PAI-1) (226,227). In Study III, the relationship between anthropometric measures of obesity and CVD mortality was not substantially altered after additional adjustment for one or more other CVD risk factors, including hypertension, diabetes and dyslipidemia.

Adipose tissue is also a highly active metabolic and endocrine organ, which expresses and secretes a variety of bioactive factors including leptin, adiponectin and other cytokines (149,228) which exerts more detrimental effects on CVD and might partly explain the greater contribution of anthropometric measures of abdominal obesity to the risk of CVD mortality than BMI. Abdominal obesity, in particular, is associated with deficiency of estrogens or testosterone (229,230), although the causal link still needs to be established (144,231). Deficiency of estrogens or testosterone has been consistently found to be associated with an increased risk of CVD (231,232). Increased leptin and decreased adiponectin levels were observed in obese individuals (233,234), but the expression
of these cytokines differed between subcutaneous and intra-abdominal fat depots (147, 235, 236). The latter were prone to empty their free fatty acids directly into the portal vein (219), exposing the liver to high concentrations of free fatty acids, which might lead to hyperinsulinaemia, dyslipidemia or hypertension (237). Thus, intra-abdominal fat is believed to be the main pathogenic fat depot that has the clinical relevance to CVD (238), particularly being more metabolically active than adipose depots located in the hip, thigh or buttocks (239). Fat could also be stored in other organs called ectopic fat depots, for example, in the liver, skeletal muscle, heart and pancreas (240, 241). In this regard, several studies have found that ectopic fat and intra-abdominal fat each contributes independently to the metabolic complications of abdominal obesity (240, 242-244).

It appears that people with the same WC would have the same CVD risk regardless of differences in height, which is invalid when the percentage of fat are higher for shorter individuals compared with taller counterparts given the same BMI (245). Some variations have been reported in the WC measurement. This may introduce a bias in absolute values of WC between studies, but less likely misclassification of individuals within a single study. A recent systematic review showed that variations in anatomic locations of WC measurement failed to influence clinical outcomes regarding mortality from all causes and CVD (246).

**Threshold for abdominal obesity**

The threshold values, at which a steeper increase in CVD mortality was observed, may have important clinical implications in the context of definition of abdominal obesity based on the clinical outcomes of mortality (Study III). Currently, the most often used definitions for abdominal obesity among Caucasians are WC of 102 cm and 88 cm (82), or 94 cm and 80 cm (83), or WHR of 0.95 and 0.80 (82) in men and in women, respectively. These existing cut-off values have, however, been determined arbitrarily based on analysis of the trade-offs between sensitivity and specificity for discrimination of diabetes or metabolic syndrome (84). Most of these previous studies were cross-sectional (82).
6.3 Sex differences in relationship between obesity and CVD mortality

Men had higher CVD mortality than women across all categories of anthropometric measures of obesity. Men tended to have a higher prevalence of abnormal levels of conventional CVD risk factors than women, such as hypertension, smoking, diabetes, lipid abnormalities and obesity (96,97). There is substantial evidence of sex differences in cardiac autonomic modulation (132-135), lipid and glucose metabolism (136-139), sex hormones (134,140-144) and cytokines (145-149), that might partially explain the sex difference in CVD mortality in this study. On average, middle-aged women have augmented sympathetic inhibition, higher cardiac vagal tone, higher heart rate variability, lower susceptibility to arrhythmias, and more decreased myocardial contractility than men (132,133,150), leading to a preponderance of vagal over sympathetic control of cardiac function (132-135). Before menopause, middle-aged women generally have lower levels of blood pressure, serum Total-C and LDL-C, TG and apolipoprotein B and higher levels of HDL-C and apolipoprotein A-I than men (136,151-153), although Total-C and LDL-C increase in women after menopause (151,152). Men tend to have higher fasting and lower post-challenge insulin levels than women (138,247), which is not fully explained by differences in fasting and post-challenge glucose levels between sexes (247). Additionally, adult men tend to have a higher prevalence of insulin resistance than women (137,139).

Sex hormones might play important roles in determining body fat mass and its distribution (141,144), exert multiple direct and indirect effects on insulin and glucose homeostasis or on cardiovascular physiology (134,140,142,143). Specifically, estrogen increases fat deposition whereas testosterone inhibits fat deposition, and accordingly, men tend to have less overall body fat than women (144), however, the distribution differs between the sexes. Men tend to have more fat in the abdominal region, even among normal weight or non-obese ones, which may be predominantly due to the accumulation of more visceral fat in men than in women during puberty (248). Women tend to accumulate more subcutaneous fat but less intra-abdominal fat than men probably due to the effects of estrogen by preventing androgen effects, with less androgen receptors in subcutaneous adipose tissue than in VAT (249,250). Intra-abdominal fat is believed to be the main pathogenic fat depot with clinical relevance to CVD (238), particularly being more metabolically active than adipose depots located in the hip, thigh or buttocks (239). Clinical studies have shown that there is higher intra-abdominal fat accumulation in men than in women for a given level of BMI, WC or WHR (251-253). Adult women tend to have a larger hip circumference than men (254), and thus have metabolically protective physiology of gluteofemoral subcutaneous fat mass, perhaps by trapping excess fatty acids and preventing chronic exposure to elevated lipid
levels, or through a beneficial adipokine profile (leptin and adiponectin) (255). It remains unclear whether CVD risk differs by site of subcutaneous fat accumulation.

Adipose tissue is a highly active metabolic and endocrine organ, which expresses and secretes a variety of bioactive factors including leptin, adiponectin and other cytokines (149,228), which might also contribute to the sex difference in CVD mortality. Women tend to have higher circulating leptin levels and higher adiponectin levels than men (145-148). Hyperleptinemia could be a sign of resistance to normal leptin signaling regulating food intake and satiety, which is believed to be a non-physiological state that could be associated with increased risks of diabetes, hypertension and CVD (233). Additionally, hypoadiponectinemia has been found to be associated with increased risks of both diabetes and CVD (256,257).

Obesity is associated with increased sympathetic activity and decreased vagal activity (258,259), hyperglycemia, insulin resistance (107,209), and is accompanied by chronic low-grade inflammation (149,260), hypertension and dyslipidemia (136,261,262), all of which might predispose to CVD. Abdominal obesity, in particular, is associated with deficiency of estrogens or testosterone (229,230), although the causal link still needs to be established (144,231). Deficiency of estrogens or testosterone has been consistently found to be associated with an increased risk of CVD (231,232). Increased leptin and decreased adiponectin levels were observed in obese individuals (233,234), but expression of these cytokines differed between subcutaneous and intra-abdominal fat depots (147,235,236).

Interestingly, the sex difference in CVD mortality appears to somewhat diminish in obese individuals, although misclassification bias between obese and non-obese individuals might occur due to sex differences in fat distribution, probably enhanced by disturbances of glucose metabolism. Mechanisms of sex differences in CVD mortality with obesity are poorly understood. In this study, the attenuation of sex differences in CVD mortality among obese individuals remained after adjustment of baseline age or other conventional CVD risk factors, or among non-diabetic individuals even when using other measures of abdominal obesity. The interactions of sex with anthropometric measures were, however, statistically significant only with WC and WHtR in the whole study population and not significant with any of the anthropometric measures in non-diabetic individuals, which suggests an effect modification by diabetes. Several studies have shown an attenuation of sex differences in CVD risk once individuals getting diabetes (96,98-100,102), perhaps as a consequence of diabetes inducing higher levels of inflammatory markers and impairment of higher rates of nitric oxide release in women compared with men, resulting in reduced protective effects of estrogen on body fat distribution, insulin action, glucose homeostasis and substrate metabolism, or a more impaired endothelial function in women (140,154,263).
there could be other potential unknown CVD risk factors clustering in obese women due to their older age.

So far, most epidemiological studies have been conducted primarily on men, leading to lesser prevention and treatment efforts in women (264), since CVD previously has been considered a ‘male disease’ because of an earlier average debut age in men than in women. Obese European women appear to be at a greater risk of psychological dysfunction than obese men probably due to increased societal pressures on women to be thin (265). Obese women tend to have left ventricular concentric and eccentric hypertrophy, whereas obese men have predominantly concentric hypertrophy, the latter probably being more strongly related to CVD mortality than eccentric hypertrophy (103).
6.4 Association between BMI and cancer outcomes

**BMI and cancer incidence**

This work showed that BMI had a non-threshold linear positive association with incidence of cancers of the colon, liver, kidney, bladder and all sites combined in men, and of cancers of the stomach, colon, gallbladder and ovary in women, an inverse association with incidence of cancers of the lung in men and the lung and breast in women, a J-shaped association with incidence of all cancers combined in women. In women, high BMI was associated with an increased overall cancer risk in never smokers but a reduced risk in smokers.

BMI was positively associated with incidence of colon cancer, but had no association with incidence of rectal cancer, which is in line with previous studies (32-37,59-62). Despite the fact that liver cancer and gallbladder cancer are relatively rare diseases, this study showed that BMI had a positive association with incidence of liver cancer in men and gallbladder cancer in women, which is in line with previous studies (33,36,71,73,74,131). Obese patients tend to have non-alcoholic fatty liver disease or gallstones, which might mediate carcinogenesis (74,266-269). In line with previous studies (11,36,42-44), this study showed that BMI was positively associated with incidence of kidney cancer in men, which may be due to promoting kidney damage through oxidative stress (270), diabetes or hypertension (271,272), or altered circulating concentrations of hormones (273,274). In this study, a non-significant linear positive association was observed between BMI and incidence of cancers of other sites including the bladder in men and the stomach and ovary in women. No association was observed between BMI and incidence of pancreatic cancer and cervical cancer. In recent studies, elevated BMI has been linked with an increased risk of incidence of cancers of the pancreas (11,33,38-41) and ovary (11,45-48), but the relationship between BMI and incidence of stomach cancer (11,36,72), bladder cancer (11,33,36,75,76) or cervical cancer remains controversial (11,33,73).

Taken together, excess body fat is associated with elevated insulin production, leading to the increase of insulin-like growth factor-I, or the secretion of a variety of cytokines and sex steroids, which subsequently stimulates cell proliferation and suppresses apoptosis, or chronic inflammation through cytokines and chemokines, including TNF-a, Interleukin-1b (IL-1b), IL-6 and chemokines such as MCP-1 and Interleukin 8 (275), and thus has been suggested to play a role in carcinogenesis (276-278).

As an endocrine organ, visceral adipose tissue has been suggested to play a more important role in carcinogenesis than the subcutaneous compartment (277). Since BMI does not accurately differentiate
fat mass from muscles, nor visceral fat from subcutaneous fat, it may be somehow misleading to use BMI as an index for obesity in relation to cancer incidence (279,280). Thus, investigations on body composition or fat distribution in relation to cancer incidence are needed but the feasibility to conduct such an observational study is low. This work showed that there was a significant inverse association between BMI and incidence of breast cancer in women. A decreasing risk association among premenopausal women but an increasing risk association among postmenopausal women has been reported in previous studies (11,33,63,66-70). Differences in these associations could be related to loss of normal ovarian function with reduced ovarian oestrogens production, by which obesity could reduce the tumor promoting effects in premenopausal women (281), but with enhanced oestrogen synthesis by adipose tissue that could contribute to an increased risk of breast cancer among postmenopausal women (279,282).

Elevated BMI was inversely associated with incidence of lung cancer, which is consistent with previous studies (11,36,49-51). Further, no significant interaction was detected between BMI and smoking status, which still needs to be confirmed for the possible metabolic effects of smoking on body weight (283,284). A recent epigenetic study reported that one allele of the fat mass and obesity-associated gene that had been linked with elevated BMI, was associated with a decreased risk of incidence of lung cancer, independent of smoking or weight loss due to the preclinical disease (285).

The possible explanation for the no association of BMI with incidence of prostate cancer observed in this study might be that although with lower levels of sex hormone-binding globulin (SHBG) detected which could be a risk factor for prostate cancer (33,52-58,68), obese men also possess lower levels of testosterone, which may exert a protective effect against the adverse effect of lower levels of SHBG (53,286). This study does not have information on stage of prostate cancer, but some studies have revealed that elevated BMI is associated with an increased risk of incidence of high-graded or aggressive prostate cancer (55,57,58), but with a decreased risk of incidence of localized or low-graded prostate cancer (56-58), the mutual coupling effect might be compensated.

**BMI and cancer mortality**

BMI had a U-shaped relationship with cancer mortality but disappeared among non-smokers, which showed no association. The relationship might be influenced by smoking status or improvement of cancer treatment. Further investigations are warranted to study site-specific cancer mortality.
6.5 Methodological considerations

AIC, as a decision criterion, is used for informal comparisons of models with differing numbers of parameters. In this study, AIC was used to judge the model fitness, the lower the AIC value the better the model fitness, with reduction of AIC evaluated by the LRT or a deviance difference test (192,193) (Studies II-IV). AIC difference ≥4 was considered to be considerably less supported relative to the lowest AIC value between non-nested models (194) (Study III). The shape of relationship between anthropometric measures of obesity and health outcomes was explored using both parametric models (conventional linear or polynomial models) and nonparametric models (the linear or restricted cubic spline regression model) (Studies II and III). Several important approaches were applied in our data analysis, including competing risk analysis and particularly paired homogeneity test, as one formal test of comparing strengths of different measures, which have not been used widely in this research field.

Age was used as the time-scale in Studies II-V, instead of follow-up time used in Study I, as many statisticians have recommended the use of age as the time-scale for the analysis of epidemiologic cohort studies with covariates of interest which were either time-dependent or strongly associated with age (287,288). Fat tissue mass increases through middle age and declines in old age (155,156). Fat is redistributed among different fat depots over time, especially during and after middle age, when fat redistributes from subcutaneous to intra-abdominal visceral depots (156-161). VAT accumulation increases more rapidly in women with aging, especially after menopause (141,162), despite the higher VAT accumulation in men than in women throughout the life span (162,163,249).

This study showed the interaction between BMI and smoking on cancer mortality and incidence of all cancers combined in women (Study I/II). Smoking is associated with both a lower body weight and an increased risk of mortality, and is interrelated with obesity in relation to mortality (16,176-178). Several recent studies have suggested that cigarette smoking aggravates abdominal obesity (164-168), perhaps through simultaneously inhibiting lipoprotein lipase activity and increasing cortisol levels (167,168). This study found a reduced visceral fat accumulation in Turkish female smokers (169). Several studies have identified cigarette smoking as a risk factor for sarcopenia (289-291), which is characterized by a muscle atrophy, along with a reduction in muscle tissue quality, a replacement of muscle fibres with fat, an increase in fibrosis, changes in muscle metabolism, oxidative stress, and degeneration of the neuromuscular junction and leading to progressive loss of muscle function and frailty (292), although the cellular and molecular mechanisms leading to smoking-induced muscle breakdown still remains elusive.
Limited evidence indicates that leisure-time physical inactivity might play an intermediate role in the relationship of anthropometric measures of abdominal obesity with mortality (186), and weaken, but not eliminate, the risk associated with excess weight (176). No significant interaction was detected between anthropometric measure of obesity and leisure-time physical activity (Studies II-V). In addition, no substantial influence was observed when further adjusting for education levels in Study II.

This study was based on several European population- or occupation-based prospective studies, with large sample size, long follow-up, reliable assessment of end-points, and detailed assessment of lifestyle variables, thus having sufficient power to investigate the association between anthropometric measurements and the risk of mortality (Studies I and III-V). Information on incidence of cancers was obtained from the FCR (Study II). The data coverage in the FCR is virtually complete, 99% for solid tumours, and the data accuracy is high as previously validated by different researchers (190).

This study does not have data on changes in anthropometric measurements before the baseline and during the follow-up, which makes it impossible to exclude the possibility of ‘reverse causation’ (106,187). In particular, this study showed that men who died within the first five years of follow-up had slightly lower age-adjusted mean values of baseline BMI than other men (Study III). Potential benefits of a lower BMI might be offset by the negative effect associated with weight loss. The potential influence of reverse causality was checked by excluding the deaths within the first five years of follow-up, or excluding the first five years of follow-up, and the results were not substantially altered (Studies I and III-V). Similarly, the results were not substantially altered much after excluding the first five years of follow-up in Study II.

This study does not have precise information on menopausal status and hormone therapies that would have been potentially affected the development of female breast cancer (63,66,67,69,70), or sex differences in obesity with CVD mortality. In addition, this study does not have information on several lifestyles or behaviour factors, for instance, dietary factors or alcohol consumption, which might contribute to obesity, and is an independent etiologic factor for several cancers, especially for stomach cancer and liver cancer (73,293). There are relatively few cases among never smokers and hence cannot rule out the possibility of interactions between smoking and BMI in relation to incidence of lung cancer. Our data are based on Caucasian-originated European surveys, and further investigations are needed due to differences in constitutions of the causes of death across countries, or different percentage of body fat across ethnic groups (294).
7 CONCLUSIONS AND FUTURE DIRECTIONS

This study confirmed the deleterious effect of obesity on mortality from various causes and incidence of cancers of certain sites. Anthropometric measures of abdominal obesity (WC, WHR, WHtR and WHHR) predicted CVD mortality better than BMI, which may imply a more important role of fat distribution than fat accumulation and also an effective obesity prevention strategy. Men had higher CVD mortality than women across all categories of anthropometric measures of obesity, which further supports the view of higher intra-abdominal fat accumulation in men than in women, even in non-obese individuals. The sex difference in CVD mortality was slightly attenuated in obese individuals, irrespective of diabetes status. This may indicate that women would gradually lose their cardiovascular advantage when they are obese, probably due to a more pronounced clustering of CVD risk factors among obese women.
8 ACKNOWLEDGEMENTS

This work was carried out at the Department of Public Health, Faculty of Medicine, University of Helsinki and Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland during the years 2009-2014. I hereby wish to thank the both institutes for providing me with excellent research facilities and creating the friendliest and most encouraging of working environment. I wish to express my gratitude to former director of Hjelt Institute, Professor Jaakko Kaprio, Adjunct Professor Ritva Halila and Professor Ossi Rahkonen for their quick and positive assistance.

I would like to express my sincere respect and deepest gratitude to my principal supervisor, Docent Qing Qiao. I have always benefited from her expert supervision, brilliant ideas, continuous enthusiasm, rigorous attitude to science, valuable advice and extensive knowledge. I would like also to thank her for providing me with research grants and the great opportunity to have received field research training by coordinating the Qingdao Diabetes Prevention Project in Qingdao, China during this time.

I am also most grateful to another supervisor, Professor Jaakko Tuomilehto, for his constructive guidance, generous support and inspired suggestions on my work during the years. He has always had shrewd insight and given valuable detailed comments and suggestions which have greatly helped to improve the work and create a better version of the manuscript and thesis. I always feel so lucky to have worked with the two excellent supervisors over these years.

I would like to thank the official reviewers of the dissertation, adjunct Professor Tea Lallukka and adjunct Professor Kai Savonen, for their careful work and valuable comments and suggestions, and Professor Per Wändell for accepting the role of Opponent in my thesis defence.

I owe my deep gratitude to all the researchers of the DECODE and FINRISK Studies and all the coauthors of my manuscript for their genuine interests, prompt response and skillful comments that greatly contributed to my manuscript. A special thank goes to Docent Janne Pitkäniemi, Professor Eero Pukkala, Professor Timo Hakulinen, Dr. Tadeusz Dyba and Dr. Vladislav Moltchanov who have actively participated in this work and kindly provided me with great helps.

I greatly appreciate Professor Zengchang Pang for his recommendation and introducing me to Qing and Jaakko. I wish to express my warm thanks to my colleagues and friends, Dr. Weiguo Gao, Dr. Lei Zhang, Dr. Regzedmaa Nyamdorj, M.Sci. Feng Ning, M.Sci. Yanlei Zhang, Dr. Xianghai Zhou, Dr. Haining Wang, M.Sci. Liang He who have always given me generous help and supports in my work and life in Finland. Meanwhile, I give my special thank to Mrs. Pirjo Saastamoinen for
her kind help in preparing for the abstract of this work in Finnish, and Mrs. Pirkko Särkijärvi and Mrs. Sirkka Koskinen for their help with other practical matters related to the work.

My deepest debt of gratitude is to my parents, my wife, my sister and brother-in-law for their unlimited love and support throughout these years here.

Helsinki, March 2015
Xin Song
9 REFERENCES


(8) Czernichow S, Kengne AP, Stamatakis E, Hamer M, Batty GD. Body mass index, waist circumference and waist-hip ratio: which is the better discriminator of cardiovascular disease mortality risk?: evidence from an individual-participant meta-analysis of 82 864 participants from nine cohort studies. Obes Rev 2011 Sep;12(9):680-687.


71


(81) Parikh RM, Joshi SR, Pandia K. Index of central obesity is better than waist circumference in defining metabolic syndrome. Metab Syndr Relat Disord 2009 Dec;7(6):525-527.


(208) Bjorbaek C, Kahn BB. Leptin signaling in the central nervous system and the periphery. Recent Prog Horm Res 2004;59:305-331.


APPENDIX

Studies and investigators in this collaborative study are:

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

**Finland East-West Study:** A. Nissinen\textsuperscript{1}, J. Pekkanen\textsuperscript{1}, J. Tuomilehto\textsuperscript{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, Finland.

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

**Finland National FINRISK 1987, 1992 and 1997 Cohorts:** J. Tuomilehto\textsuperscript{1,2,3}, P. Jousilahti\textsuperscript{1}, J. Lindström\textsuperscript{1}. 1. Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki; 2. Center for Vascular Prevention, Danube University Krems, Krems, Austria; 3 King Abdulaziz University, Jeddah, Saudi Arabia.

**Finland National FINRISK 2002 Study:** J. Tuomilehto\textsuperscript{1,2,3}, T. Laatikainen\textsuperscript{1,4,5}, M. Peltonen\textsuperscript{1}, J. Lindström\textsuperscript{1}. 1. Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki; 2. Center for Vascular Prevention, Danube University Krems, Krems, Austria; 3 King Abdulaziz University, Jeddah, Saudi Arabia; 4. Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland; 5. Hospital Distric of North Karelia, Joensuu, Finland.

**Finland Oulu Study:** S Keinänen-Kiukaanniemi\textsuperscript{1,2,3}, U. Rajala\textsuperscript{1}, M. Laakso\textsuperscript{1,3}. 1. The Institute of Health Sciences, University of Oulu, Oulu; 2. Oulu Health Centre; 3. Oulu University Hospital, Unit of General Practice.

**Finland Vantaa Study:** R. Tilvis\textsuperscript{1}, J. Tuomilehto\textsuperscript{2,3}, 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. University of Iceland, Reykjavik, Iceland; Icelandic Heart Association, Kopavogur, Iceland; Landspitali-Univerisity Hospital, Reykjavik, Iceland.

**Israel GOH-I Study:** R. Dankner. Unit for Cardiovascular Epidemiology, The Gertner Institute, Sheba Medical Center, Tel Hashomer, Israel; Division of Epidemiology and Prevention, School of Public Health, Sackler School of Medicine, Tel Aviv University, Israel.
**Italy Cremona Study:** M.P. Garancini¹, G. Calori¹, G. Ruotolo¹,², S. Mannino³, M. Villa³. 1. Division of Metabolic and Cardiovascular Diseases, San Raffaele Scientific Institute, Milan, Italy; 2. AstraZeneca R&D Mölndal, Sweden; 3. ASL Provincia di Cremona, Cremona.

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

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

**Sweden Northern Sweden MONICA Survey:** S. Söderberg¹,², M. Eliasson¹, 1. Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; 2. Baker IDI Heart and Diabetes Institute, Melbourne, Australia.

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

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

**The Netherlands The Hoorn Study:** J.M. Dekker¹, G. Nijpels¹, C.D.A. Stehouwer². 1. Department of Epidemiology and Biostatistics and the EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands; 2. Department of Internal Medicine and Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, The Netherlands.

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

**Turkey Turkish Adult Risk Factor Study (TARFS):** A Onat. 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.

**United Kingdom Newcastle Heart Project:** N. Unwin¹, N. Ahmad¹, K.G.M.M. Alberti², L. Hayes¹, 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.

**United Kingdom The 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.
United Kingdom Whitehall II Study: M.G. Marmot\textsuperscript{1}, A.G. Tabák\textsuperscript{1,2}, M. Kivimäki\textsuperscript{1,3}, E.J. Brunner\textsuperscript{1}, D.R. Witte\textsuperscript{1,4}, 1. Department of Epidemiology and Public Health, University College London, London, UK; 2. Semmelweis University Faculty of Medicine, 1\textsuperscript{st} Department of Medicine, Budapest, Hungary; 3. Finnish Institute of Occupational Health, Helsinki, Finland; 4. Steno Diabetes Center, Gentofte, Denmark.