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Relationship between body mass index and mortality among Europeans

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24

25 Abstract

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

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

32 Results: Over a median follow-up of 16.8 years, 29 071 participants died, 13 502 from
33 CVD and 8 748 from cancers of all types. All-cause and cancer mortality showed a
34 U-shaped relationship: decreased first, leveled off, and then increased with increasing BMI
35 with the lowest mortality risk approximately between 23.0 to 28.0 kg/m² of BMI in men
36 and 21.0 to 28.0 kg/m² in women. The U-shaped relationship hold for all-cause mortality
37 but disappeared for cancer mortality among non-smokers. The CVD mortality was constant
38 until a BMI of approximately 28.0 kg/m² and then increased gradually in both men and
39 women, which was independent of age, cohort and smoking status.

40 Conclusions: A U-shaped relationship of BMI with all-cause mortality but a graded
41 relationship with CVD mortality at BMI greater than 28.0 kg/m² was detected. The
42 relationship between cancer mortality and BMI largely depended on smoking status, and
43 need to be further investigated with site-specific cancers.

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

45 Introduction

46 Obesity had become the sixth most important risk factor contributing to the overall burden
47 of various diseases worldwide (Ezzati *et al.*,2002) according to the World Health Organization
48 (WHO) 2002 report. It has been well recognized that obesity defined as having a body
49 mass index (BMI) equal or higher than 30 kg/m² is associated with many diseases that
50 contribute to premature death, such as cardiovascular disease (CVD), diabetes and certain
51 types of cancers (Hubert *et al.*,1983; Kurth *et al.*,2002; Nyamdorj *et al.*,2009; Colditz *et al.*,1990;
52 Batty *et al.*,2005; Calle *et al.*,2003). However, the association of BMI with mortality of various
53 causes is controversial: a positive(Lee *et al.*,1993), a J-shaped(Manson *et al.*,1995; Calle *et*
54 *al.*,1999; Moore *et al.*,2008) or U-shaped(Seidell *et al.*,1996; Shaper *et al.*,1997; Rosengren *et al.*,1999;
55 Baik *et al.*,2000; Flegal *et al.*,2005; Breeze *et al.*,2006; Pischon *et al.*,2008; Klenk *et al.*,2009) relation
56 with all-cause mortality; a positive(Lee *et al.*,1993; Seidell *et al.*,1996; Kivimaki *et al.*,2008; Flegal
57 *et al.*,2007), or a J-shaped(Jonsson *et al.*,2002) relation with CVD mortality; a positive(Calle *et*
58 *al.*,1999; Calle *et al.*,2003; Hu *et al.*,2004; Berrington de Gonzalez *et al.*, 2010), a J-shaped(Reeves *et*
59 *al.*,2007) relation, and no association(Baik *et al.*,2000; Meyer *et al.*,2002; Batty *et al.*,2005; Flegal *et*
60 *al.*,2007) with cancer mortality have all been reported.

61 Recently, the WHO definition for overweight has been questioned by several studies
62 which showed that overweight (BMI between 25.0 and 30 kg/m²) was not associated with
63 increased risk of death (Flegal *et al.*,2005; Lenz *et al.*,2009; McGee & Diverse Populations
64 Collaboration,2005). The controversy between previous studies may be due to differences in
65 study design and study populations. To clarify shape of the relationship of BMI with
66 mortality of various causes may extend our understanding on the role of underweight,

67 overweight and obesity in relation to the development of diseases and mortality of various
68 causes, and could help to improve the definition of underweight and obesity. This is
69 important considering the increase in the prevalence of obesity and its adverse health
70 consequences worldwide. In the current study, the BMI-mortality relationship is
71 investigated based on the data of the large Diabetes Epidemiology: Collaborative analysis
72 Of Diagnostic criteria in Europe (DECODE) study.

73 Subjects and methods

74 Study population

75 Data were collected from 33 prospective studies in 11 European countries and the study
76 population comprised 142 885 Europeans including 76 226 men and 66 659 women aged
77 24-99 at baseline. This involved the completion of a self-reported questionnaire on
78 smoking and participation in a medical examination to measure body weight and height,
79 described in detail in previous DECODE publications (DECODE, 2001). Participants with
80 missing data on body weight and height (n=2 588), and on smoking status (n=4 490) were
81 excluded. Subjects who had emigrated but the dates of the emigration were recorded were
82 treated as censored cases. Individuals without exact date of emigration or completely lost to
83 follow-up were also excluded (n=50). Thus the final sample for this analysis included a
84 total of 135 745 participants (72 947 men and 62 798 women) with a median follow-up of
85 16.8 years.

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

89 was approved by the ethics committee of the National Institute for Health and Welfare.

90 Definition of covariates

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

102 Definition of fatal events

103 Vital status and cause of deaths were recorded in all of the studies included. CVD mortality
104 was defined according to the International Classification of Disease (ICD) codes 331, 420
105 (7th revision), 401-448 (8th or 9th revision), and codes I10-I79 (10th revision). Cancer
106 mortality was defined as cancers of all types by ICD codes 158, 162, 181, 193, 199, 200,
107 204 (7th revision), 140-239 (8th or 9th revision) and codes C00-C97, D00-D09 (10th
108 revision).

109 Statistical analysis

110 Participants were classified into the following 18 BMI categories of <19.0, 19.0-19.9,

111 20.0-20.9, 21.0-21.9, 22.0-22.9, 23.0-23.9, 24.0-24.9, 25.0-25.9, 26.0-26.9, 27.0-27.9,
112 28.0-28.9, 29.0-29.9, 30.0-30.9, 31.0-31.9, 32.0-32.9, 33.0-33.9, 34.0-34.9, and ≥ 35.0
113 kg/m^2 . Crude mortality was calculated and plotted for each BMI category. The category
114 with the lowest mortality rate was chosen as the reference category to estimate the relative
115 risk or hazard ratio (HR) using Cox proportional hazards models adjusting for age, cohort,
116 and smoking status. A sensitivity analysis by excluding the participants who died in the
117 first five-year follow-up was performed to assess the reverse causation. Because current
118 smokers were leaner and had increased mortality compared to current non-smokers in this
119 study, a further analysis was performed stratified by current smoking status using nine
120 BMI categories of <19.0 , 19.0-21.0, 21.0-23.0, 23.0-25.0, 25.0-27.0, 27.0-29.0, 29.0-31.0,
121 31.0-33.0 and $\geq 33.0 \text{ kg/m}^2$ to explore to what extent smoking has contributed to the
122 increased mortality in the low BMI categories. The formal interaction between smoking
123 status and the BMI categories was also tested. In addition, we performed analyses for
124 competing risks using STATA 11.0 to estimate the probability of the CVD mortality in the
125 presence of competing risk of cancer mortality, or vice versa.

126 Results

127 Baseline characteristics of the cohorts are presented in table 1. Over a median follow-up of
128 16.8 years, 29 071 participants died, 13 502 from CVD and 8 748 from cancers. Old age
129 was associated with both CVD and cancer mortality (table 2). Current smoking was
130 associated with cancer mortality in both genders and with CVD mortality in men but not in
131 women. Mean BMI was significantly higher in individuals who died of CVD but not in
132 those who died of cancers compared with those who were still alive.

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

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

154 Discussion

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

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

176 For CVD mortality, most studies have consistently reported a positive relationship at the

177 upper BMI levels, with varying cutoff values from 22.5 to 30.0 kg/m²(Lee *et al.*,1993; Seidell
178 *et al.*,1996; Kivimaki *et al.*,2008; Prospective Studies Collaboration,2009; Flegal *et al.*,2007). There
179 were two studies, however, showing a U-shaped relationship with the lowest CVD
180 mortality at the BMI interval of 20.0 to 29.9 kg/m² in Swedish men(Jonsson *et al.*,2002), and
181 22.5 to 24.9 kg/m² in Austrian adults(Klenk *et al.*,2009). Our study with a large sample size
182 showed a strong positive relationship between CVD mortality and BMI among
183 non-smokers at BMI levels above approximately 28.0 kg/m² in both men and women.

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

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

198 A relative limitation of the study is the lack of information on weight changes before the

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

212 In spite of a decrease in mortality, BMI has increased slightly during the last three
213 decades in Europe(Flegal *et al.*,2002; Hedley *et al.*,2004; Vartiainen *et al.*,2010) that might
214 suggest that cohort effects may play a role in our findings, however the increase in BMI in
215 the current study is too small to substantially affect the results (mean BMI 25.6 kg/m² in
216 the 1970s, 25.6 kg/m² in the 1980s and 26.3 kg/m² in the 1990s). The shift of the BMI
217 distribution towards the right in the general population can increase the risk of
218 obesity-related disorders such as diabetes and CVD, but its direct impact on mortality is not
219 straight forward, since mortality is a complex outcome of many factors including
220 occurrence of a disease and its treatment. Therefore, obesity defined by BMI maybe a

221 useful indicator for intervention for diabetes and CVD, but a poor measure of mortality
222 from all-causes and certain cancers. Considering the complex underlying causes of cancer
223 deaths and the vague relationship found in our study, further investigations are required to
224 study site-specific cancer mortality.

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

229 Conflict of interest

230 There are no conflicts of interest.

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303

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References

- 305 Baik I, Ascherio A, Rimm EB, Giovannucci E, Spiegelman D, Stampfer MJ *et al.*(2000).
306 Adiposity and mortality in men. *Am J Epidemiol* **152**,264-271.
- 307 Batty GD, Shipley MJ, Jarrett RJ, Breeze E, Marmot MG,Smith GD,(2005). Obesity and
308 overweight in relation to organ-specific cancer mortality in london (UK): Findings from the
309 original whitehall study. *Int J Obes (Lond)* **29**,1267-1274.
- 310 Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ *et*
311 *al.*,(2010). Body-mass index and mortality among 1.46 million white adults. *N Engl J Med*
312 **363**,2211-2219.
- 313 Breeze E, Clarke R, Shipley MJ, Marmot MG,Fletcher AE(2006). Cause-specific mortality
314 in old age in relation to body mass index in middle age and in old age: Follow-up of the
315 whitehall cohort of male civil servants. *Int J Epidemiol* **35**,169-178.
- 316 Calle EE, Thun MJ, Petrelli JM, Rodriguez C,Heath CJ(1999). Body-mass index and
317 mortality in a prospective cohort of U.S. adults. *N Engl J Med* **341**,1097-1105.
- 318 Calle EE, Rodriguez C, Walker-Thurmond K,Thun MJ(2003). Overweight, obesity, and
319 mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*
320 **348**,1625-1638.
- 321 Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA *et al.*,(1990).
322 Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* **132**,501-513.
- 323 DECODE Study Group, the European Diabetes Epidemiology Group (2001). Glucose
324 tolerance and cardiovascular mortality: Comparison of fasting and 2-hour diagnostic
325 criteria. *Arch Intern Med* **161**,397-405.
- 326 Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ,Comparative Risk
327 Assessment Collaborating Group (2002). Selected major risk factors and global and
328 regional burden of disease. *Lancet* **360**,1347-1360.
- 329 Flegal KM, Carroll MD, Ogden CL,Johnson CL,(2002). Prevalence and trends in obesity
330 among US adults, 1999-2000. *JAMA* **288**,1723-1727.
- 331 Flegal KM, Graubard BI, Williamson DF,Gail MH (2005). Excess deaths associated with
332 underweight, overweight, and obesity. *JAMA* **293**,1861-1867.
- 333 Flegal KM, Graubard BI, Williamson DF,Gail MH (2007). Cause-specific excess deaths
334 associated with underweight, overweight, and obesity. *JAMA* **298**,2028-2037.

- 335 Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM,(2004).
336 Prevalence of overweight and obesity among US children, adolescents, and adults,
337 1999-2002. *JAMA* **291**,2847-2850.
- 338 Hoover LW and Boote EJ,(2000). Longitudinal assessment of intra-abdominal fat in
339 postmenopausal women. *Ann N Y Acad Sci* **904**,520-525.
- 340 Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE,(2004). Adiposity as
341 compared with physical activity in predicting mortality among women. *N Engl J Med*
342 **351**,2694-2703.
- 343 Hubert HB, Feinleib M, McNamara PM, Castelli WP,(1983). Obesity as an independent
344 risk factor for cardiovascular disease: A 26-year follow-up of participants in the
345 framingham heart study. *Circulation* **67**,968-977.
- 346 Jonsson S, Hedblad B, Engstrom G, Nilsson P, Berglund G, Janzon L(2002). Influence of
347 obesity on cardiovascular risk. twenty-three-year follow-up of 22,025 men from an urban
348 swedish population. *Int J Obes Relat Metab Disord* **26**,1046-1053.
- 349 Kivimaki M, Ferrie JE, Batty GD, Davey Smith G, Elovainio M, Marmot MG *et al.*(2008).
350 Optimal form of operationalizing BMI in relation to all-cause and cause-specific mortality:
351 The original whitehall study. *Obesity (Silver Spring)* **16**,1926-1932.
- 352 Klenk J, Nagel G, Ulmer H, Strasak A, Concini H, Diem G *et al.*(2009). Body mass index
353 and mortality: Results of a cohort of 184,697 adults in austria. *Eur J Epidemiol* **24**,83-91.
- 354 Kurth T, Gaziano JM, Berger K, Kase CS, Rexrode KM, Cook NR *et al.*,(2002). Body
355 mass index and the risk of stroke in men. *Arch Intern Med* **162**,2557-2562.
- 356 Lawlor DA, Hart CL, Hole DJ, Davey Smith G (2006). Reverse causality and confounding
357 and the associations of overweight and obesity with mortality. *Obesity (Silver Spring)*
358 **14**,2294-2304.
- 359 Lee IM, Manson JE, Hennekens CH, Paffenbarger RJ(1993). Body weight and mortality. A
360 27-year follow-up of middle-aged men. *JAMA* **270**,2823-2828.
- 361 Lenz M, Richter T, Muhlhauser I (2009). The morbidity and mortality associated with
362 overweight and obesity in adulthood: A systematic review. *Dtsch Arztebl Int* **106**,641-648.
- 363 Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE *et al.*(1995).
364 Body weight and mortality among women. *N Engl J Med* **333**,677-685.
- 365 McGee DL and Diverse Populations Collaboration (2005). Body mass index and mortality:
366 A meta-analysis based on person-level data from twenty-six observational studies. *Ann*
367 *Epidemiol* **15**,87-97.

- 368 Meyer HE, Sogaard AJ, Tverdal A, Selmer RM, (2002). Body mass index and mortality:
369 The influence of physical activity and smoking. *Med Sci Sports Exerc* **34**,1065-1070.
- 370 Moore SC, Mayne ST, Graubard BI, Schatzkin A, Albanes D, Schairer C *et al.* (2008). Past
371 body mass index and risk of mortality among women. *Int J Obes (Lond)* **32**,730-739.
- 372 Nyamdorj R, Qiao Q, Soderberg S, Pitkaniemi JM, Zimmet PZ, Shaw JE *et al.*, (2009).
373 BMI compared with central obesity indicators as a predictor of diabetes incidence in
374 mauritius. *Obesity (Silver Spring)* **17**,342-348.
- 375 Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K *et al.*, (2008).
376 General and abdominal adiposity and risk of death in Europe. *N Engl J Med*
377 **359**,2105-2120.
- 378 Poehlman ET, Toth MJ, Gardner AW, (1995). Changes in energy balance and body
379 composition at menopause: A controlled longitudinal study. *Ann Intern Med*
380 **123**,673-675.
- 381 Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, Clarke R,
382 Emberson J *et al.* (2009). Body-mass index and cause-specific mortality in 900 000 adults:
383 Collaborative analyses of 57 prospective studies. *Lancet* **373**,1083-1096.
- 384 Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D *et al.* (2007). Cancer incidence
385 and mortality in relation to body mass index in the million women study: Cohort study.
386 *BMJ* **335**,1134.
- 387 Rosengren A, Wedel H, Wilhelmsen L (1999). Body weight and weight gain during adult
388 life in men in relation to coronary heart disease and mortality. A prospective population
389 study. *Eur Heart J* **20**,269-277.
- 390 Seidell JC, Verschuren WM, van Leer EM, Kromhout D (1996). Overweight, underweight,
391 and mortality. A prospective study of 48,287 men and women. *Arch Intern Med*
392 **156**,958-963.
- 393 Shaper AG, Wannamethee SG, Walker M (1997). Body weight: Implications for the
394 prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of
395 middle aged men. *BMJ* **314**,1311-1317.
- 396 Vartiainen E, Laatikainen T, Peltonen M, Juolevi A, Mannisto S, Sundvall J *et al.*, (2010).
397 Thirty-five-year trends in cardiovascular risk factors in finland. *Int J Epidemiol*
398 **39**,504-518.
- 399 Willett WC, Dietz WH, Colditz GA (1999). Guidelines for healthy weight. *N Engl J Med*
400 **341**,427-434.
- 401 -
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403 Figure legends

404 Figure 1 Crude mortality rate per 1000 PY (person-years) (open circles), age- and cohort-
405 adjusted hazard ratios (open triangles), and age-, cohort- and smoking- adjusted hazard
406 ratios (solid circles) with their 95% confidence intervals (vertical bars) for mortality
407 corresponding to a one unit increase in body mass index (BMI, kg/m²). In men, the BMI
408 reference category was 23.0-23.9 kg/m² for all-cause mortality, 20.0-20.9 kg/m² for CVD
409 mortality and 25.0-25.9 kg/m² for cancer mortality. In women, the BMI reference category
410 for all these three was 20.0-20.9 kg/m².

Body mass index and mortality among Europeans

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

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

Body mass index and mortality among Europeans

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

CVD, cardiovascular diseases; NA, not available.

Data are means (standard deviation) or as noted.

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

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

^a $P < 0.05$ for differences between Yes and No.

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

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

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

Body mass index and mortality among Europeans

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

Body mass index and mortality among Europeans

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

*Adjusted for age and cohort.

