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Obesity in young men and individual and combined risks of type 2 diabetes, cardiovascular morbidity, and death before 55 years of age: A Danish 33-year follow-up study

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Title: Obesity in young men and individual and combined risks of type 2 diabetes, cardiovascular morbidity, and death before 55 years of age: A Danish 33-year follow-up study

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ABSTRACT

Objectives: To examine the association between body mass index (BMI) in young adulthood and cardiovascular risks, including venous thromboembolism, before 55 years of age.

Design: Cohort study using population-based medical databases.

Setting: Outcomes registered from all hospitals in Denmark from 1977 onwards.

Participants: 6,502 males born in 1955 and eligible for conscription in Northern Denmark.

Main outcome measures: Follow-up began at subjects' 22nd birthday and continued until death, emigration, or 55 years of age, whichever came first. Using regression analyses, we calculated risks and hazard ratios, adjusting for cognitive test score and years of education.

Results: 48% of all obese young men (BMI: ≥30 kg/m^2) were either diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke, or venous thromboembolism or died before reaching 55 years of age. Comparing obese men with normal weight men (BMI: 18.5 to <25.0 kg/m^2), the risk difference for any outcome was 28% (95% confidence interval: 19% to 38%) and the hazard ratio was 3.0 (95% confidence interval: 2.3 to 4.0). Compared with normal weight, obesity was associated with an event rate that was increased more than 8-fold for type 2 diabetes, 4-fold for venous thromboembolism, and 2-fold for hypertension, myocardial infarction, and death.

Conclusions: In this cohort of young men, obesity was strongly associated with adverse cardiometabolic events before 55 years of age, including venous thromboembolism. Compared with those of normal weight, young obese men had an absolute risk increase for type 2 diabetes, cardiovascular morbidity or premature death of almost 30%.

Key words: Body mass index; diabetes mellitus type 2; hypertension; myocardial infarction; stroke; venous thromboembolism; premature death

INTRODUCTION

Tripling in prevalence over the last three decades and now exceeding 30% in the US,[1-3] obesity in young adulthood is as a major public health concern worldwide, leading to a shorter lifespan for today's children.[4] Despite the obesity epidemic, cardiovascular morbidity and mortality have continued to decrease in the Western world.[5 6]

Although obesity in adulthood is a risk factor for type 2 diabetes,[1-3 7] cardiovascular disease,[4 8] and mortality,[5 6 9] it remains unclear whether an elongated history of overweight, starting early in life, poses additional risks. Previous reports indicate that age modifies the effect of obesity on cardiovascular death, with greater impact in younger age groups, including childhood and young adulthood.[10 11] However, whereas obese children reduce their additional cardiovascular risks (compared with non-obese children) by ceasing to be overweight before adulthood,[12] new studies indicate that the risks among obese young adults persist independently of weight changes in later adulthood.[13 14] These findings emphasize the need to study the adverse outcomes associated with obesity within the age group of young adults specifically.

Several studies have examined the association between body mass index (BMI) in young adults and premature death.[10 13 15-24] Fewer studies have examined long-term risks of type 2 diabetes[14] and ischemic heart disease.[14 23 25] However, despite the link between atherosclerosis, metabolic syndrome, and venous thromboembolism,[26-28] none of the previous studies have included venous thromboembolism as an outcome. Moreover, estimates of the absolute risk, in addition to the relative risk, of adverse events are important for clinical decision making, particular when counselling patients on risk modification associated with weight, diet, and exercise. Nonetheless, no study has examined the combined risk of type 2 diabetes, numerous cardiovascular outcomes, and premature death in one study, thereby assessing the complete cardiometabolic risks associated with young adulthood obesity.

We therefore followed a cohort of 22-year old men for 33 years to examine the association

between BMI in young adulthood and the risk of type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before 55 years of age.

METHODS

Setting

We conducted this population-based cohort study in the Fifth Military Conscription District in Denmark, populated by approximately 700,000 inhabitants.[29] The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals and partial reimbursement for prescribed medications. Accurate and unambiguous individual-level linkage of all Danish registries is possible using the unique central personal registration (CPR) number assigned to all residents at birth or upon immigration.[30]

Study cohort

Nearly all Danish men have had to register with the military board for an examination of fitness to serve when reaching 18 years of age or shortly thereafter (median age 19 years).[31] In connection with the registration, all examinees complete a health questionnaire, in which they report chronic diseases that could preclude military service, *e.g.*, asthma, epilepsy or spinal osteochondrosis, but not obesity.[3] The Draft Board verifies such reports with health care providers, and men deemed ineligible for military service are excused from the draft at this point (approximately 15%).[32] Information obtained at the examination is registered and stored in regional and national databases.[29] Using a conscription research database, we identified all persons from the 1955 birth cohort who later appeared before the draft board in Northern Denmark (n=6,502).

Body mass index

All potential conscripts undergo a physical and mental examination. The physical examination includes measurements of height (without shoes) and body weight (wearing trunks only and using sliding scales and calibrated balances). Using these height and weight measurements, we calculated the BMI. Values of weight <45 kg (n=6) were considered to be data entry errors and recoded as missing. We categorized BMI as underweight (<18.5 kg/m^2), normal (18.5 to <25.0 kg/m^2), overweight (25.0 to <30.0 kg/m^2), or obese (≥30 kg/m^2).

Covariates

From the conscription database, we obtained data on cognitive function as measured by the validated Boerge Prien test.[31 33] The Boerge Prien test is a 78-item group intelligence test with four subscales (letter matrices, verbal analogies, number sequences, and geometric figures) and a single final score, recorded as the number of correctly answered items (range 0–78).[31] The scores are strongly correlated with conventional intelligence-test scores (*e.g.*, correlation of 0.82 with the Wechsler Adult Intelligence Scale).[31] Based on quartiles, we categorized the test scores as low (0–31), moderate (32–39), high (40–46), and very high (47–78).

From the conscription database, we also obtained information on years of education at the time of examination.[33] Based on quartiles, we categorized the education length as short, moderate, long, and very long.

Outcomes

The Danish National Registry of Patients records information on patients discharged from all Danish non-psychiatric hospitals since 1 January 1977 and from all emergency room and outpatient specialty clinic visits since 1995.[34] Each hospital discharge or outpatient visit is recorded in the registry with one primary diagnosis and one or more secondary diagnoses

classified according to the *International Classification of Diseases*, 8th revision (ICD-8) until the end of 1993 and the 10th revision (ICD-10) thereafter.[34]

Using the Danish National Registry of Patients, we identified all examinees with a first diagnosis of type 2 diabetes, hypertension, myocardial infarction, stroke (ischemic stroke, intracerebral haemorrhage, or subarachnoid haemorrhage), or venous thromboembolism (deep venous thromboembolism or pulmonary embolism). To ensure more complete identification of examinees with type 2 diabetes, we also searched the Aarhus University Prescription Database,[35] covering the study region, for any use of antidiabetic drugs from 1 January 1989 through 2010. ICD and ATC codes are provided as supplementary online material.

We obtained information on all-cause mortality from the Danish Civil Registration System.[30] This registry has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[30] Finally, a combined outcome was defined as the first-time occurrence of any of the individual outcomes.

Statistical analyses

Initially, we used descriptive statistics to characterize the study population by categories of BMI, cognitive test score, and years of education. To ensure that the Danish National Registry of Patients (initiated in 1977) would capture events, follow-up started at examinee´s 22nd birthday. We excluded all men who were censored between their date of examination and their 22nd birthday (17 died and 8 emigrated). Follow-up continued until first occurrence of an outcome, emigration, or 33 years of follow-up (*i.e.*, their 55th birthday), whichever came first. First, we illustrated graphically the association between BMI and the predicted cumulative incidence function for each outcome using the proportional subhazards model by Fine and Gray.[36] We used the pseudo-value method to calculate the 33-year risk for each BMI group, as well as the risk

differences compared with normal weight.[37] We treated death as a competing risk in all analyses of non-fatal outcomes.

We calculated rates for each BMI group and used Cox proportional hazards regression to compute hazard ratios associating BMI with all outcomes. BMI was analysed both as a categorical and continuous variable. For the categorical BMI variable, the proportional hazard assumption was assessed by log-log plots and Schoenfeld's test and found valid. We assessed the scale of the continuous BMI variable using fractional polynomials. There was no suggestion that BMI was not linear in the log hazard for the individual outcomes and was, thus, included as a linear term in these models. We repeated all regression analyses adjusting for cognitive test score and years of education. Because there was no recent validation study available for hypertension, we estimated the proportion of patients registered with hypertension in the Danish National Registry of Patients that also redeemed at least one prescription for antihypertensive medication (registered in the prescription database).

The study was approved by the Danish Data Protection Agency (2011-41-5807). All analyses were conducted in STATA® software version 12.1 (STATA, College Station, TX, USA).

RESULTS

Characteristics

The characteristics of the study population are presented in Table 1. We identified 6,502 male examinees from the 1955 birth cohort in Northern Denmark. Among these, 5407 (83%) were of normal weight, 353 (5%) were underweight, 639 (10%) were overweight, and 97 (1.5%) were obese. BMI ranged from a minimum of 14.4 kg/m^2 to a maximum of 42.7 kg/m^2. The median BMI was 21.7 kg/m^2 (interquartile range: 20.3 to 23.4 kg/m^2). Compared with men of normal weight (25%), a higher proportion of those who were overweight (32%) or obese (41%) scored low on the cognitive test. Also, compared with subjects of normal weight (24%), a higher proportion of

overweight (32%) or obese (33%) persons belonged to the lowest quartile of years of education. The validation analysis revealed that 88% of patients with a diagnosis of hypertension redeemed one or more prescriptions for antihypertensive medication.

Combined outcome

Compared with 20% of men of normal weight, 48% of all obese men were diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke, or venous thromboembolism or died before their 55-year birthday (Table 2 and Figure 1). After adjusting for cognitive test score and years of education, the absolute risk difference between the groups was 28% (95% confidence interval: 19% to 38%) and the hazard ratio was 3.0 (95% confidence interval: 2.3 to 4.0).

Individual outcomes

Obesity was strongly associated with all individual outcomes except stroke (Table 3 and Figure 2). With a risk difference of 22% (95% confidence interval: 13% to 31%) and hazard ratio of 8.2 (95% confidence interval: 5.4 to 12.3) the absolute and relative associations for obesity, compared with normal weight, were strongest for type 2 diabetes. However, there was also a more than 4-fold increased rate of venous thromboembolism and more than 2-fold increased rate of hypertension, myocardial infarction, and death. For stroke, there was a 40% increased rate among overweight persons. The wide confidence intervals made the association between obesity and stroke inconclusive. In the analysis of BMI as a continuous variable, a unit increase in BMI corresponded to an increased rate of approximately 5% for myocardial infarction, 10% for hypertension and venous thromboembolism, and 20% for type 2 diabetes (Table 4).

DISCUSSION

In this population-based 33-year follow-up study, we found that nearly half of all obese young men either were diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke, or venous thromboembolism or died before reaching 55 years of age. Obesity was associated with an event rate that, compared with normal weight, was increased more than 8-fold for type 2 diabetes, 4-fold for venous thromboembolism, and 2-fold for hypertension, myocardial infarction, and premature death. The strong association between young adulthood obesity and venous thromboembolism was of particular importance because it, to our knowledge, has not previously been reported. Obese subjects had a 3-fold increased event rate of any of these diseases compared with persons of normal weight, yielding a notable absolute risk increase of almost 30%. The magnitude of the relative and absolute risk estimates emphasize the major clinical and public health implications associated with obesity in young adulthood.

Strengths and limitations of study

Several issues should be considered when interpreting our results. With military examination in anticipation of conscription being mandatory and participation enforced by law, the population-based design reduced potential selection bias. We used measured instead of self-reported height and weight. Doing so, we eliminated differential misclassification of BMI, which may have biased other studies[13 16] because underweight people tend to overestimate their BMI and overweight people tend to underestimate their BMI.[38] The Danish Civil Registration System ensured complete follow-up of all examinees with accurate mortality data.[30] The tax-supported universal healthcare system allowed for complete ascertainment of all hospital admissions throughout the 33-year follow-up period. In addition to our estimate for hypertension (88%), the positive predictive values of diagnoses in the Danish National Registry of Patients have previously been validated and found to be approximately 90% for diabetes[39] and myocardial infarction,[39 40] and 80% for stroke,[39 41] and venous thromboembolism.[42]

There were, however, some limitations. Examinees had to survive from their examination date until start of follow-up at 22 years of age. Although BMI is a widely used proxy for adiposity, it does not distinguish adipose from muscle tissue nor does it take the anthropometric distribution of fat into account. Some degree of misclassification is therefore inevitable (for all studies on this topic). Nevertheless, BMI is a valuable tool to provide a standardized definition of obesity, allowing for a comparison of its associated risks across decades. Any potential underreporting of diabetes and hypertension in the Danish National Registry of Patients would provide underestimates of the absolute risks, and thus cannot explain the increased risks.

We cannot exclude confounding from exercise, diet, weight changes, and smoking. An advantage of studying mortality rates among young subjects is that adjustments for other conditions are largely unnecessary. Moreover, analyses of myocardial infarction and death should not adjust for hypercholesterolemia, hypertension, diabetes or other factors associated with the metabolic syndrome because all of these risk factors may be on the causal pathway.[43] We were unable to consider the impact of weight changes later in life. However, weight loss among obese or weight gain among normal weight conscripts would bias the results towards unity, and thus cannot explain our findings. Furthermore, other studies have found the associations between young adulthood BMI and coronary artery disease[14] and death[13] independent of later weight changes. Smoking is associated with low and not high BMI.[44] Thus, any unmeasured confounding from smoking would also tend to bias the results towards unity. Supporting the robustness of our results, previous studies have found similar mortality rates among smokers and non-smokers[17] or even higher mortality rates among non-smokers.[16] In addition, as a surrogate measure of lifestyle, we did adjust for cognitive test score and years of education. Finally, although the results derive from a study that included only young men, previous reports suggest the associations are likely also to hold for young women.[45]

Comparison with other studies

Our results are in line with previous reports on the individual outcomes. The increased premature mortality risk is consistent.[10 13 15-24] Among prior studies, a similar Swedish study on male conscripts with mean age of 18.7 years found an almost identical association between obesity and premature mortality (hazard ratio: 2.14, 95% confidence interval: 1.61 to 2.85).[17] In contrast to reports on a U-shaped relationship between BMI and mortality in young adults,[15] our results supported the absence of any association between underweight and premature mortality.[17]

Our results for type 2 diabetes and myocardial infarction are also supported by previous reports. Reporting on the magnitude of the association between BMI and diabetes, a recent meta-analysis of 18 cohort studies reported relative risk estimates almost identical to ours for both overweight (2.92, 95% confidence interval: 2.57 to 3.32) and obesity (7.28, 95% confidence interval: 6.47 to 8.28).[7] Tirosh *et al.*[14] also examined young adults and found a hazard ratio for each unit increase in BMI of 1.10 (95% confidence interval: 1.08 to 1.12) for diabetes[14] and of 1.12 (95% confidence interval: 1.07 to 1.18) for coronary heart disease.[14] In addition, a recent meta-analysis that pooled the results from 7 studies of subjects between 18 and 30 years found a relative risk of 1.08 (95% confidence interval: 1.05 to 1.11) associating 1 kg/m^2 higher BMI with coronary heart disease.[25] Another recent meta-analysis[28] found that obesity overall was associated with a 2-fold increased risk of venous thromboembolism. However, none of the included studies examined the risk among young adults specifically. Our finding of a more than 4-fold increased risk in this age group is thus important.

Pathophysiological explanations and implications

There may be several pathophysiological explanations for our findings. First, the apparent higher cardiovascular risks associated with BMI in young adulthood compared with older adulthood[10 11] may be caused by early development and clustering of cardiovascular risk factors, in particular the

metabolic syndrome.[46] Thus, overweight and obesity are both associated with insulin resistance, higher blood pressure, and adverse blood lipid profiles.[46] These risk factors increase short- and long-term incidence of type 2 diabetes,[46] venous thromboembolism,[28] premature coronary artery disease (through enhanced progression of atherosclerosis),[14 26 27] and finally, as a result, the cardiovascular mortality rate. Second, physical effects of body fat may limit venous return and create a proinflammatory, prothrombotic, and hypofibrinolytic milieu that enhances venous thromboembolic risks.[47]

The current and projected continued increase in obesity prevalence[1 48] may affect negatively the current trends of declining cardiovascular mortality rates.[5 6 49] Thus, obesity related morbidity and mortality will, in decades to come, place an unprecedented burden on healthcare systems worldwide.[48] This forecast reinforces the importance of understanding the effects of adiposity in young adults to plan future strategies for weight management and primary prevention.

Conclusions

In this cohort of young men, obesity was strongly associated with adverse cardiometabolic events before 55 years of age, including venous thromboembolism. Compared with those of normal weight, young obese men had an absolute risk increase for type 2 diabetes, cardiovascular morbidity or premature death of almost 30%.

Article summary

Article Focus

- Little is known about the association between young adulthood obesity and long-term risks of venous thromboembolism and combined cardiometabolic outcomes.
- We followed a cohort of 22-year old men for 33 years to examine the association between young adulthood and the risk of type 2 diabetes, cardiovascular morbidity, and death before 55 years of age.

Key Messages

- Nearly 50% of obese young men were either diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke, or venous thromboembolism or died before reaching 55 years of age.
- Obese men had a 4-fold increased rate of venous thromboembolism and a 3-fold increased rate of any of these diseases compared with men of normal weight, yielding an absolute risk increase of almost 30%.

Strengths and Limitations

- The population-based design reduced potential selection biases, provided access to valid exposure and outcome data, and ensured complete 33-year follow-up for all persons.
- Unmeasured confounding cannot be excluded due to the non-randomized design.

Ethics approval: As this study did not involve any contact with patients or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Committee.

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Contributorship: MS and HTS conceived the study idea. MS designed the study. SPU and HTS collected the data. MS and HTS reviewed the literature. MS, SAJ, SL, TLL, HEB and HTS directed the analyses, which were carried out by MS. All authors participated in the discussion and interpretation of the results. MS organised the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. HTS is the guarantor.

Data sharing: There is no additional data available

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Table 1. Characteristics of the study population at time of examination

	Body mass index*				Total
	Normal weight	Underweight	Overweight	Obesity	
	n=5,407	n=353	n=639	n=97	n=6,502
Cognitive test score					
Low	1339 (25)	87 (25)	206 (32)	40 (41)	1676 (26)
Moderate	1369 (25)	84 (24)	178 (28)	24 (25)	1655 (26)
High	1396 (26)	95 (27)	160 (25)	20 (21)	1672 (26)
Very high	1303 (24)	87 (25)	95 (15)	13 (13)	1499 (23)
Education, years					
Short	1277 (24)	74 (21)	202 (32)	32 (33)	1588 (24)
Moderate	1506 (28)	96 (27)	176 (28)	32 (33)	1811 (28)
Long	1645 (30)	120 (34)	181 (28)	23 (24)	1971 (30)
Very long	979 (18)	63 (18)	80 (13)	10 (10)	1132 (17)

* BMI groups were defined as underweight (<18.5), normal (18.5 to <25.0), overweight (25.0 to <30), and obese (≥30.0). 6 persons had missing data.

Table 2. Body mass index in young adulthood and the combined risk of type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before age 55 years*

BMI categories	Number	Risk, %	Risk difference†, %	Rate‡	Hazard ratio†
Combined outcome					
Normal	1,083	20 (16 to 23)	0	649 (612 to 689)	1
Underweight	63	18 (12 to 23)	-2 (-6 to 2)	574 (448 to 734)	0.9 (0.7 to 1.1)
Overweight	205	31 (26 to 36)	11 (7 to 15)	1086 (947 to 1245)	1.7 (1.4 to 1.9)
Obesity	48	48 (38 to 59)	28 (19 to 38)	1814 (1367 to 2407)	3.0 (2.3 to 4.0)

* Among the 1955 birth cohort that appeared for military examination in Northern Denmark and who survived until their 22nd year birthday.

† In all regression analyses, adjustments were made for cognitive test score and years of education.

‡ Rates per 100,000 person years

Table 3. Body mass index in young adulthood and the risks of type 2 diabetes, cardiovascular morbidity, or death before age 55 years*

BMI categories	Number	Risk, %	Risk difference†, %	Rate‡	Hazard ratio†
Type 2 diabetes					
Normal	207	5 (3 to 7)	0	122 (106 to 139)	1
Underweight	7	4 (1 to 6)	-2 (-3 to 0)	63 (30 to 132)	0.5 (0.2 to 1.1)
Overweight	76	13 (10 to 16)	8 (5 to 10)	387 (309 to 485)	3.1 (2.4 to 4.0)
Obesity	26	27 (18 to 36)	22 (13 to 31)	946 (644 to 1390)	8.2 (5.4 to 12.3)
Hypertension					
Normal	394	7 (4 to 9)	0	233 (211 to 257)	1
Underweight	24	6 (3 to 10)	0 (-3 to 3)	215 (144 to 321)	0.9 (0.6 to 1.4)
Overweight	92	13 (10 to 17)	7 (4 to 10)	469 (382 to 575)	2.0 (1.6 to 2.5)
Obesity	14	14 (7 to 21)	8 (1 to 16)	494 (292 to 833)	2.1 (1.2 to 3.6)
Myocardial infarction					
Normal	134	3 (1 to 4,5)	0	79 (66 to 93)	1
Underweight	12	4 (1 to 6)	1 (-1 to 3)	107 (61 to 189)	1.4 (0.8 to 2.5)
Overweight	18	3 (1 to 5)	0 (-1 to 2)	90 (56 to 142)	1.1 (0.7 to 1.8)
Obesity	6	7 (2 to 11)	4 (-1 to 9)	208 (93 to 462)	2.5 (1.1 to 5.6)

Stroke					
Normal	128	2 (1 to 4)	0	75 (63 to 89)	1
Underweight	8	2 (0 to 4)	0 (-2 to 2)	71 (36 to 143)	1.0 (0.5 to 2.0)
Overweight	22	3 (1 to 5)	1 (-1 to 2)	109 (72 to 166)	1.4 (0.9 to 2.2)
Obesity	2	2 (-1 to 5)	0 (-3 to 3)	69 (17 to 276)	0.9 (0.2 to 3.6)
Venous thromboembolism					
Normal	57	2 (1 to 3)	0	33 (26 to 43)	1
Underweight	2	1 (0 to 3)	0 (-1 to 0)	18 (4 to 71)	0.6 (0.1 to 2.3)
Overweight	7	2 (0 to 3)	0 (-1 to 1)	35 (17 to 73)	0.9 (0.4 to 2.1)
Obesity	5	6 (1 to 10)	4 (0 to 8)	173 (72 to 415)	4.7 (1.9 to 11.9)
Death					
Normal	416	7 (5 to 10)	0	243 (220 to 267)	1
Underweight	28	7 (3 to 11)	0 (-3 to 2)	249 (172 to 361)	1.0 (0.7 to 1.5)
Overweight	47	6 (3 to 9)	-1 (-3 to 1)	232 (174 to 309)	0.9 (0.7 to 1.2)
Obesity	16	16 (8 to 23)	8 (1 to 16)	547 (335 to 893)	2.1 (1.3 to 3.5)

* Among the 1955 birth cohort that appeared for military examination in Northern Denmark and who survived until their 22nd year birthday.

† In all regression analyses, adjustments were made for cognitive test score and education level. In all non-fatal outcomes, death was treated as a competing risk.

‡ Rates per 100,000 person years

Table 4. The association between a one unit increase in body mass index in young adulthood and type 2 diabetes, cardiovascular morbidity, or death before 55 years of age*

Outcomes	Hazard ratio (95% confidence interval)†
Type 2 diabetes	1.19 (1.16 to 1.22)
Hypertension	1.11 (1.08 to 1.13)
Myocardial infarction	1.05 (1.00 to 1.10)
Stroke	1.02 (0.97 to 1.08)
Venous thromboembolism	1.10 (1.03 to 1.18)
Death	1.01 (0.98 to 1.04)

* Among the 1955 birth cohort that appeared for military examination in Northern Denmark and who survived until their 22nd year birthday.

† BMI analysed as a continuous variable in a linear regression model adjusted for cognitive test score and education level

Figure 1. Body mass index in young adulthood and predicted cumulative incidence (risk) of type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before age 55 years

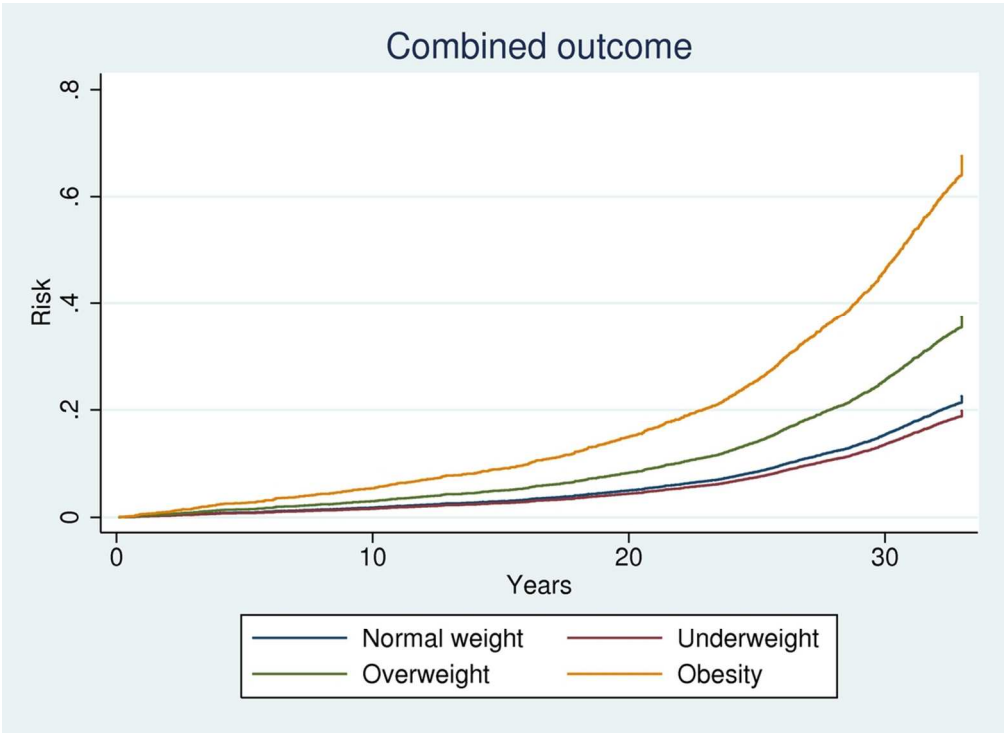
Log-rank test: $p<0.00001$

Figure 2. Normal weight (blue), underweight (red), overweight (green), and obesity (yellow) in young adulthood and predicted cumulative incidence (risk) of type 2 diabetes, cardiovascular morbidity, or death before age 55 years (note that the maximum risk is not constant on the y-axis of the various panels)

SUPPLEMENTARY ONLINE MATERIAL

ICD and ATC codes

Type 2 diabetes	ICD-8: 250.00; 250.06; 250.07; 250.09
	ICD-10: E11.0; E11.1; E11.9
	ATC: A10B
Hypertension	ICD-8: 400-404
	ICD-10: DI10-DI15
Myocardial infarction	ICD-8: 410
	ICD-10: I21
Stroke	ICD-8: 430, 431, 433, 434
	ICD-10: I60, I61, I63, I64
Venous thromboembolism	ICD-8: 450.99, 451.00
	ICD-10: I26, I80.1-3



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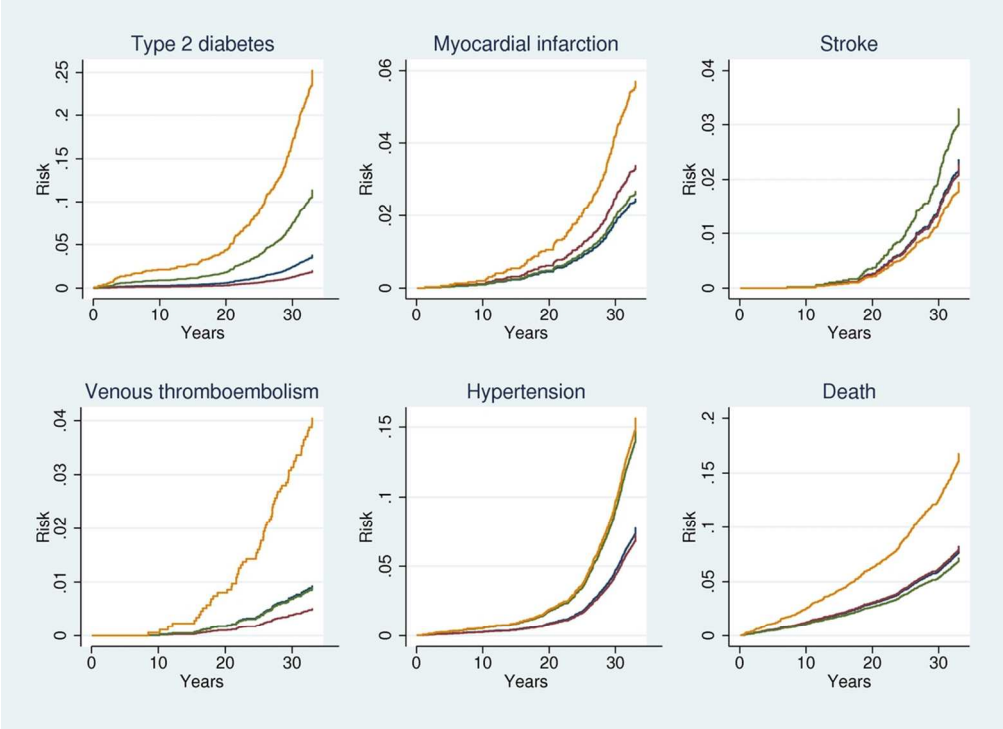

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**:1453-7

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Obesity in young men and individual and combined risks of type 2 diabetes, cardiovascular morbidity, and death before 55 years of age: A Danish 33-year follow-up study

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Title: Obesity in young men and individual and combined risks of type 2 diabetes, cardiovascular morbidity, and death before 55 years of age: A Danish 33-year follow-up study

Running head: Cardiometabolic risks associated with young adulthood obesity

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ABSTRACT

Objectives: To examine the association between body mass index (BMI) in young adulthood and cardiovascular risks, including venous thromboembolism, before 55 years of age.

Design: Cohort study using population-based medical databases.

Setting: Outcomes registered from all hospitals in Denmark from 1977 onwards.

Participants: 6,502 males born in 1955 and eligible for conscription in Northern Denmark.

Main outcome measures: Follow-up began at subjects' 22nd birthday and continued until death, emigration, or 55 years of age, whichever came first. Using regression analyses, we calculated risks and hazard ratios, adjusting for cognitive test score and years of education.

Results: 48% of all obese young men (BMI: ≥30 kg/m^2) were either diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke, or venous thromboembolism or died before reaching 55 years of age. Comparing obese men with normal weight men (BMI: 18.5 to <25.0 kg/m^2), the risk difference for any outcome was 28% (95% confidence interval: 19% to 38%) and the hazard ratio was 3.0 (95% confidence interval: 2.3 to 4.0). Compared with normal weight, obesity was associated with an event rate that was increased more than 8-fold for type 2 diabetes, 4-fold for venous thromboembolism, and 2-fold for hypertension, myocardial infarction, and death.

Conclusions: In this cohort of young men, obesity was strongly associated with adverse cardiometabolic events before 55 years of age, including venous thromboembolism. Compared with those of normal weight, young obese men had an absolute risk increase for type 2 diabetes, cardiovascular morbidity or premature death of almost 30%.

Key words: Body mass index; diabetes mellitus type 2; hypertension; myocardial infarction; stroke; venous thromboembolism; premature death

INTRODUCTION

Tripling in prevalence over the last three decades and now exceeding 30% in the US,[1-3] obesity in young adulthood is as a major public health concern worldwide, leading to a shorter lifespan for today's children.[4] Despite the obesity epidemic, cardiovascular morbidity and mortality have continued to decrease in the Western world.[5 6]

Although obesity in adulthood is a risk factor for type 2 diabetes,[1-3 7] cardiovascular disease,[4 8] and mortality,[5 6 9] it remains unclear whether an elongated history of overweight, starting early in life, poses additional risks. Previous reports indicate that age modifies the effect of obesity on cardiovascular death, with greater impact in younger age groups, including childhood and young adulthood.[10 11] However, whereas obese children reduce their additional cardiovascular risks (compared with non-obese children) by ceasing to be overweight before adulthood,[12] new studies indicate that the risks among obese young adults persist independently of weight changes in later adulthood.[13 14] These findings emphasize the need to study the adverse outcomes associated with obesity within the age group of young adults specifically.

Several studies have examined the association between body mass index (BMI) in young adults and premature death.[10 13 15-24] Fewer studies have examined long-term risks of type 2 diabetes[14] and ischemic heart disease.[14 23 25] However, despite the link between atherosclerosis, metabolic syndrome, and venous thromboembolism,[26-28] none of the previous studies have included venous thromboembolism as an outcome. Moreover, estimates of the absolute risk, in addition to the relative risk, of adverse events are important for clinical decision making, particular when counselling patients on risk modification associated with weight, diet, and exercise. Nonetheless, no study has examined the combined risk of type 2 diabetes, numerous cardiovascular outcomes, and premature death in one study, thereby assessing the complete cardiometabolic risks associated with young adulthood obesity.

We therefore followed a cohort of 22-year old men for 33 years to examine the association

between BMI in young adulthood and the risk of type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before 55 years of age.

METHODS

Setting

We conducted this population-based cohort study in the Fifth Military Conscription District in Denmark, populated by approximately 700,000 inhabitants.[29] The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals and partial reimbursement for prescribed medications. Accurate and unambiguous individual-level linkage of all Danish registries is possible using the unique central personal registration (CPR) number assigned to all residents at birth or upon immigration.[30]

Study cohort

Nearly all Danish men have had to register with the military board for an examination of fitness to serve when reaching 18 years of age or shortly thereafter (median age 19 years).[31] In connection with the registration, all examinees complete a health questionnaire, in which they report chronic diseases that could preclude military service, *e.g.*, asthma, epilepsy or spinal osteochondrosis, but not obesity.[3] The Draft Board verifies such reports with health care providers, and men deemed ineligible for military service are excused from the draft at this point (approximately 15%).[32] Information obtained at the examination is registered and stored in regional and national databases.[29] Using a conscription research database, we identified all persons from the 1955 birth cohort who later appeared before the draft board in Northern Denmark (n=6,502).

Body mass index

All potential conscripts undergo a physical and mental examination. The physical examination includes measurements of height (without shoes) and body weight (wearing trunks only and using sliding scales and calibrated balances). Using these height and weight measurements, we calculated the BMI. Values of weight <45 kg (n=6) were considered to be data entry errors and recoded as missing. We categorized BMI as underweight (<18.5 kg/m^2), normal (18.5 to <25.0 kg/m^2), overweight (25.0 to <30.0 kg/m^2), or obese (≥30 kg/m^2).

Covariates

From the conscription database, we obtained data on cognitive function as measured by the validated Boerge Prien test.[31 33] The Boerge Prien test is a 78-item group intelligence test with four subscales (letter matrices, verbal analogies, number sequences, and geometric figures) and a single final score, recorded as the number of correctly answered items (range 0–78).[31] The scores are strongly correlated with conventional intelligence-test scores (*e.g.*, correlation of 0.82 with the Wechsler Adult Intelligence Scale).[31] Based on quartiles, we categorized the test scores as low (0–31), moderate (32–39), high (40–46), and very high (47–78).

From the conscription database, we also obtained information on years of education at the time of examination.[33] Based on quartiles, we categorized the education length as short, moderate, long, and very long.

Outcomes

The Danish National Registry of Patients records information on patients discharged from all Danish non-psychiatric hospitals since 1 January 1977 and from all emergency room and outpatient specialty clinic visits since 1995.[34] Each hospital discharge or outpatient visit is recorded in the registry with one primary diagnosis and one or more secondary diagnoses

classified according to the *International Classification of Diseases*, 8th revision (ICD-8) until the end of 1993 and the 10th revision (ICD-10) thereafter.[34]

Using the Danish National Registry of Patients, we identified all examinees with a first diagnosis of type 2 diabetes, hypertension, myocardial infarction, stroke (ischemic stroke, intracerebral haemorrhage, or subarachnoid haemorrhage), or venous thromboembolism (deep venous thromboembolism or pulmonary embolism). To ensure more complete identification of examinees with type 2 diabetes, we also searched the Aarhus University Prescription Database,[35] covering the study region, for any use of antidiabetic drugs from 1 January 1989 through 2010. ICD and ATC codes are provided as supplementary online material.

We obtained information on all-cause mortality from the Danish Civil Registration System.[30] This registry has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[30] Finally, a combined outcome was defined as the first-time occurrence of any of the individual outcomes.

Statistical analyses

Initially, we used descriptive statistics to characterize the study population by categories of BMI, cognitive test score, and years of education. To ensure that the Danish National Registry of Patients (initiated in 1977) would capture events, follow-up started at examinee´s 22nd birthday. We excluded all men who were censored between their date of examination and their 22nd birthday (17 died and 8 emigrated). Follow-up continued until first occurrence of an outcome, emigration, or 33 years of follow-up (*i.e.*, their 55th birthday), whichever came first. First, we illustrated graphically the association between BMI and the predicted cumulative incidence function for each outcome using the proportional subhazards model by Fine and Gray.[36] We used the pseudo-value method to calculate the 33-year risk for each BMI group, as well as the risk

differences compared with normal weight.[37] We treated death as a competing risk in all analyses of non-fatal outcomes.

We calculated rates for each BMI group and used Cox proportional hazards regression to compute hazard ratios associating BMI with all outcomes. BMI was analysed both as a categorical and continuous variable. For the categorical BMI variable, the proportional hazard assumption was assessed by log-log plots and Schoenfeld's test and found valid. We assessed the scale of the continuous BMI variable using fractional polynomials and found no evidence of nonlinearity in the log hazard. We repeated all regression analyses adjusting for cognitive test score and years of education. Because there was no recent validation study available for hypertension, we estimated the proportion of patients registered with hypertension in the Danish National Registry of Patients that also redeemed at least one prescription for antihypertensive medication (registered in the prescription database).

The study was approved by the Danish Data Protection Agency (2011-41-5807). All analyses were conducted in STATA® software version 12.1 (STATA, College Station, TX, USA).

RESULTS

Characteristics

The characteristics of the study population are presented in Table 1. We identified 6,502 male examinees from the 1955 birth cohort in Northern Denmark. Among these, 5407 (83%) were of normal weight, 353 (5%) were underweight, 639 (10%) were overweight, and 97 (1.5%) were obese. BMI ranged from a minimum of 14.4 kg/m^2 to a maximum of 42.7 kg/m^2. The median BMI was 21.7 kg/m^2 (interquartile range: 20.3 to 23.4 kg/m^2). Compared with men of normal weight (25%), a higher proportion of those who were overweight (32%) or obese (41%) scored low on the cognitive test. Also, compared with subjects of normal weight (24%), a higher proportion of overweight (32%) or obese (33%) persons belonged to the lowest quartile of years of education.

The validation analysis revealed that 88% of patients with a diagnosis of hypertension redeemed one or more prescriptions for antihypertensive medication.

Combined outcome

The cohort contributed a total of 199,430 person years of follow-up, providing a mean follow-up time of 31 years. Compared with 20% of men of normal weight, 48% of all obese men were diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke, or venous thromboembolism or died before their 55-year birthday (Table 2 and Figure 1). After adjusting for cognitive test score and years of education, the absolute risk difference between the groups was 28% (95% confidence interval: 19% to 38%) and the hazard ratio was 3.0 (95% confidence interval: 2.3 to 4.0).

Individual outcomes

Obesity was strongly associated with all individual outcomes except stroke (Table 3 and Figure 2). With a risk difference of 22% (95% confidence interval: 13% to 31%) and hazard ratio of 8.2 (95% confidence interval: 5.4 to 12.3) the absolute and relative associations for obesity, compared with normal weight, were strongest for type 2 diabetes. However, there was also a more than 4-fold increased rate of venous thromboembolism and more than 2-fold increased rate of hypertension, myocardial infarction, and death. For stroke, there was a 40% increased rate among overweight persons. The wide confidence intervals made the association between obesity and stroke inconclusive. In the analysis of BMI as a continuous variable, a unit increase in BMI corresponded to an increased rate of approximately 5% for myocardial infarction, 10% for hypertension and venous thromboembolism, and 20% for type 2 diabetes (Table 4).

DISCUSSION

In this population-based 33-year follow-up study, we found that nearly half of all obese young men either were diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke, or venous thromboembolism or died before reaching 55 years of age. Obesity was associated with an event rate that, compared with normal weight, was increased more than 8-fold for type 2 diabetes, 4-fold for venous thromboembolism, and 2-fold for hypertension, myocardial infarction, and premature death. The strong association between young adulthood obesity and venous thromboembolism was of particular importance because it, to our knowledge, has not previously been reported. Obese subjects had a 3-fold increased event rate of any of these diseases compared with persons of normal weight, yielding a notable absolute risk increase of almost 30%. The magnitude of the relative and absolute risk estimates emphasize the major clinical and public health implications associated with obesity in young adulthood.

Strengths and limitations of study

Several issues should be considered when interpreting our results. With military examination in anticipation of conscription being mandatory and participation enforced by law, the population-based design reduced potential selection bias. We used measured instead of self-reported height and weight. Doing so, we eliminated differential misclassification of BMI, which may have biased other studies[13 16] because underweight people tend to overestimate their BMI and overweight people tend to underestimate their BMI.[38] The Danish Civil Registration System ensured complete follow-up of all examinees with accurate mortality data.[30] The tax-supported universal healthcare system allowed for complete ascertainment of all hospital admissions throughout the 33-year follow-up period. In addition to our estimate for hypertension (88%), the positive predictive values of diagnoses in the Danish National Registry of Patients have previously been validated and found to be approximately 90% for diabetes[39] and myocardial infarction,[39 40] and 80% for stroke,[39 41] and venous thromboembolism.[42]

There were, however, some limitations. Examinees had to survive from their examination date until start of follow-up at 22 years of age. Although BMI is a widely used proxy for adiposity, it does not distinguish adipose from muscle tissue nor does it take the anthropometric distribution of fat into account. Some degree of misclassification is therefore inevitable (for all studies on this topic). Nevertheless, BMI is a valuable tool to provide a standardized definition of obesity, allowing for a comparison of its associated risks across decades. The Aarhus University Prescription Database did not cover the entire study period. However, any potential underreporting of diabetes and hypertension in the Danish National Registry of Patients would provide underestimates of the absolute risks, and thus cannot explain the increased risks.

We cannot exclude confounding from exercise, diet, weight changes, and smoking. An advantage of studying mortality rates among young subjects is that adjustments for other conditions are largely unnecessary. Moreover, analyses of myocardial infarction and death should not adjust for hypercholesterolemia, hypertension, diabetes or other factors associated with the metabolic syndrome because all of these risk factors may be on the causal pathway.[43] We were unable to consider the impact of weight changes later in life. However, weight loss among obese or weight gain among normal weight conscripts would bias the results towards unity, and thus cannot explain our findings. Furthermore, other studies have found the associations between young adulthood BMI and coronary artery disease[14] and death[13] independent of later weight changes. Smoking is associated with low and not high BMI.[44] Thus, any unmeasured confounding from smoking would also tend to bias the results towards unity. Supporting the robustness of our results, previous studies on young obese adults have found similar mortality rates among smokers and non-smokers[17] or even higher mortality rates among non-smokers.[16] In addition, as a surrogate measure of lifestyle, we did adjust for cognitive test score and years of education. Finally, although the results derive from a study that included only young men, previous reports suggest the associations are likely also to hold for young women.[45]

Comparison with other studies

Our results are in line with previous reports on the individual outcomes. The increased premature mortality risk is consistent.[10 13 15-24] Among prior studies, a similar Swedish study on male conscripts with mean age of 18.7 years found an almost identical association between obesity and premature mortality (hazard ratio: 2.14, 95% confidence interval: 1.61 to 2.85).[17] In contrast to reports of a U-shaped relationship between BMI and mortality in young adults,[15] our results supported the absence of any association between underweight and premature mortality.[17]

Our results for type 2 diabetes and myocardial infarction are also supported by previous reports. Reporting on the magnitude of the association between BMI and diabetes, a recent meta-analysis of 18 cohort studies reported relative risk estimates almost identical to ours for both overweight (2.92, 95% confidence interval: 2.57 to 3.32) and obesity (7.28, 95% confidence interval: 6.47 to 8.28).[7] Tirosh *et al*.[14] also examined young adults and found a hazard ratio for each unit increase in BMI of 1.10 (95% confidence interval: 1.08 to 1.12) for diabetes[14] and of 1.12 (95% confidence interval: 1.07 to 1.18) for coronary heart disease.[14] In addition, a recent meta-analysis that pooled the results from 7 studies of subjects between 18 and 30 years found a relative risk of 1.08 (95% confidence interval: 1.05 to 1.11) associating 1 kg/m^2 higher BMI with coronary heart disease.[25] Another recent meta-analysis[28] found that obesity overall was associated with a 2-fold increased risk of venous thromboembolism. However, none of the included studies examined the risk among young adults specifically. Our finding of a more than 4-fold increased risk in this age group is thus important.

Pathophysiological explanations and implications

There may be several pathophysiological explanations for our findings. First, the apparent higher cardiovascular risks associated with BMI in young adulthood compared with older adulthood[10 11]

may be caused by early development and clustering of cardiovascular risk factors, in particular the metabolic syndrome.[46] Thus, overweight and obesity are both associated with insulin resistance, higher blood pressure, and adverse blood lipid profiles.[46] These risk factors increase short- and long-term incidence of type 2 diabetes,[46] venous thromboembolism,[28] premature coronary artery disease (through enhanced progression of atherosclerosis),[14 26 27] and finally, as a result, the cardiovascular mortality rate. Second, physical effects of body fat may limit venous return and create a proinflammatory, prothrombotic, and hypofibrinolytic milieu that enhances venous thromboembolic risks.[47]

The current and projected continued increase in obesity prevalence[1 48] may affect negatively the current trends of declining cardiovascular mortality rates.[5 6 49] Thus, obesity related morbidity and mortality will, in decades to come, place an unprecedented burden on healthcare systems worldwide.[48] This forecast reinforces the importance of understanding the effects of adiposity in young adults to plan future strategies for weight management and primary prevention.

Conclusions

In this cohort of young men, obesity was strongly associated with adverse cardiometabolic events before 55 years of age, including venous thromboembolism. Compared with those of normal weight, young obese men had an absolute risk increase for type 2 diabetes, cardiovascular morbidity or premature death of almost 30%.

Article summary

Article Focus

- Little is known about the association between young adulthood obesity and long-term risks of venous thromboembolism and combined cardiometabolic outcomes.
- We followed a cohort of 22-year old men for 33 years to examine the association between young adulthood and the risk of type 2 diabetes, cardiovascular morbidity, and death before 55 years of age.

Key Messages

- Nearly 50% of obese young men were either diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke, or venous thromboembolism or died before reaching 55 years of age.
- Obese men had a 4-fold increased rate of venous thromboembolism and a 3-fold increased rate of any of these diseases compared with men of normal weight, yielding an absolute risk increase of almost 30%.

Strengths and Limitations

- The population-based design reduced potential selection biases, provided access to valid exposure and outcome data, and ensured complete 33-year follow-up for all persons.
- Unmeasured confounding cannot be excluded due to the non-randomized design.

Ethics approval: As this study did not involve any contact with patients or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Committee.

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Contributorship: MS and HTS conceived the study idea. MS designed the study. SPU and HTS collected the data. MS and HTS reviewed the literature. MS, SAJ, SL, TLL, HEB and HTS directed the analyses, which were carried out by MS. All authors participated in the discussion and interpretation of the results. MS organised the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. HTS is the guarantor.

Data sharing: There is no additional data available

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Table 1. Characteristics of the study population at time of examination

	Body mass index*				Total
	Normal weight	Underweight	Overweight	Obesity	
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	5,407 (100)	353 (100)	639 (100)	97 (100)	6,502 (100)
Cognitive test score					
Low	1339 (25)	87 (25)	206 (32)	40 (41)	1676 (26)
Moderate	1369 (25)	84 (24)	178 (28)	24 (25)	1655 (26)
High	1396 (26)	95 (27)	160 (25)	20 (21)	1672 (26)
Very high	1303 (24)	87 (25)	95 (15)	13 (13)	1499 (23)
Education, years					
Short	1277 (24)	74 (21)	202 (32)	32 (33)	1588 (24)
Moderate	1506 (28)	96 (27)	176 (28)	32 (33)	1811 (28)
Long	1645 (30)	120 (34)	181 (28)	23 (24)	1971 (30)
Very long	979 (18)	63 (18)	80 (13)	10 (10)	1132 (17)

* BMI groups were defined as underweight (<18.5), normal (18.5 to <25.0), overweight (25.0 to <30), and obese (≥30.0). 6 persons had missing data.

Table 2. Body mass index in young adulthood and the combined risk of type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before age 55 years*

BMI categories	Number	Risk, % (95% CI)	Risk difference†, % (95% CI)	Rate‡ (95% CI)	Hazard ratio† (95% CI)
Combined outcome					
Normal	1,083	20 (16 to 23)	0	649 (612 to 689)	1
Underweight	63	18 (12 to 23)	-2 (-6 to 2)	574 (448 to 734)	0.9 (0.7 to 1.1)
Overweight	205	31 (26 to 36)	11 (7 to 15)	1086 (947 to 1245)	1.7 (1.4 to 1.9)
Obesity	48	48 (38 to 59)	28 (19 to 38)	1814 (1367 to 2407)	3.0 (2.3 to 4.0)

* Among the 1955 birth cohort that appeared for military examination in Northern Denmark and who survived until their 22nd year birthday.

† In all regression analyses, adjustments were made for cognitive test score and years of education.

‡ Rates per 100,000 person years

Table 3. Body mass index in young adulthood and the risks of type 2 diabetes, cardiovascular morbidity, or death before age 55 years*

BMI categories	Number	Risk, % (95% CI)	Risk difference†, % (95% CI)	Rate‡ (95% CI)	Hazard ratio† (95% CI)
Type 2 diabetes					
Normal	207	5 (3 to 7)	0	122 (106 to 139)	1
Underweight	7	4 (1 to 6)	-2 (-3 to 0)	63 (30 to 132)	0.5 (0.2 to 1.1)
Overweight	76	13 (10 to 16)	8 (5 to 10)	387 (309 to 485)	3.1 (2.4 to 4.0)
Obesity	26	27 (18 to 36)	22 (13 to 31)	946 (644 to 1390)	8.2 (5.4 to 12.3)
Hypertension					
Normal	394	7 (4 to 9)	0	233 (211 to 257)	1
Underweight	24	6 (3 to 10)	0 (-3 to 3)	215 (144 to 321)	0.9 (0.6 to 1.4)
Overweight	92	13 (10 to 17)	7 (4 to 10)	469 (382 to 575)	2.0 (1.6 to 2.5)
Obesity	14	14 (7 to 21)	8 (1 to 16)	494 (292 to 833)	2.1 (1.2 to 3.6)
Myocardial infarction					
Normal	134	3 (1 to 5)	0	79 (66 to 93)	1
Underweight	12	4 (1 to 6)	1 (-1 to 3)	107 (61 to 189)	1.4 (0.8 to 2.5)
Overweight	18	3 (1 to 5)	0 (-1 to 2)	90 (56 to 142)	1.1 (0.7 to 1.8)

Obesity	6	7 (2 to 11)	4 (-1 to 9)	208 (93 to 462)	2.5 (1.1 to 5.6)
Stroke					
Normal	128	2 (1 to 4)	0	75 (63 to 89)	1
Underweight	8	2 (0 to 4)	0 (-2 to 2)	71 (36 to 143)	1.0 (0.5 to 2.0)
Overweight	22	3 (1 to 5)	1 (-1 to 2)	109 (72 to 166)	1.4 (0.9 to 2.2)
Obesity	2	2 (-1 to 5)	0 (-3 to 3)	69 (17 to 276)	0.9 (0.2 to 3.6)
Venous thromboembolism					
Normal	57	2 (1 to 3)	0	33 (26 to 43)	1
Underweight	2	1 (0 to 3)	0 (-1 to 0)	18 (4 to 71)	0.6 (0.1 to 2.3)
Overweight	7	2 (0 to 3)	0 (-1 to 1)	35 (17 to 73)	0.9 (0.4 to 2.1)
Obesity	5	6 (1 to 10)	4 (0 to 8)	173 (72 to 415)	4.7 (1.9 to 11.9)
Death					
Normal	416	7 (5 to 10)	0	243 (220 to 267)	1
Underweight	28	7 (3 to 11)	0 (-3 to 2)	249 (172 to 361)	1.0 (0.7 to 1.5)
Overweight	47	6 (3 to 9)	-1 (-3 to 1)	232 (174 to 309)	0.9 (0.7 to 1.2)
Obesity	16	16 (8 to 23)	8 (1 to 16)	547 (335 to 893)	2.1 (1.3 to 3.5)

* Among the 1955 birth cohort that appeared for military examination in Northern Denmark and who survived until their 22nd year birthday.

† In all regression analyses, adjustments were made for cognitive test score and education level. In all non-fatal outcomes, death was treated as a competing risk.

‡ Rates per 100,000 person years

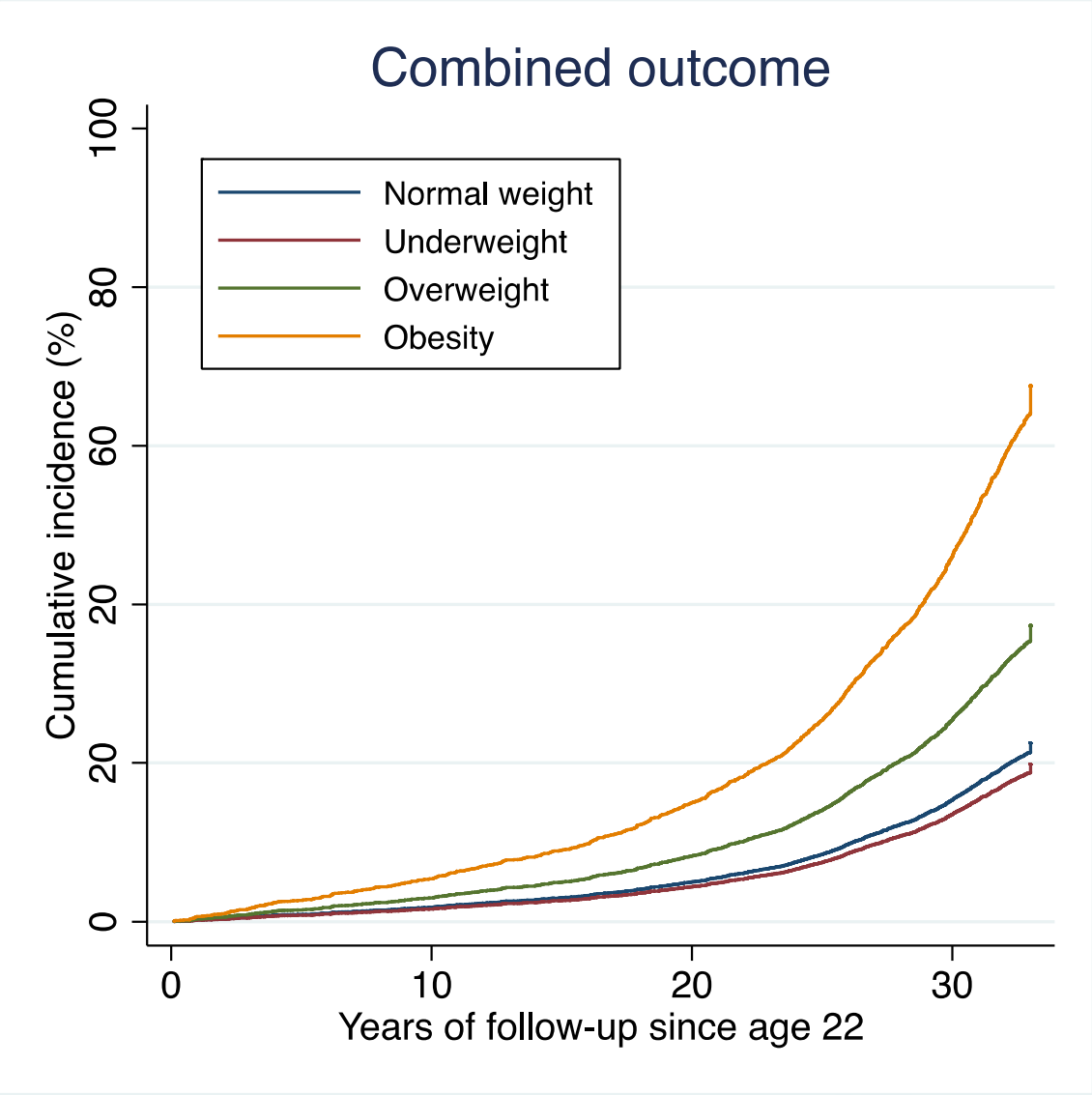
Table 4. The association between a one unit increase in body mass index in young adulthood and type 2 diabetes, cardiovascular morbidity, or death before 55 years of age*

Outcomes	Hazard ratio (95% CI)†
Type 2 diabetes	1.19 (1.16 to 1.22)
Hypertension	1.11 (1.08 to 1.13)
Myocardial infarction	1.05 (1.00 to 1.10)
Stroke	1.02 (0.97 to 1.08)
Venous thromboembolism	1.10 (1.03 to 1.18)
Death	1.01 (0.98 to 1.04)

* Among the 1955 birth cohort that appeared for military examination in Northern Denmark and who survived until their 22nd year birthday.

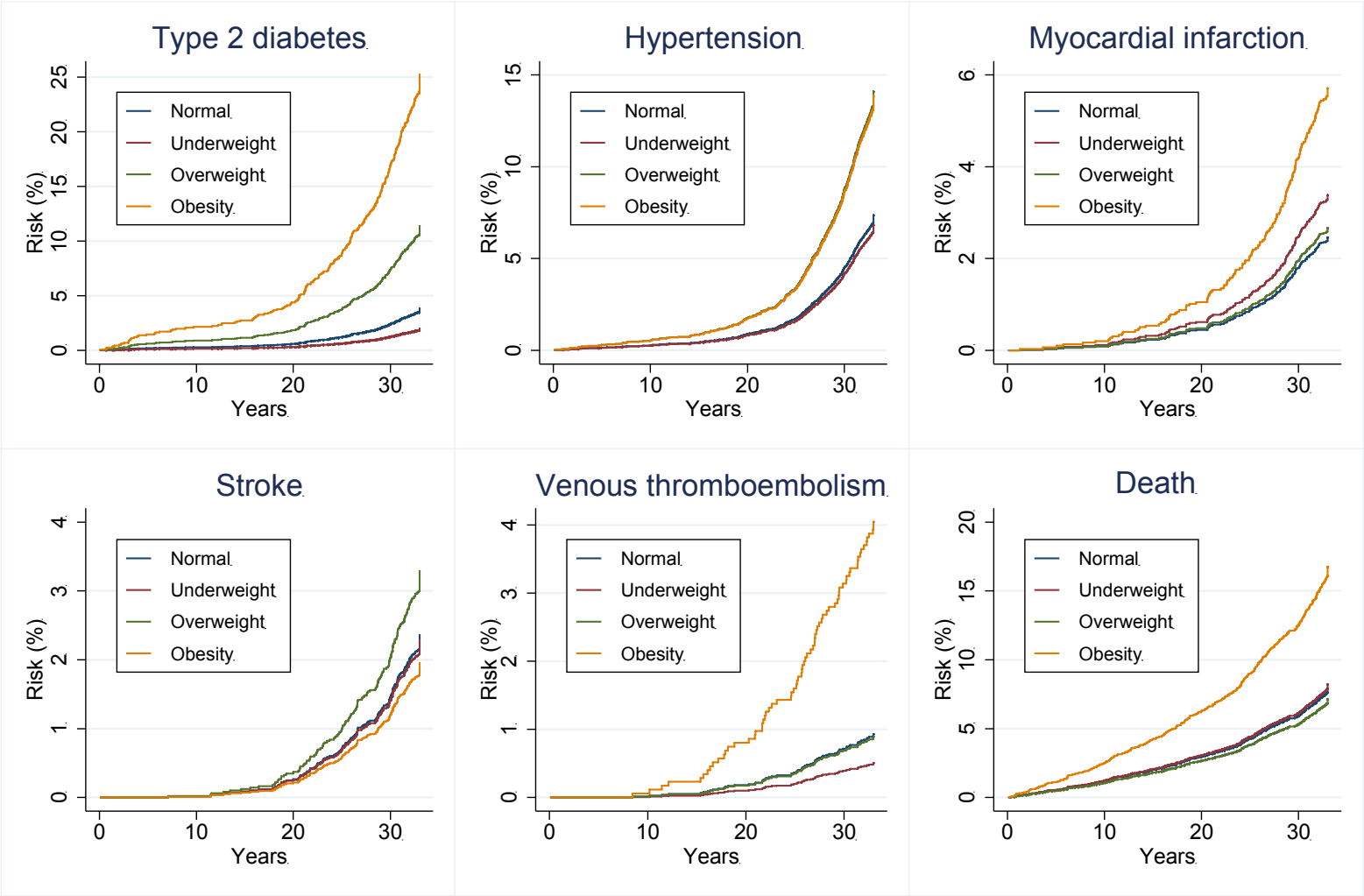
† BMI analysed as a continuous variable in a linear regression model adjusted for cognitive test score and education level

Figure 1. Body mass index in young adulthood and predicted cumulative incidence (risk) of type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before age 55 years



Log-rank test: p<0.00001

Figure 2. Body mass index in young adulthood and cumulative incidence (risk) of type 2 diabetes, cardiovascular morbidity, or death before age 55 years (note that follow-up starts at age 22 and that the maximum risk is not constant on the y-axis of the various panels)



SUPPLEMENTARY ONLINE MATERIAL

ICD and ATC codes

Type 2 diabetes	ICD-8: 250.00; 250.06; 250.07; 250.09
	ICD-10: E11.0; E11.1; E11.9
	ATC: A10B
Hypertension	ICD-8: 400-404
	ICD-10: DI10-DI15
Myocardial infarction	ICD-8: 410
	ICD-10: I21
Stroke	ICD-8: 430, 431, 433, 434
	ICD-10: I60, I61, I63, I64
Venous thromboembolism	ICD-8: 450.99, 451.00
	ICD-10: I26, I80.1-3

Title: Obesity in young men and individual and combined risks of type 2 diabetes, cardiovascular morbidity, and death before 55 years of age: A Danish 33-year follow-up study

Running head: Cardiometabolic risks associated with young adulthood obesity

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) no authors have support from any company for the submitted work. Department of Clinical Epidemiology is, however, involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of the company funded studies have relation to the present study; (2) no authors have relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) no authors have non-financial interests that may be relevant to the submitted work.

ABSTRACT

Objectives: To examine the association between body mass index (BMI) in young adulthood and cardiovascular risks, including venous thromboembolism, before 55 years of age.

Design: Cohort study using population-based medical databases.

Setting: Outcomes registered from all hospitals in Denmark from 1977 onwards.

Participants: 6,502 males born in 1955 and eligible for conscription in Northern Denmark.

Main outcome measures: Follow-up began at subjects' 22nd birthday and continued until death, emigration, or 55 years of age, whichever came first. Using regression analyses, we calculated risks and hazard ratios, adjusting for cognitive test score and years of education.

Results: 48% of all obese young men (BMI: ≥30 kg/m^2) were either diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke, or venous thromboembolism or died before reaching 55 years of age. Comparing obese men with normal weight men (BMI: 18.5 to <25.0 kg/m^2), the risk difference for any outcome was 28% (95% confidence interval: 19% to 38%) and the hazard ratio was 3.0 (95% confidence interval: 2.3 to 4.0). Compared with normal weight, obesity was associated with an event rate that was increased more than 8-fold for type 2 diabetes, 4-fold for venous thromboembolism, and 2-fold for hypertension, myocardial infarction, and death.

Conclusions: In this cohort of young men, obesity was strongly associated with adverse cardiometabolic events before 55 years of age, including venous thromboembolism. Compared with those of normal weight, young obese men had an absolute risk increase for type 2 diabetes, cardiovascular morbidity or premature death of almost 30%.

Key words: Body mass index; diabetes mellitus type 2; hypertension; myocardial infarction; stroke; venous thromboembolism; premature death

INTRODUCTION

Tripling in prevalence over the last three decades and now exceeding 30% in the US,[1-3] obesity in young adulthood is as a major public health concern worldwide, leading to a shorter lifespan for today's children.[4] Despite the obesity epidemic, cardiovascular morbidity and mortality have continued to decrease in the Western world.[5 6]

Although obesity in adulthood is a risk factor for type 2 diabetes,[1-3 7] cardiovascular disease,[4 8] and mortality,[5 6 9] it remains unclear whether an elongated history of overweight, starting early in life, poses additional risks. Previous reports indicate that age modifies the effect of obesity on cardiovascular death, with greater impact in younger age groups, including childhood and young adulthood.[10 11] However, whereas obese children reduce their additional cardiovascular risks (compared with non-obese children) by ceasing to be overweight before adulthood,[12] new studies indicate that the risks among obese young adults persist independently of weight changes in later adulthood.[13 14] These findings emphasize the need to study the adverse outcomes associated with obesity within the age group of young adults specifically.

Several studies have examined the association between body mass index (BMI) in young adults and premature death.[10 13 15-24] Fewer studies have examined long-term risks of type 2 diabetes[14] and ischemic heart disease.[14 23 25] However, despite the link between atherosclerosis, metabolic syndrome, and venous thromboembolism,[26-28] none of the previous studies have included venous thromboembolism as an outcome. Moreover, estimates of the absolute risk, in addition to the relative risk, of adverse events are important for clinical decision making, particular when counselling patients on risk modification associated with weight, diet, and exercise. Nonetheless, no study has examined the combined risk of type 2 diabetes, numerous cardiovascular outcomes, and premature death in one study, thereby assessing the complete cardiometabolic risks associated with young adulthood obesity.

We therefore followed a cohort of 22-year old men for 33 years to examine the association

between BMI in young adulthood and the risk of type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before 55 years of age.

METHODS

Setting

We conducted this population-based cohort study in the Fifth Military Conscription District in Denmark, populated by approximately 700,000 inhabitants.[29] The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals and partial reimbursement for prescribed medications. Accurate and unambiguous individual-level linkage of all Danish registries is possible using the unique central personal registration (CPR) number assigned to all residents at birth or upon immigration.[30]

Study cohort

Nearly all Danish men have had to register with the military board for an examination of fitness to serve when reaching 18 years of age or shortly thereafter (median age 19 years).[31] In connection with the registration, all examinees complete a health questionnaire, in which they report chronic diseases that could preclude military service, *e.g.*, asthma, epilepsy or spinal osteochondrosis, but not obesity.[3] The Draft Board verifies such reports with health care providers, and men deemed ineligible for military service are excused from the draft at this point (approximately 15%).[32] Information obtained at the examination is registered and stored in regional and national databases.[29] Using a conscription research database, we identified all persons from the 1955 birth cohort who later appeared before the draft board in Northern Denmark (n=6,502).

Body mass index

All potential conscripts undergo a physical and mental examination. The physical examination includes measurements of height (without shoes) and body weight (wearing trunks only and using sliding scales and calibrated balances). Using these height and weight measurements, we calculated the BMI. Values of weight <45 kg (n=6) were considered to be data entry errors and recoded as missing. We categorized BMI as underweight (<18.5 kg/m^2), normal (18.5 to <25.0 kg/m^2), overweight (25.0 to <30.0 kg/m^2), or obese (≥30 kg/m^2).

Covariates

From the conscription database, we obtained data on cognitive function as measured by the validated Boerge Prien test.[31 33] The Boerge Prien test is a 78-item group intelligence test with four subscales (letter matrices, verbal analogies, number sequences, and geometric figures) and a single final score, recorded as the number of correctly answered items (range 0–78).[31] The scores are strongly correlated with conventional intelligence-test scores (*e.g.*, correlation of 0.82 with the Wechsler Adult Intelligence Scale).[31] Based on quartiles, we categorized the test scores as low (0–31), moderate (32–39), high (40–46), and very high (47–78).

From the conscription database, we also obtained information on years of education at the time of examination.[33] Based on quartiles, we categorized the education length as short, moderate, long, and very long.

Outcomes

The Danish National Registry of Patients records information on patients discharged from all Danish non-psychiatric hospitals since 1 January 1977 and from all emergency room and outpatient specialty clinic visits since 1995.[34] Each hospital discharge or outpatient visit is recorded in the registry with one primary diagnosis and one or more secondary diagnoses

classified according to the *International Classification of Diseases*, 8th revision (ICD-8) until the end of 1993 and the 10th revision (ICD-10) thereafter.[34]

Using the Danish National Registry of Patients, we identified all examinees with a first diagnosis of type 2 diabetes, hypertension, myocardial infarction, stroke (ischemic stroke, intracerebral haemorrhage, or subarachnoid haemorrhage), or venous thromboembolism (deep venous thromboembolism or pulmonary embolism). To ensure more complete identification of examinees with type 2 diabetes, we also searched the Aarhus University Prescription Database,[35] covering the study region, for any use of antidiabetic drugs from 1 January 1989 through 2010. ICD and ATC codes are provided as supplementary online material.

We obtained information on all-cause mortality from the Danish Civil Registration System.[30] This registry has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[30] Finally, a combined outcome was defined as the first-time occurrence of any of the individual outcomes.

Statistical analyses

Initially, we used descriptive statistics to characterize the study population by categories of BMI, cognitive test score, and years of education. To ensure that the Danish National Registry of Patients (initiated in 1977) would capture events, follow-up started at examinee´s 22nd birthday. We excluded all men who were censored between their date of examination and their 22nd birthday (17 died and 8 emigrated). Follow-up continued until first occurrence of an outcome, emigration, or 33 years of follow-up (*i.e.*, their 55th birthday), whichever came first. First, we illustrated graphically the association between BMI and the predicted cumulative incidence function for each outcome using the proportional subhazards model by Fine and Gray.[36] We used the pseudo-value method to calculate the 33-year risk for each BMI group, as well as the risk

differences compared with normal weight.[37] We treated death as a competing risk in all analyses of non-fatal outcomes.

We calculated rates for each BMI group and used Cox proportional hazards regression to compute hazard ratios associating BMI with all outcomes. BMI was analysed both as a categorical and continuous variable. For the categorical BMI variable, the proportional hazard assumption was assessed by log-log plots and Schoenfeld's test and found valid. We assessed the scale of the continuous BMI variable using fractional polynomials and found no evidence of nonlinearity in the log hazard. There was no suggestion that BMI was not linear in the log hazard for the individual outcomes and was, thus, included as a linear term in these models. We repeated all regression analyses adjusting for cognitive test score and years of education. Because there was no recent validation study available for hypertension, we estimated the proportion of patients registered with hypertension in the Danish National Registry of Patients that also redeemed at least one prescription for antihypertensive medication (registered in the prescription database).

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The study was approved by the Danish Data Protection Agency (2011-41-5807). All analyses were conducted in STATA® software version 12.1 (STATA, College Station, TX, USA).

RESULTS

Characteristics

The characteristics of the study population are presented in Table 1. We identified 6,502 male examinees from the 1955 birth cohort in Northern Denmark. Among these, 5407 (83%) were of normal weight, 353 (5%) were underweight, 639 (10%) were overweight, and 97 (1.5%) were obese. BMI ranged from a minimum of 14.4 kg/m^2 to a maximum of 42.7 kg/m^2. The median BMI was 21.7 kg/m^2 (interquartile range: 20.3 to 23.4 kg/m^2). Compared with men of normal weight (25%), a higher proportion of those who were overweight (32%) or obese (41%) scored low on the cognitive test. Also, compared with subjects of normal weight (24%), a higher proportion of

overweight (32%) or obese (33%) persons belonged to the lowest quartile of years of education. The validation analysis revealed that 88% of patients with a diagnosis of hypertension redeemed one or more prescriptions for antihypertensive medication.

Combined outcome

The cohort contributed a total of 199,430 person years of follow-up, providing a mean follow-up time of 31 years. Compared with 20% of men of normal weight, 48% of all obese men were diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke, or venous thromboembolism or died before their 55-year birthday (Table 2 and Figure 1). After adjusting for cognitive test score and years of education, the absolute risk difference between the groups was 28% (95% confidence interval: 19% to 38%) and the hazard ratio was 3.0 (95% confidence interval: 2.3 to 4.0).

Individual outcomes

Obesity was strongly associated with all individual outcomes except stroke (Table 3 and Figure 2). With a risk difference of 22% (95% confidence interval: 13% to 31%) and hazard ratio of 8.2 (95% confidence interval: 5.4 to 12.3) the absolute and relative associations for obesity, compared with normal weight, were strongest for type 2 diabetes. However, there was also a more than 4-fold increased rate of venous thromboembolism and more than 2-fold increased rate of hypertension, myocardial infarction, and death. For stroke, there was a 40% increased rate among overweight persons. The wide confidence intervals made the association between obesity and stroke inconclusive. In the analysis of BMI as a continuous variable, a unit increase in BMI corresponded to an increased rate of approximately 5% for myocardial infarction, 10% for hypertension and venous thromboembolism, and 20% for type 2 diabetes (Table 4).

DISCUSSION

In this population-based 33-year follow-up study, we found that nearly half of all obese young men either were diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke, or venous thromboembolism or died before reaching 55 years of age. Obesity was associated with an event rate that, compared with normal weight, was increased more than 8-fold for type 2 diabetes, 4-fold for venous thromboembolism, and 2-fold for hypertension, myocardial infarction, and premature death. The strong association between young adulthood obesity and venous thromboembolism was of particular importance because it, to our knowledge, has not previously been reported. Obese subjects had a 3-fold increased event rate of any of these diseases compared with persons of normal weight, yielding a notable absolute risk increase of almost 30%. The magnitude of the relative and absolute risk estimates emphasize the major clinical and public health implications associated with obesity in young adulthood.

Strengths and limitations of study

Several issues should be considered when interpreting our results. With military examination in anticipation of conscription being mandatory and participation enforced by law, the population-based design reduced potential selection bias. We used measured instead of self-reported height and weight. Doing so, we eliminated differential misclassification of BMI, which may have biased other studies[13 16] because underweight people tend to overestimate their BMI and overweight people tend to underestimate their BMI.[38] The Danish Civil Registration System ensured complete follow-up of all examinees with accurate mortality data.[30] The tax-supported universal healthcare system allowed for complete ascertainment of all hospital admissions throughout the 33-year follow-up period. In addition to our estimate for hypertension (88%), the positive predictive values of diagnoses in the Danish National Registry of Patients have previously been validated and found to be approximately 90% for diabetes[39] and myocardial

infarction,[39 40] and 80% for stroke,[39 41] and venous thromboembolism.[42]

There were, however, some limitations. Examinees had to survive from their examination date until start of follow-up at 22 years of age. Although BMI is a widely used proxy for adiposity, it does not distinguish adipose from muscle tissue nor does it take the anthropometric distribution of fat into account. Some degree of misclassification is therefore inevitable (for all studies on this topic). Nevertheless, BMI is a valuable tool to provide a standardized definition of obesity, allowing for a comparison of its associated risks across decades. The Aarhus University Prescription Database did not cover the entire study period. However, ~~Any~~ any potential underreporting of diabetes and hypertension in the Danish National Registry of Patients would provide underestimates of the absolute risks, and thus cannot explain the increased risks.

We cannot exclude confounding from exercise, diet, weight changes, and smoking. An advantage of studying mortality rates among young subjects is that adjustments for other conditions are largely unnecessary. Moreover, analyses of myocardial infarction and death should not adjust for hypercholesterolemia, hypertension, diabetes or other factors associated with the metabolic syndrome because all of these risk factors may be on the causal pathway.[43] We were unable to consider the impact of weight changes later in life. However, weight loss among obese or weight gain among normal weight conscripts would bias the results towards unity, and thus cannot explain our findings. Furthermore, other studies have found the associations between young adulthood BMI and coronary artery disease[14] and death[13] independent of later weight changes. Smoking is associated with low and not high BMI.[44] Thus, any unmeasured confounding from smoking would also tend to bias the results towards unity. Supporting the robustness of our results, previous studies on young obese adults have found similar mortality rates among smokers and non-smokers[17] or even higher mortality rates among non-smokers.[16] In addition, as a surrogate measure of lifestyle, we did adjust for cognitive test score and years of education. Finally, although the results derive from a study that included only young men, previous reports

suggest the associations are likely also to hold for young women.[45]

Comparison with other studies

Our results are in line with previous reports on the individual outcomes. The increased premature mortality risk is consistent.[10 13 15-24] Among prior studies, a similar Swedish study on male conscripts with mean age of 18.7 years found an almost identical association between obesity and premature mortality (hazard ratio: 2.14, 95% confidence interval: 1.61 to 2.85).[17] In contrast to reports ~~on~~ of a U-shaped relationship between BMI and mortality in young adults,[15] our results supported the absence of any association between underweight and premature mortality.[17]

Our results for type 2 diabetes and myocardial infarction are also supported by previous reports. Reporting on the magnitude of the association between BMI and diabetes, a recent meta-analysis of 18 cohort studies reported relative risk estimates almost identical to ours for both overweight (2.92, 95% confidence interval: 2.57 to 3.32) and obesity (7.28, 95% confidence interval: 6.47 to 8.28).[7] Tirosh *et al.*[14] also examined young adults and found a hazard ratio for each unit increase in BMI of 1.10 (95% confidence interval: 1.08 to 1.12) for diabetes[14] and of 1.12 (95% confidence interval: 1.07 to 1.18) for coronary heart disease.[14] In addition, a recent meta-analysis that pooled the results from 7 studies of subjects between 18 and 30 years found a relative risk of 1.08 (95% confidence interval: 1.05 to 1.11) associating 1 kg/m^2 higher BMI with coronary heart disease.[25] Another recent meta-analysis[28] found that obesity overall was associated with a 2-fold increased risk of venous thromboembolism. However, none of the included studies examined the risk among young adults specifically. Our finding of a more than 4-fold increased risk in this age group is thus important.

Pathophysiological explanations and implications

There may be several pathophysiological explanations for our findings. First, the apparent higher cardiovascular risks associated with BMI in young adulthood compared with older adulthood[10 11] may be caused by early development and clustering of cardiovascular risk factors, in particular the metabolic syndrome.[46] Thus, overweight and obesity are both associated with insulin resistance, higher blood pressure, and adverse blood lipid profiles.[46] These risk factors increase short- and long-term incidence of type 2 diabetes,[46] venous thromboembolism,[28] premature coronary artery disease (through enhanced progression of atherosclerosis),[14 26 27] and finally, as a result, the cardiovascular mortality rate. Second, physical effects of body fat may limit venous return and create a proinflammatory, prothrombotic, and hypofibrinolytic milieu that enhances venous thromboembolic risks.[47]

The current and projected continued increase in obesity prevalence[1 48] may affect negatively the current trends of declining cardiovascular mortality rates.[5 6 49] Thus, obesity related morbidity and mortality will, in decades to come, place an unprecedented burden on healthcare systems worldwide.[48] This forecast reinforces the importance of understanding the effects of adiposity in young adults to plan future strategies for weight management and primary prevention.

Conclusions

In this cohort of young men, obesity was strongly associated with adverse cardiometabolic events before 55 years of age, including venous thromboembolism. Compared with those of normal weight, young obese men had an absolute risk increase for type 2 diabetes, cardiovascular morbidity or premature death of almost 30%.

Article summary

Article Focus

- Little is known about the association between young adulthood obesity and long-term risks of venous thromboembolism and combined cardiometabolic outcomes.
- We followed a cohort of 22-year old men for 33 years to examine the association between young adulthood and the risk of type 2 diabetes, cardiovascular morbidity, and death before 55 years of age.

Key Messages

- Nearly 50% of obese young men were either diagnosed with type 2 diabetes, hypertension, myocardial infarction, stroke, or venous thromboembolism or died before reaching 55 years of age.
- Obese men had a 4-fold increased rate of venous thromboembolism and a 3-fold increased rate of any of these diseases compared with men of normal weight, yielding an absolute risk increase of almost 30%.

Strengths and Limitations

- The population-based design reduced potential selection biases, provided access to valid exposure and outcome data, and ensured complete 33-year follow-up for all persons.
- Unmeasured confounding cannot be excluded due to the non-randomized design.

Ethics approval: As this study did not involve any contact with patients or any intervention, it was not necessary to obtain permission from the Danish Scientific Ethical Committee.

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Contributorship: MS and HTS conceived the study idea. MS designed the study. SPU and HTS collected the data. MS and HTS reviewed the literature. MS, SAJ, SL, TLL, HEB and HTS directed the analyses, which were carried out by MS. All authors participated in the discussion and interpretation of the results. MS organised the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. HTS is the guarantor.

Data sharing: There is no additional data available

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Table 1. Characteristics of the study population at time of examination

	Body mass index*				Total
	Normal weight	Underweight	Overweight	Obesity	
	n (%)~~n=5,407~~	n (%)~~n=353~~	n (%)~~n=639~~	n (%)~~n=97~~	n~~N~~ (%)~~=6,502~~
Total	5,407 (100)	353 (100)	639 (100)	97 (100)	6,502 (100)
Cognitive test score					
Low	1339 (25)	87 (25)	206 (32)	40 (41)	1676 (26)
Moderate	1369 (25)	84 (24)	178 (28)	24 (25)	1655 (26)
High	1396 (26)	95 (27)	160 (25)	20 (21)	1672 (26)
Very high	1303 (24)	87 (25)	95 (15)	13 (13)	1499 (23)
Education, years					
Short	1277 (24)	74 (21)	202 (32)	32 (33)	1588 (24)
Moderate	1506 (28)	96 (27)	176 (28)	32 (33)	1811 (28)
Long	1645 (30)	120 (34)	181 (28)	23 (24)	1971 (30)
Very long	979 (18)	63 (18)	80 (13)	10 (10)	1132 (17)

* BMI groups were defined as underweight (<18.5), normal (18.5 to <25.0), overweight (25.0 to <30), and obese (≥30.0). 6 persons had missing data.

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Table 2. Body mass index in young adulthood and the combined risk of type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before age 55 years*

BMI categories	Number	Risk, % (95% CI)	Risk difference†, % (95% CI)	Rate‡ (95% CI)	Hazard ratio† (95% CI)
Combined outcome					
Normal	1,083	20 (16 to 23)	0	649 (612 to 689)	1
Underweight	63	18 (12 to 23)	-2 (-6 to 2)	574 (448 to 734)	0.9 (0.7 to 1.1)
Overweight	205	31 (26 to 36)	11 (7 to 15)	1086 (947 to 1245)	1.7 (1.4 to 1.9)
Obesity	48	48 (38 to 59)	28 (19 to 38)	1814 (1367 to 2407)	3.0 (2.3 to 4.0)

* Among the 1955 birth cohort that appeared for military examination in Northern Denmark and who survived until their 22nd year birthday.

† In all regression analyses, adjustments were made for cognitive test score and years of education.

‡ Rates per 100,000 person years

Table 3. Body mass index in young adulthood and the risks of type 2 diabetes, cardiovascular morbidity, or death before age 55 years*

BMI categories	Number	Risk, % (95% CI)	Risk difference†, % (95% CI)	Rate‡ (95% CI)	Hazard ratio† (95% CI)
Type 2 diabetes					
Normal	207	5 (3 to 7)	0	122 (106 to 139)	1
Underweight	7	4 (1 to 6)	-2 (-3 to 0)	63 (30 to 132)	0.5 (0.2 to 1.1)
Overweight	76	13 (10 to 16)	8 (5 to 10)	387 (309 to 485)	3.1 (2.4 to 4.0)
Obesity	26	27 (18 to 36)	22 (13 to 31)	946 (644 to 1390)	8.2 (5.4 to 12.3)
Hypertension					
Normal	394	7 (4 to 9)	0	233 (211 to 257)	1
Underweight	24	6 (3 to 10)	0 (-3 to 3)	215 (144 to 321)	0.9 (0.6 to 1.4)
Overweight	92	13 (10 to 17)	7 (4 to 10)	469 (382 to 575)	2.0 (1.6 to 2.5)
Obesity	14	14 (7 to 21)	8 (1 to 16)	494 (292 to 833)	2.1 (1.2 to 3.6)
Myocardial infarction					
Normal	134	3 (1 to 5)	0	79 (66 to 93)	1
Underweight	12	4 (1 to 6)	1 (-1 to 3)	107 (61 to 189)	1.4 (0.8 to 2.5)
Overweight	18	3 (1 to 5)	0 (-1 to 2)	90 (56 to 142)	1.1 (0.7 to 1.8)

Obesity	6	7 (2 to 11)	4 (-1 to 9)	208 (93 to 462)	2.5 (1.1 to 5.6)
Stroke					
Normal	128	2 (1 to 4)	0	75 (63 to 89)	1
Underweight	8	2 (0 to 4)	0 (-2 to 2)	71 (36 to 143)	1.0 (0.5 to 2.0)
Overweight	22	3 (1 to 5)	1 (-1 to 2)	109 (72 to 166)	1.4 (0.9 to 2.2)
Obesity	2	2 (-1 to 5)	0 (-3 to 3)	69 (17 to 276)	0.9 (0.2 to 3.6)
Venous thromboembolism					
Normal	57	2 (1 to 3)	0	33 (26 to 43)	1
Underweight	2	1 (0 to 3)	0 (-1 to 0)	18 (4 to 71)	0.6 (0.1 to 2.3)
Overweight	7	2 (0 to 3)	0 (-1 to 1)	35 (17 to 73)	0.9 (0.4 to 2.1)
Obesity	5	6 (1 to 10)	4 (0 to 8)	173 (72 to 415)	4.7 (1.9 to 11.9)
Death					
Normal	416	7 (5 to 10)	0	243 (220 to 267)	1
Underweight	28	7 (3 to 11)	0 (-3 to 2)	249 (172 to 361)	1.0 (0.7 to 1.5)
Overweight	47	6 (3 to 9)	-1 (-3 to 1)	232 (174 to 309)	0.9 (0.7 to 1.2)
Obesity	16	16 (8 to 23)	8 (1 to 16)	547 (335 to 893)	2.1 (1.3 to 3.5)

* Among the 1955 birth cohort that appeared for military examination in Northern Denmark and who survived until their 22nd year birthday.

† In all regression analyses, adjustments were made for cognitive test score and education level. In all non-fatal outcomes, death was treated as a competing risk.

‡ Rates per 100,000 person years

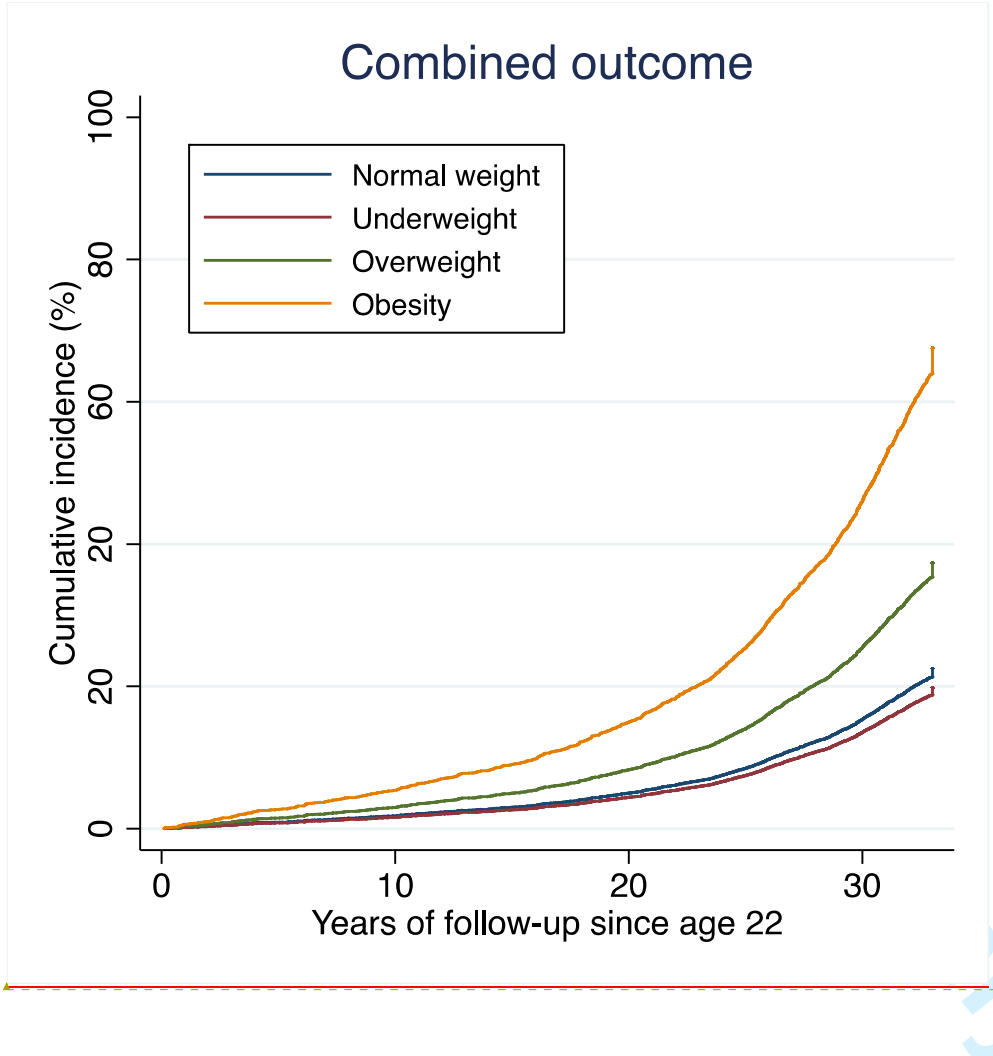
Table 4. The association between a one unit increase in body mass index in young adulthood and type 2 diabetes, cardiovascular morbidity, or death before 55 years of age*

Outcomes	Hazard ratio (95% ~~confidence interval~~CI)†
Type 2 diabetes	1.19 (1.16 to 1.22)
Hypertension	1.11 (1.08 to 1.13)
Myocardial infarction	1.05 (1.00 to 1.10)
Stroke	1.02 (0.97 to 1.08)
Venous thromboembolism	1.10 (1.03 to 1.18)
Death	1.01 (0.98 to 1.04)

* Among the 1955 birth cohort that appeared for military examination in Northern Denmark and who survived until their 22nd year birthday.

† BMI analysed as a continuous variable in a linear regression model adjusted for cognitive test score and education level

Figure 1. Body mass index in young adulthood and predicted cumulative incidence (risk) of type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before age 55 years



Log-rank test: p<0.00001

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Figure 2. Body mass index ~~Normal weight (blue), underweight (red), overweight (green), and obesity (yellow)~~ in young adulthood and ~~predicted~~ cumulative incidence (risk) of type 2 diabetes, cardiovascular morbidity, or death before age 55 years (note that follow-up starts at age 22 and that the maximum risk is not constant on the y-axis of the various panels)

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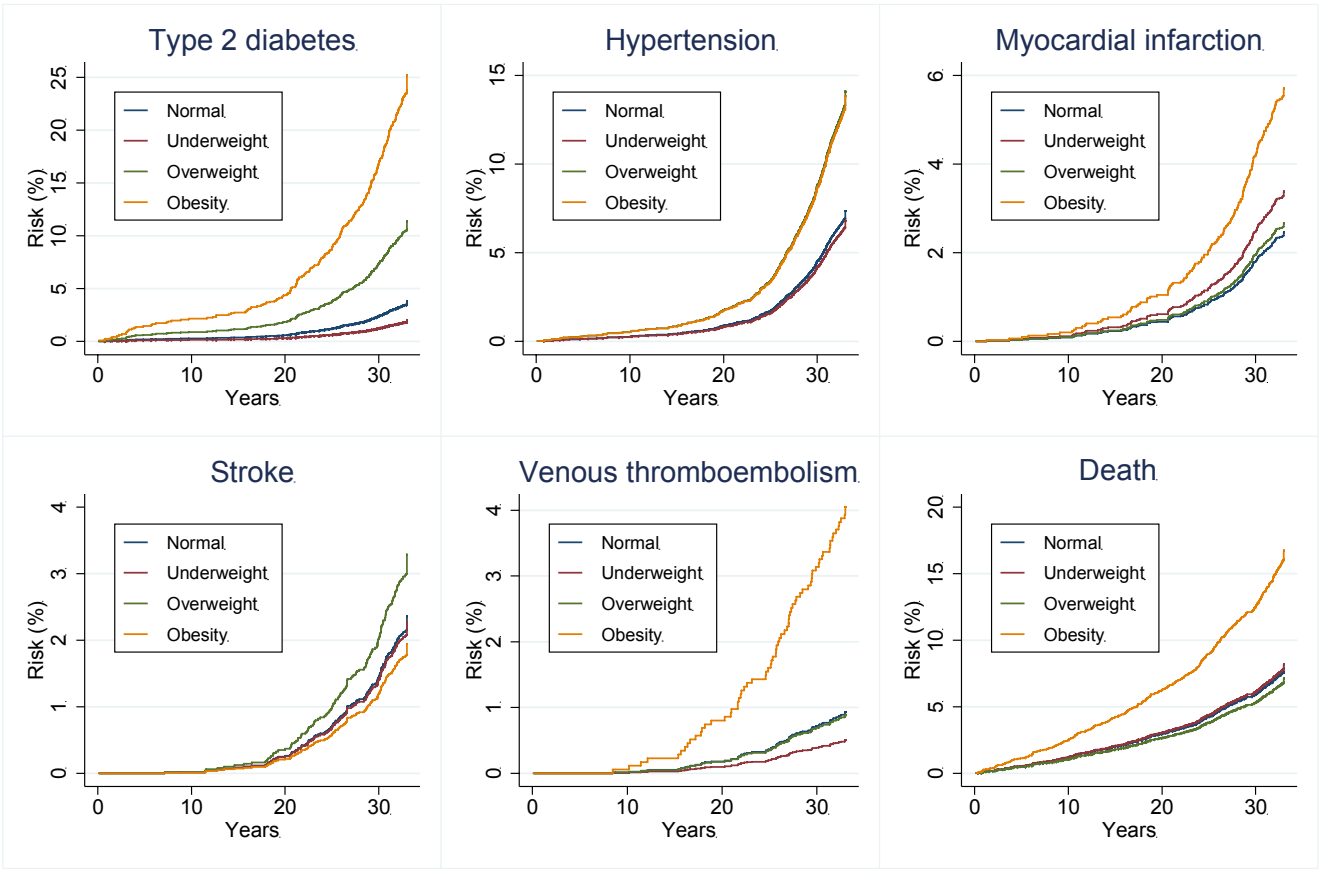

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SUPPLEMENTARY ONLINE MATERIAL

ICD and ATC codes

Type 2 diabetes	ICD-8: 250.00; 250.06; 250.07; 250.09
	ICD-10: E11.0; E11.1; E11.9
	ATC: A10B
Hypertension	ICD-8: 400-404
	ICD-10: DI10-DI15
Myocardial infarction	ICD-8: 410
	ICD-10: I21
Stroke	ICD-8: 430, 431, 433, 434
	ICD-10: I60, I61, I63, I64
Venous thromboembolism	ICD-8: 450.99, 451.00
	ICD-10: I26, I80.1-3

Reply to reviewer(s) Reports:

Reviewer: Anders Gaarsdal Holst, MD, PhD
Department of Cardiology, B2142
University Hospital Rigshospitalet
Blegdamsvej 9, 2100 Copenhagen
Denmark

No competing interests to declare.

Using a combination of different Danish registries, including a military conscription database, Schmidt et al. examined the association of BMI at the median age of 19 years with type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before 55 years of age. They found that overweight was associated with all of the noted end points.

I do not have much knowledge in the field of obesity research and thus I have focused my review on the data and statistical methods used. Both of which I have experience with. Data was analyzed using well accepted and contemporary methods, among these Fine & Gray competing risk regression. In general the manuscript is very well written, their methods are sound and the conclusions valid. Thus, I only have some minor comments:

Minor comments

1.1. There is no reporting of follow-up time: As mentioned in the STROBE-statement this should be reported.

Reply: In the method statistical section we write: "…follow-up started at examinee´s 22nd birthday… Follow-up continued until first occurrence of an outcome, emigration, or 33 years of follow-up (*i.e.*, their 55th birthday), whichever came first." Thus, we had a potential 33 years of follow-up time for all persons as indicated in the subtitle: "A Danish 33-year follow-up study". Moreover, we have now added the following sentence to the result section:

"The cohort contributed a total of 199,430 person years of follow-up, providing a mean

follow-up time of 31 years."

1.2. The authors used the "Aarhus University Prescription Database", which as far as I understand, only holds data on some dispensed prescriptions, unlike the Danish National Prescription Registry, which holds data on all dispensed prescriptions (but only from 1995 and onwards). Do the authors have references comparing the two? Furthermore using only the local database instead of the national registry means that all subjects emigrating from central/northern Jutland are lost to follow-up with regard to prescription data.

Reply: The reviewer understands correctly. The Aarhus University Prescription Database have similar data as the Danish National Prescription Registry, except it does not contain data on drugs that do not receive general or conditional reimbursement (for example, oral contraceptives). All drugs obtained in this study are reimbursed and thus included in the registry. Reference 35 is a review of the registry, which also provide a cross-tabulation between the two prescription datebases that shows good correlation.[1]

The Aarhus University Prescription Database covers the population of the Central Denmark Region and the North Denmark Region. These are two of the five Danish regions, with a combined population of 1.8 million inhabitants, or about one-third of the total Danish population. Thus, the coverage area are actually considerable larger than the Fifth Military Conscription District in Denmark, populated by approximately 700,000 inhabitants, from which our cohort originated. Still, as the reviewer points out, some examinee could have moved outside the community pharmacies of the two regions and thus would not be covered for the whole study period. It should be noted that the hospital data on diabetes had nationwide coverage. Still, we agree that the limitation should be mentioned. We therefore now write in the discussion:

"The Aarhus University Prescription Database did not cover the entire study period. However, any potential underreporting of diabetes and hypertension in the Danish National Registry of Patients would provide underestimates of the absolute risks, and thus cannot explain the increased risks."

1.3. Page 10, line 46: "Supporting the robustness of our results, previous studies have found

similar mortality rates among smokers and non-smokers17 or even higher mortality rates among non-smokers.16" Please state that this is with regards to obesity and not in general.

Reply: We have revised as recommended and now write:

"Supporting the robustness of our results, previous studies on young obese adults have found similar mortality rates among smokers and non-smokers[2] or even higher mortality rates among non-smokers.[3]"

1.4. When I look at figure 2 - Death, I see no indication of a (linear) dose response relationship but on page 7, line 18 the authors state that "There was no suggestion that BMI was not linear in the log hazard for the individual outcomes". Can the authors explain this for me? If true, I find it interesting that especially with regards to death there were no indication of a (linear) dose response relationship. I think this is relevant with regard to the current discussion about what the ideal weight is.

Reply: We used Cox proportional hazards regression to compute hazard ratios associating BMI with all outcomes. BMI was analysed both as a categorical and continuous variable. We assessed the scale of the continuous BMI variable using fractional polynomials and found no evidence of nonlinearity in the log hazard. The fact that it was nonlinear in the log hazard suggests that there was no fractional polynomial that fitted the model better than the linear model.

Please note that for the continuous BMI variable, we only calculated hazard ratios and not cumulative incidence function (as figure 2). Thus, the linear function should not be reflected in figure 2.

1.5. The, without doubt, weakest endpoint with regard to validity is hypertension as taken from the National Patient Registry. Especially the sensitivity of this, I believe is very low. Also I think it is very likely that the chance of a subject receiving a hypertension diagnosis code is associated to being hospitalized or seen in an outpatient clinic because of some of the other endpoints studied. This is especially true for type 2 diabetes as the cut off for hypertension is lower in subjects with this disease and there is a much greater probability that they will be seen in an outpatient clinic. This will lead to some degree of diagnostic bias and artificial

correlation between the endpoints.

Reply: The combined outcome measures the first diagnoses of any of the outcomes. Thus, correlation between the individual outcomes will not affect the risk of the combined outcome. Regarding the completeness of the hypertension diagnoses we agree with the reviewer and comment on the limitation in the discussion (please see reply to comment 1.2).

1.6. I would prefer to state the BMI cut offs for each BMI group instead of normal, underweight, etc.

Reply: In the section "Body mass index", we define the terms of the BMI categories: "We categorized BMI as underweight (<18.5 kg/m^2), normal (18.5 to <25.0 kg/m^2), overweight (25.0 to <30.0 kg/m^2), or obese (≥30 kg/m^2)." We hope the reviewer will agree that it is a matter of preference whether to use the category names or the cut offs consistently throughout the paper. By defining the BMI categories as above, we believe the cut offs for each category is clear. We prefer using the category terms throughout instead of the cut offs because we believe it makes the text easier to read.

1.7. In tables, please indicate that the numbers in parentheses are 95% confidence intervals.

Reply: We have revised as recommended.

Reviewer 2:

PD Dr Harald J. Schneider

Staff

Medizinische Klinik und Poliklinik IV

LMU Munich

80336 Munich, Germany

No conflicts of interest

2.1. A large and broadly discussed meta-analysis showed that mortality was not increased in overweight and grade 1-obesity. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. Flegal KM, Kit BK, Orpana H, Graubard BI. JAMA. 2013 Jan 2;309(1):71-82. doi: 10.1001/jama.2012.113905. Review. This should be discussed ion the light of the current findings.

Reply: We thank the reviewer for his insight into the literature. However, an important difference between our study and the study by Flegal et al (JAMA. 2013 Jan 2;309(1):71-82) is the age group studied. Thus, previous reports indicate that age modifies the effect of obesity on cardiovascular death, with greater impact in younger age groups, including childhood and young adulthood.[4 5] This was the reason for undertaking this study and the discussion is therefore based on the previous literature on this specific age group. In the introduction, we therefore write ""Several studies have examined the association between body mass index (BMI) in young adults and premature death.[2-4 6-14]" and in the discussion we state that all studies on the association between young adulthood BMI and premature death show consistent results. We cite all 12 studies.[2-4 6-14]

2.2. Many other studies report a U-shaped association of BMI with mortality and health risks as opposed to this study (not only underweight but also normal weight being associated with increased risks). This previously reported obesity paradox should be discussed. Possibly it is an effect of age, as most studies reporting this paradox studied older populations. Please put into context.

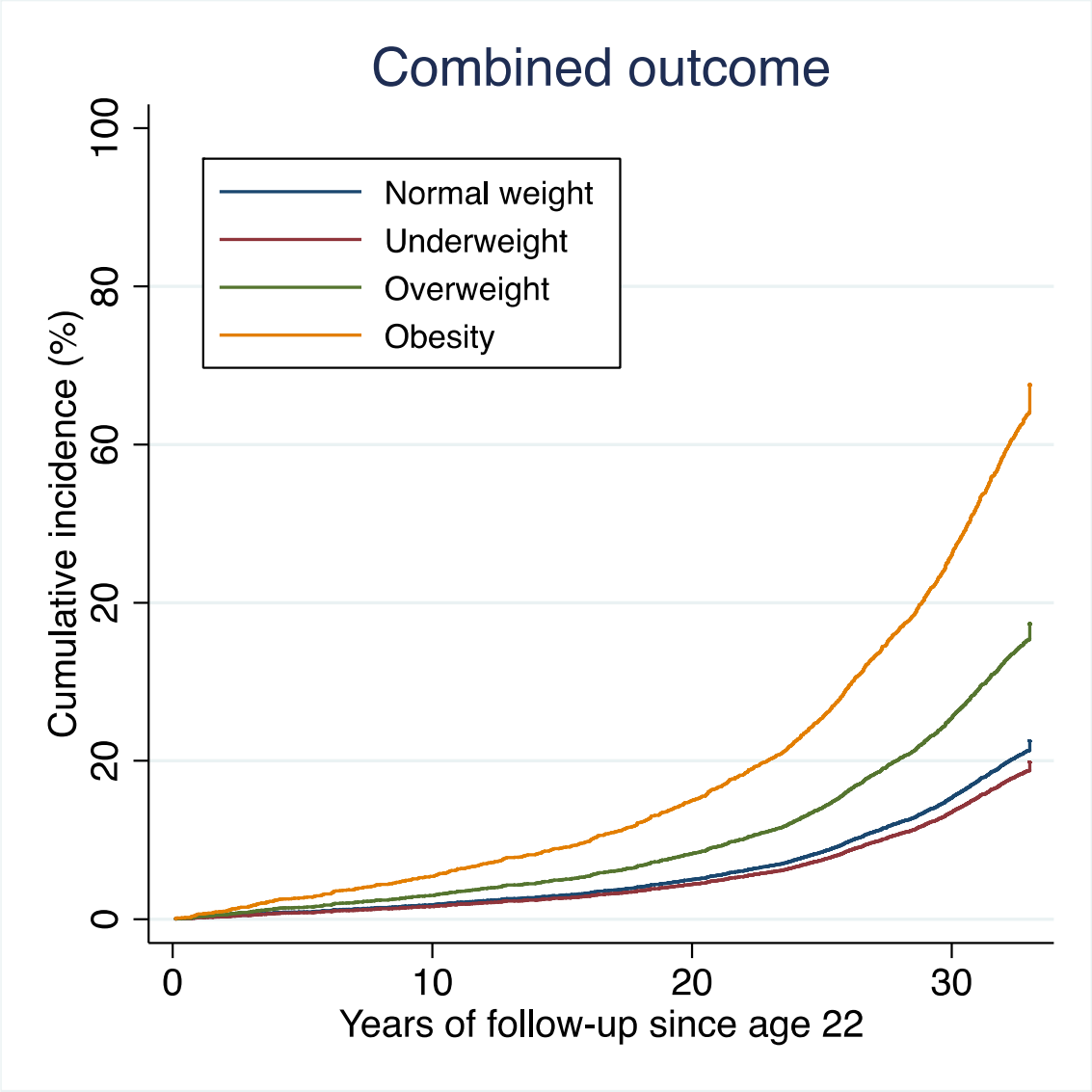
Reply: Please see reply to comment 2.1 on the specific age group of interest. We agree this should be mentioned in relation to the studies reporting on the association between

young adulthood BMI and premature death. In the discussion, we therefore write:

"In contrast to reports of a U-shaped relationship between BMI and mortality in young adults,[6] our results supported the absence of any association between underweight and premature mortality.[2]"

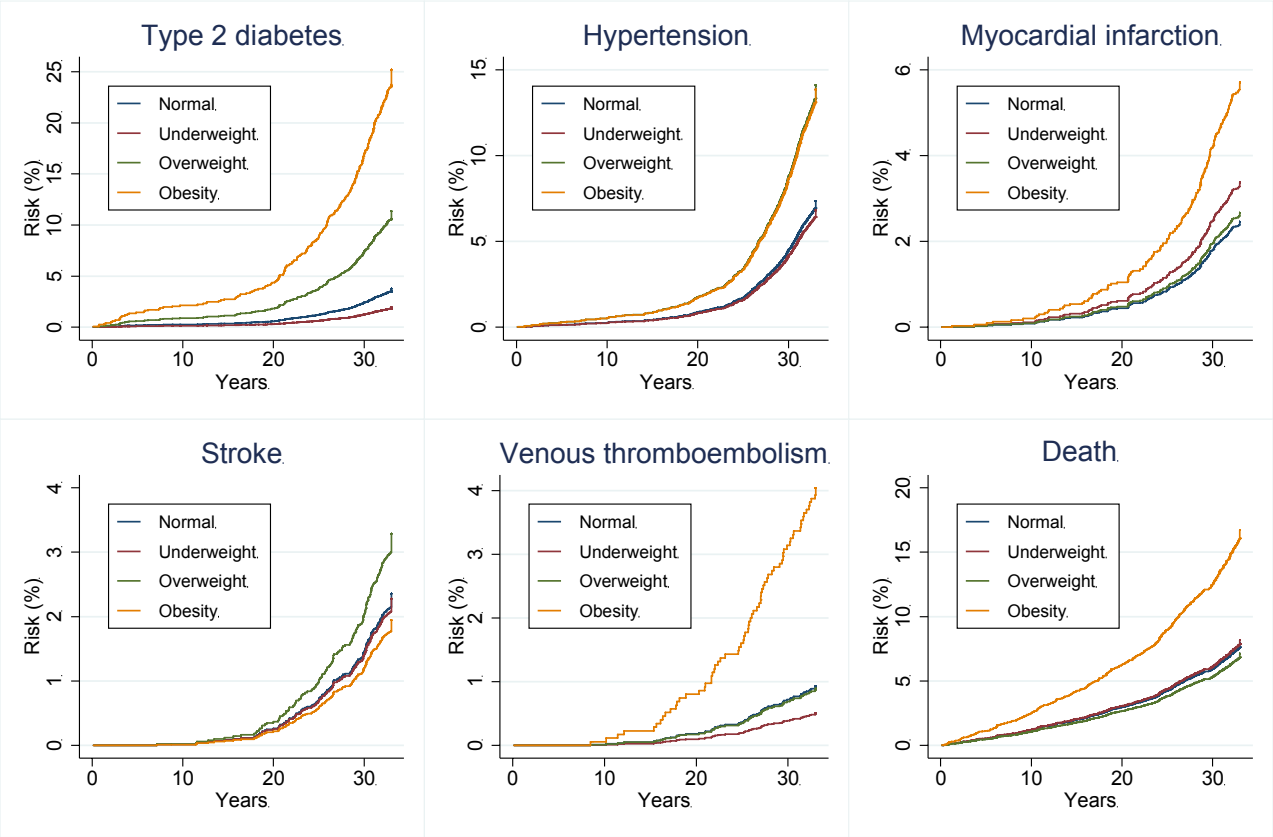
Finally, we have improved the layout of the figures, which now look:

Figure 1. Body mass index in young adulthood and predicted cumulative incidence (risk) of type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before age 55 years



Log-rank test: p<0.00001

Figure 2. Body mass index in young adulthood and cumulative incidence (risk) of type 2 diabetes, cardiovascular morbidity, or death before age 55 years (note that follow-up starts at age 22 and that the maximum risk is not constant on the y-axis of the various panels)



References for reply

1 Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clinical Epidemiology* 2010;**2**:273–9.

2 Neovius M, Sundstrom J, Rasmussen F. Combined effects of overweight and smoking in late adolescence on subsequent mortality: nationwide cohort study. *BMJ* 2009;**338**:b496–6.

3 Ma J, Flanders WD, Ward EM, *et al.* Body Mass Index in Young Adulthood and Premature Death: Analyses of the US National Health Interview Survey Linked Mortality Files. *American Journal of Epidemiology* 2011;**174**:934–44.

4 Park HSH, Song Y-MY, Cho S-IS. Obesity has a greater impact on cardiovascular mortality in younger men than in older men among non-smoking Koreans. *International journal of epidemiology* 2006;**35**:181–7.

5 Flegal KM, Graubard BI, Williamson DF, *et al.* Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA* 2007;**298**:2028–37.

6 Strand BH, Kuh D, Shah I, *et al.* Childhood, adolescent and early adult body mass index in relation to adult mortality: results from the British 1946 birth cohort. *J Epidemiol Community Health* 2012;**66**:225–32.

7 Stevens JJ, Truesdale KPK, Wang C-HC, *et al.* Body mass index at age 25 and all-cause mortality in whites and African Americans: the Atherosclerosis Risk in Communities study. *J Adolesc Health* 2012;**50**:221–7.

8 Bjørge T, Engeland A, Tverdal A, *et al.* Body mass index in adolescence in relation to cause-specific mortality: a follow-up of 230,000 Norwegian adolescents. *American Journal of Epidemiology* 2008;**168**:30–7.

9 Engeland AA, Bjørge TT, Tverdal AA, *et al.* Obesity in adolescence and adulthood and the risk of adult mortality. *Epidemiology* 2004;**15**:79–85.

10 Jeffreys M, McCarron P, Gunnell D, *et al.* Body mass index in early and mid-adulthood, and subsequent mortality: a historical cohort study. *Int J Obes Relat Metab Disord* 2003;**27**:1391–7.

11 Engeland AA, Bjørge TT, Søgaard AJA, *et al.* Body mass index in adolescence in relation to total mortality: 32-year follow-up of 227,000 Norwegian boys and girls. *American Journal of Epidemiology* 2003;**157**:517–23.

12 Engeland AA, Bjørge TT, Selmer RMR, *et al.* Height and body mass index in relation to total mortality. *Epidemiology* 2003;**14**:293–9.

13 Yarnell JWG, Patterson CC, Thomas HF, *et al.* Comparison of weight in middle age, weight at 18 years, and weight change between, in predicting subsequent 14 year mortality and coronary

events: Caerphilly Prospective Study. *J Epidemiol Community Health* 2000;**54**:344–8.

14 Zimmermann E, Holst C, Sorensen TIA. Lifelong doubling of mortality in men entering adult life as obese. *Int J Obes (Lond)* 2011;**35**:1193–9.

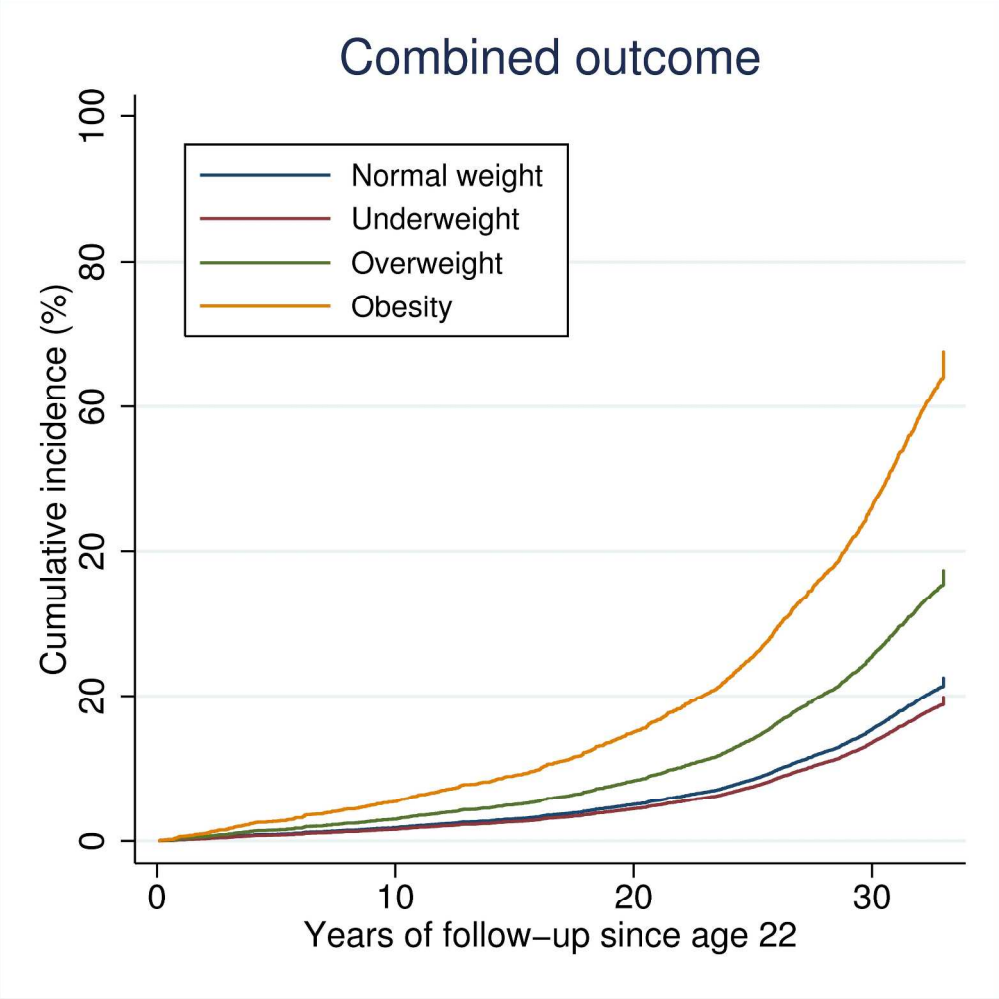


Figure 1. Body mass index in young adulthood and predicted cumulative incidence (risk) of type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before age 55 years
254x254mm (300 x 300 DPI)

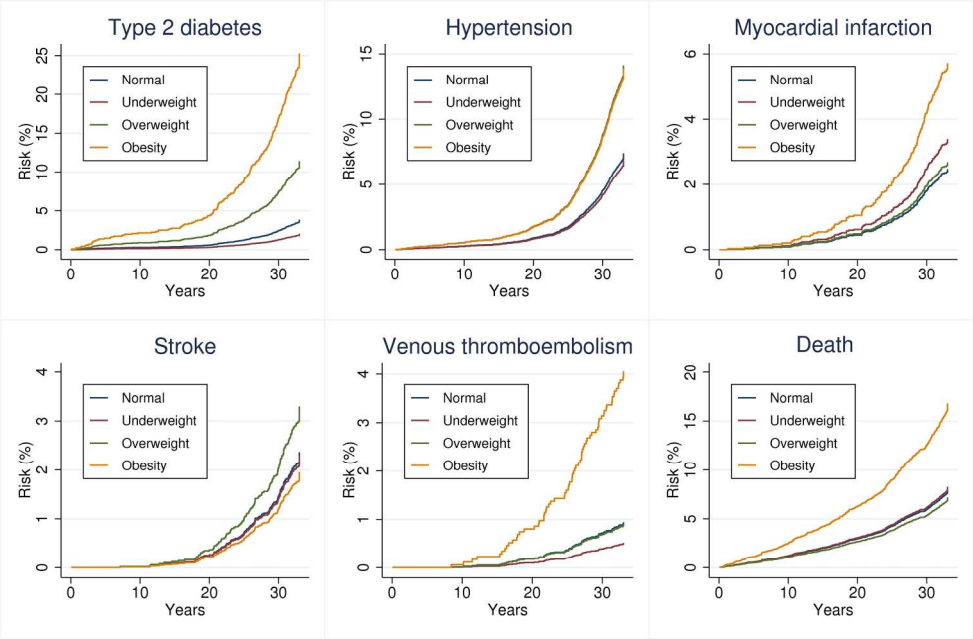


Figure 2. Body mass index in young adulthood and cumulative incidence (risk) of type 2 diabetes, cardiovascular morbidity, or death before age 55 years (note that follow-up starts at age 22 and that the maximum risk is not constant on the y-axis of the various panels)
203x135mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	-
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	7-8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	-
		Cross-sectional study—Report numbers of outcome events or summary measures	-
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	7-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; **370**:1453-7