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Association of time of obesity onset with comorbidities in treatment-seeking men and women with severe obesity

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Summary

Objectives

Early obesity onset is a risk factor for specific comorbidities in adulthood, but whether this relationship is present in men and women with severe obesity is unknown. This study aimed to examine whether obesity onset in childhood or adolescence, as compared with adulthood, is associated with higher odds of comorbidities in men and women with severe obesity.

Methods

A cross-sectional study of treatment-seeking men and women with severe obesity attending a tertiary care centre in Norway, from 2006 to 2017, was performed.

Results

A total of 4,583 participants (69.13% women) were included. Almost all men (99.69%) and women (99.18%) suffered from ≥1 comorbidities. Compared with women, men were older (mean [SD]) (45.54 [12.14] vs. 42.56 [12.00] years, $p < 0.001$) and had higher body mass index (44.06 [6.16] vs. 43.39 [5.80] kg m^{-2}, $p < 0.001$). The most prevalent comorbidities were non-alcoholic fatty liver disease, dyslipidaemia and hypertension among men and dyslipidaemia, non-alcoholic fatty liver disease and joint pain among women. After current age and body mass index were adjusted, childhood onset of obesity (0–11 years), compared with adult onset (>20 years), was associated with lower odds (OR [95% CI]) of obstructive sleep apnoea (OSA) in men (0.69 [0.53, 0.91], $p < 0.01$) and higher odds of OSA (1.49 [1.16, 1.91], $p < 0.01$) in women, and the interaction was significant ($p < 0.01$). Childhood onset of obesity was also associated with higher odds of coronary heart disease in men (1.82 [1.15, 2.89], $p = 0.01$) and type 2 diabetes in women (1.25 [1.01, 1.54], $p = 0.04$).

Conclusion

Childhood onset of obesity was associated with higher odds of coronary heart disease in men and OSA and type 2 diabetes in women, but with lower odds of OSA in men.

Keywords: Comorbidity, gender, obesity, obesity onset.

Introduction

Obesity in childhood and adolescence increases the risk of premature mortality (1) and morbidities such as cardiovascular disease, hypertension, type 2 diabetes, obstructive sleep apnoea (OSA), asthma and depression in adulthood (2–6). The associations often persist even after controlling for adult body mass index (BMI), suggesting that early obesity onset is a predictor for premature mortality and morbidity independent of the duration of obesity. Men and women with obesity generally present with different comorbidities: The prevalence of metabolic syndrome, as well as its individual components (type 2 diabetes, hypertension and dyslipidaemia), OSA and coronary heart disease, is higher among men (7–11), while depression is more strongly correlated with obesity in women (12). However, despite known gender differences, studies examining the associations between

early obesity onset and risk of comorbidities in men and women separately are limited. The *et al*. showed that women who develop obesity in childhood have increased risk of type 2 diabetes than do women who develop obesity in adulthood, but no such association was observed among men (13). Whether there is a relationship between early obesity onset and risk of comorbidities in adults with severe obesity and whether the associations differ between men and women are not known. Knowledge about these potential relationships may be important for individualized prevention and treatment of obesity-related disorders in clinical practice. The hypotheses of the present study are that early onset of obesity (childhood or adolescence), as compared with obesity onset later in life (adulthood), is associated with higher odds of obesity-related comorbidities in patients with severe obesity and that the associations are gender specific.

Materials and methods

Study design, setting and population

A total of 4,636 consecutive men and women referred for treatment of severe obesity (BMI $\geq$ 40.00 kg m^{-2} or BMI $\geq$ 35.00 kg m^{-2} with at least one obesity-related comorbidity) and attending the Morbid Obesity Center at Vestfold Hospital Trust, Norway, during the period from 20 January 2006 until 10 March 2017 were assessed for eligibility. The Morbid Obesity Center is a tertiary care centre providing both specialized medical and surgical obesity treatment to patients with severe obesity. Men and women with incorrect or missing data on time of obesity onset (n = 18) or BMI (n = 35) were excluded, leaving 4,583 men and women to be included in the analysis. A small percentage (2.38%) of the patients had a current BMI between 30.00 and 34.99 kg m^{-2}. The Regional Committee for Medical and Health Research Ethics approved the study (S-05175). The participants provided written informed consent, and the study was performed in accordance with the Declaration of Helsinki.

Variables, data sources, measurements and definitions

A detailed medical history on obesity-related comorbidities and data on relevant current medication use were obtained through clinical records and clinical outcome assessments by trained physicians. All anthropometric and blood pressure measurements were performed by trained study personnel. The patients had their weight and height measured wearing light clothing, without shoes; and BMI was subsequently calculated (kg m^{-2}). Waist circumference (WC) was measured with a tape measure midway between the lowest rib margin and the iliac crest. Blood pressure was measured with an appropriate cuff after at least 5-min rest with the patient seated in an upright position. Three measurements were registered, and the average of the second and third measurements was used in the study.

Hypertension

Patients were classified with hypertension if the systolic blood pressure was $\geq$140 mmHg and/or the diastolic blood pressure $\geq$90 mmHg (14) or if blood-pressure-lowering medication was used.

Dyslipidaemia

Patients were classified as having dyslipidaemia if low-density lipoprotein (LDL) cholesterol $\geq$ 2.6 mmol L^{-1} at study visit (15) or if lipid-lowering agents was used.

Non-alcoholic fatty liver disease

The non-alcoholic fatty liver disease (NAFLD) liver fat score was used to evaluate the presence of NAFLD ($\geq$55.6 mg triglyceride per gram liver tissue or $\geq$5.56% of liver tissue weight) (16). The NAFLD liver fat score has been validated against magnetic resonance spectroscopy and yielded 86% sensitivity and 71% specificity in a population with obesity. The score was calculated using the following formula: 2.89 + 1.18 * metabolic syndrome (yes = 1/no = 0) + 0.45 * type 2 diabetes (yes = 2/no = 0) + 0.15 * fasting serum insulin (mU L^{-1}) + 0.04 * fasting serum aspartate transaminase (U L^{-1}) − 0.94 * aspartate transaminase/alanine aminotransferase.

The presence or absence of other obesity-related comorbidities such as coronary heart disease, type 2 diabetes, reflux disease, gout, gall bladder disease, asthma, joint pain, OSA and anxiety and/or depression was based on clinical outcome assessments in combination with clinical records, biomarkers and current use of medications.

Through a thorough conversation between the patient and the physician, time of obesity onset was agreed to be childhood onset (0–11 years), adolescent onset (12–20 years) or adult onset (>20 years).

Biochemical analysis

Blood samples were obtained after an overnight fast by venipuncture and collected in Vacutainer® (Greiner Bio-One GmbH, Kremsmunster, Austria) gel tubes, and serum

was separated from cells within 2 h. Analyses of serum glucose and blood lipids were performed using dry reagent slide technology on the Vitros 950 Analyzer until November 2006 and thereafter on the Vitros FS 5.1 (Ortho-Clinical Diagnostics, Rochester, NY). Sera for analysis of insulin were stored at −20°C and analysed within 1 week of blood sampling at the Hormone Laboratory, Oslo University Hospital, Aker. Insulin was analysed in serum by radioimmunoassay (Linco Research Inc., St Charles, MO, and DiaSorin, Stillwater, MN). All other analyses were performed on the day of blood sampling at the Department of Clinical Chemistry at Vestfold Hospital Trust.

Statistical methods

Data are presented as means (standard deviation [SD]) or proportions (%). Continuous variables were compared using independent samples *t*-test or one-way ANOVA and categorical variables with χ^2 test. Logistic regression analyses were used to examine the associations between time of obesity onset and obesity-related comorbidities (dependent variables) in men and women separately. The independent variable 'time of obesity onset' was categorized into childhood onset, adolescent onset and adult onset, and the latter was selected as reference category. Current age and BMI were identified as possible confounding factors and were included in the multivariable model. WC was included in supplementary multivariable models. All probability values are two tailed and considered significant when <0.05. Statistical analyses were performed with SPSS 22 (SPSS Inc., Chicago, IL).

Results

Demographic and clinical characteristics

Almost all patients were of Caucasian ethnicity (97.40%). Men made up 30.87% of the population, and they were on average 3 years older than the women (mean [SD]) (45.54 [12.14] years vs. 42.56 [12.00] years, $p < 0.001$) (Table 1). Fewer men than women had higher education (23.07% vs. 26.43%, $p = 0.02$); however, men were more often currently employed (56.83% vs. 53.26%, $p = 0.03$) and less often receivers of disability benefits (20.70% vs. 25.30%, $p < 0.01$). Compared with women, men had slightly higher BMI (44.06 [6.16] kg m^{-2} vs. 43.39 [5.80] kg m^{-2}, $p < 0.001$), had larger WC (139.01 [13.62] cm vs. 125.18 [12.64] cm, $p < 0.001$) and were less often current smokers (21.02% vs. 26.41%, $p < 0.001$). Blood pressure, triglyceride levels, fasting glucose, insulin, aspartate transaminase and alanine aminotransferase levels were higher among men, while LDL and total cholesterol levels were lower than those among women.

Almost all men (99.69%) and women (99.18%) suffered from one or more obesity-related comorbidities, and more men than women suffered from multiple (two or more) comorbidities (97.41% vs. 94.03%, $p < 0.001$). NAFLD was the most prevalent comorbidity among men (93.67%), followed by dyslipidaemia (81.82%) and hypertension (60.47%), while dyslipidaemia (81.12%), NAFLD (73.66%) and joint pain (61.07%) were the most prevalent comorbidities among women (Table 1). Hypertension, type 2 diabetes, coronary heart disease, OSA and gout were more prevalent in men compared with women; while asthma, gall bladder disease and anxiety and/or depression were more prevalent among the female participants. The prevalence of joint pain and reflux did not significantly differ between genders.

A total of 35.55% of the male population reported obesity onset in childhood, while 18.59% and 45.87% developed obesity in adolescence and adulthood, respectively (Table 2). Men who developed obesity as adults were significantly older (51.47 [10.10] years) and had lower BMI (42.98 [5.71] kg m^{-2}) and WC (137.50 [12.50] cm) than were men who reported obesity onset in childhood (40.66 [12.08] years, 45.20 [6.57] kg m^{-2} and 140.71 [14.49] cm) and adolescence (40.23 [10.10] years, 44.55 [6.01] kg m^{-2} and 139.50 [14.17] cm). Smoking was more common among men with obesity onset in childhood (24.70%) than among men who developed obesity in adolescence (19.01%) or adulthood (18.98%).

There was a similar pattern among women; 33.68% of the women developed obesity in childhood, while 26.45% and 39.87% reported onset of obesity in adolescence and adulthood, respectively (Table 3). Women who developed obesity during adulthood were significantly older (48.61 [9.82] years) and had lower BMI (42.38 [5.30] kg m^{-2}) and WC (123.85 [11.64] cm) than were those who reported onset of obesity in childhood (38.05 [12.37] years, 44.44 [6.34] kg m^{-2} and 126.64 [13.47] cm) and adolescent years (39.21 [10.58] years, 43.59 [5.54] kg m^{-2} and 125.31 [12.77] cm). Women who developed obesity as adults were less often current smokers (20.84%) than were those who developed obesity during childhood (31.58%) or adolescence (28.20%).

Odds ratios of comorbidities according to time of obesity onset in men and women

After adjustments for current age and BMI, men who reported obesity onset during childhood had higher odds (OR [95% confidence interval]) of coronary heart disease (1.82 [1.15, 2.89], $p = 0.01$) and lower odds of OSA (0.69

Table 1 Clinical characteristics of treatment-seeking men and women with severe obesity

	Men	Women	*p*-value
N (%)	1,415 (30.87)	3,168 (69.13)	
Age (years), mean (SD)	45.54 (12.14)	42.56 (12.00)	<0.001
Ethnicity (non-Caucasian), *n* (%)	35 (2.48)	84 (2.65)	0.73
Higher education,[a,b] *n* (%)	296 (23.07)	764 (26.43)	0.02
Current employment,[a] *n* (%)	736 (56.83)	1,553 (53.26)	0.03
Disability benefits,[a,c] *n* (%)	267 (20.70)	732 (25.30)	<0.01
Current smoker,[a] *n* (%)	297 (21.02)	836 (26.41)	<0.001
BMI (kg m^{-2}), mean (SD)	44.06 (6.16)	43.39 (5.80)	<0.001
Weight (kg), mean (SD)	143.61 (22.47)	121.11 (18.04)	<0.001
Waist circumference (cm), mean (SD)	139.01 (13.62)	125.18 (12.64)	<0.001
SBP (mmHg), mean (SD)	135 (15)	129 (15)	<0.001
DBP (mmHg), mean (SD)	83 (11)	81 (10)	<0.001
Biochemical parameters, mean (SD)			
Total cholesterol (mmol L^{-1})	4.91 (1.01)	5.15 (0.96)	<0.001
LDL cholesterol (mmol L^{-1})	2.90 (0.89)	3.09 (0.87)	<0.001
HDL cholesterol (mmol L^{-1})	1.09 (0.26)	1.29 (0.31)	<0.001
Non-HDL cholesterol (mmol L^{-1})	3.82 (1.00)	3.86 (0.95)	0.14
Triglycerides (mmol L^{-1})	2.12 (1.51)	1.77 (1.26)	<0.001
Fasting glucose (mmol L^{-1})	6.54 (2.49)	5.89 (2.15)	<0.001
Fasting insulin (pmol L^{-1})	168 (162)	131 (124)	<0.001
ASAT (U L^{-1})	33 (18)	26 (12)	<0.001
ALAT (U L^{-1})	43 (25)	29 (19)	<0.001
Comorbidity, *n* (%)			
Hypertension	855 (60.47)	1,249 (39.44)	<0.001
Type 2 diabetes	501 (35.43)	707 (22.35)	<0.001
Dyslipidaemia	1,112 (81.82)	2,522 (81.12)	0.58
Coronary heart disease	121 (8.55)	56 (1.77)	<0.001
Obstructive sleep apnoea	543 (38.37)	462 (14.58)	<0.001
Asthma	186 (13.14)	684 (21.59)	<0.001
NAFLD	1,243 (93.67)	2,190 (73.66)	<0.001
Gall bladder disease	67 (4.73)	460 (14.52)	<0.001
Reflux	214 (15.12)	545 (17.21)	0.08
Gout	141 (9.96)	128 (4.04)	<0.001
Joint pain	853 (60.28)	1,934 (61.07)	0.62
Anxiety and/or depression	468 (33.07)	1,561 (49.31)	<0.001

[a]Owing to missing values, the total number of participants varied for each of the following variables: higher education, *n* = 4,174 (1,283 men and 2,891 women); current employment, *n* = 4,211 (1,295 men and 2,916 women); disability benefits, *n* = 4,183 (1,290 men and 2,893 women); and current smoker, *n* = 4,578 (1,413 men and 3,165 women).

[b]College or university degree.

[c]Currently receiving disability benefits.

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; SBP, systolic blood pressure; SD, standard deviation.

[0.53, 0.91], $p < 0.01$) than had men who developed obesity as adults (Table 4). Additional adjustments for WC did not significantly influence the results (Table S1), while among women, those who reported obesity onset during childhood had higher odds of type 2 diabetes (1.25 [1.01, 1.54], $p = 0.04$) and OSA (1.49 [1.16, 1.91], $p < 0.01$) than had women who developed obesity during adulthood (Table 5). However, after additional adjustments for WC, there was no significant association between time of obesity onset and type 2 diabetes (Table S1). Adjustment for smoking, higher education, current employment and disability benefits did not significantly influence the results (data not shown).

There was a significant interaction between time of obesity onset and gender with regard to OSA ($p < 0.01$), and the reported estimates were not significantly influenced by additional adjustments for WC.

Discussion

In this cross-sectional study of 4,583 consecutive treatment-seeking men and women with severe obesity,

Table 2 Clinical characteristics of treatment-seeking men with severe obesity according to the time of obesity onset[a]

	Childhood	Adolescent	Adult	*p*-value[b]
N (%)	503 (35.55)	263 (18.59)	649 (45.87)	
Age (years), mean (SD)	40.66 (12.08)	40.23 (10.10)	51.47 (10.10)	<0.001
Ethnicity (non-Caucasian), *n* (%)	11 (2.19)	3 (1.14)	21 (3.24)	0.16
Higher education,[c,d] *n* (%)	84 (18.46)	50 (20.83)	162 (27.55)	<0.01
Current employment,[c] *n* (%)	282 (61.30)	148 (61.67)	306 (51.43)	<0.01
Disability benefits,[c,e] *n* (%)	59 (12.88)	36 (15.06)	172 (29.01)	<0.01
Current smoker,[c] *n* (%)	124 (24.70)	50 (19.01)	123 (18.98)	0.04
BMI (kg m^{-2}), mean (SD)	45.20 (6.57)	44.55 (6.01)	42.98 (5.71)	<0.001
Weight (kg), mean (SD)	148.37 (23.57)	146.00 (23.20)	138.95 (20.29)	<0.001
Waist circumference (cm), mean (SD)	140.71 (14.49)	139.50 (14.17)	137.50 (12.50)	<0.001
SBP (mmHg), mean (SD)	134 (16)	133 (14)	137 (16)	<0.01
DBP (mmHg), mean (SD)	83 (10)	83 (13)	84 (10)	0.52
Biochemical parameters, mean (SD)				
Total cholesterol (mmol L^{-1})	4.87 (0.96)	5.07 (1.03)	4.88 (1.03)	0.02
LDL cholesterol (mmol L^{-1})	2.86 (0.84)	3.07 (0.91)	2.86 (0.91)	<0.01
HDL cholesterol (mmol L^{-1})	1.09 (0.24)	1.08 (0.24)	1.10 (0.28)	0.65
Non-HDL cholesterol (mmol L^{-1})	3.78 (0.97)	3.98 (1.03)	3.78 (1.00)	0.01
Triglycerides (mmol L^{-1})	2.12 (1.60)	2.06 (1.16)	2.14 (1.56)	0.75
Fasting glucose (mmol L^{-1})	6.31 (2.37)	6.21 (2.13)	6.85 (2.67)	<0.001
Fasting insulin (pmol L^{-1})	173 (179)	157 (102)	169 (167)	0.41
ASAT (U L^{-1})	33 (15)	34 (27)	33 (16)	0.56
ALAT (U L^{-1})	45 (27)	45 (27)	41 (22)	0.03
Comorbidity, *n* (%)				
Hypertension	265 (52.68)	132 (50.19)	458 (70.68)	<0.001
Type 2 diabetes	148 (29.42)	79 (30.04)	274 (42.28)	<0.001
Dyslipidaemia	381 (79.71)	204 (79.69)	527 (84.32)	0.09
Coronary heart disease	40 (7.95)	11 (4.18)	70 (10.79)	<0.01
Obstructive sleep apnoea	155 (30.82)	87 (33.08)	301 (46.38)	<0.001
Asthma	63 (12.52)	35 (13.31)	88 (13.56)	0.87
NAFLD	433 (92.72)	225 (91.46)	585 (95.28)	0.07
Gall bladder disease	23 (4.57)	12 (4.56)	32 (4.93)	0.95
Reflux	70 (13.92)	36 (13.69)	108 (16.64)	0.34
Gout	40 (7.95)	21 (7.98)	80 (12.33)	0.02
Joint pain	288 (57.26)	149 (56.65)	416 (64.10)	0.03
Anxiety and/or depression	167 (33.20)	83 (31.56)	218 (33.59)	0.84

[a]Time of obesity onset was categorized as childhood onset (age 0–11), adolescent onset (age 12–20) and adult onset (age > 20).
[b]Comparing childhood, adolescence and adulthood. Continuous variables were compared using one-way ANOVA and categorical variables with χ^2 test.
[c]Owing to missing values, the total number of participants varied for each of the following variables: higher education, *n* = 1,283; current employment, *n* = 1,295; disability benefits, *n* = 1,290; and current smoker, *n* = 1,413.
[d]College or university degree.
[e]Currently receiving disability benefits.
Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; SBP, systolic blood pressure; SD, standard deviation.

childhood onset of obesity, as compared with adult onset of obesity, was associated with 82% higher odds of coronary heart disease among men and 25% higher odds of type 2 diabetes among women. Surprisingly, childhood onset of obesity was associated with 31% lower odds of OSA in men but 51% higher odds of OSA in women, and the interaction was statistically significant.

One of the hypotheses of the present study was that earlier onset of obesity was associated with increased odds of comorbidities; however, this relationship was only evident for a limited number of comorbid disorders. Among men, onset of obesity in childhood was associated with higher odds of coronary heart disease compared with adult onset of obesity. In accordance with the results of the present study, previous studies have found childhood obesity to be related to earlier appearance of atherosclerotic lesions (17) and that longer duration of obesity is positively associated with risk of

Table 3 Clinical characteristics of treatment-seeking women with severe obesity according to the time of obesity onset[a]

	Childhood	Adolescent	Adult	*p*-value[b]
N (%)	1,067 (33.68)	838 (26.45)	1,263 (39.87)	
Age (years), mean (SD)	38.05 (12.37)	39.21 (10.58)	48.61 (9.82)	<0.001
Ethnicity (non-Caucasian), *n* (%)	20 (1.88)	12 (1.43)	52 (4.12)	<0.001
Higher education,[c,d] *n* (%)	248 (25.57)	189 (24.64)	327 (28.34)	0.15
Current employment,[c] *n* (%)	532 (54.40)	456 (59.14)	565 (48.41)	<0.001
Disability benefits,[c,e] *n* (%)	193 (19.94)	145 (18.93)	394 (33.99)	<0.001
Current smoker,[c] *n* (%)	337 (31.58)	236 (28.20)	263 (20.84)	<0.001
BMI (kg m^{-2}), mean (SD)	44.44 (6.34)	43.59 (5.54)	42.38 (5.30)	<0.001
Weight (kg), mean (SD)	124.60 (19.56)	122.68 (17.08)	117.11 (16.51)	<0.001
Waist circumference (cm), mean (SD)	126.64 (13.47)	125.31 (12.77)	123.85 (11.64)	<0.001
SBP (mmHg), mean (SD)	127 (15)	128 (15)	131 (15)	<0.001
DBP (mmHg), mean (SD)	80 (10)	81 (9)	81 (9)	<0.01
Biochemical parameters, mean (SD)				
Total cholesterol (mmol L^{-1})	5.13 (0.96)	5.09 (0.94)	5.21 (0.97)	0.01
LDL cholesterol (mmol L^{-1})	3.09 (0.85)	3.05 (0.83)	3.11 (0.90)	0.31
HDL cholesterol (mmol L^{-1})	1.26 (0.32)	1.27 (0.30)	1.31 (0.32)	<0.001
Non-HDL cholesterol (mmol L^{-1})	3.86 (0.94)	3.81 (0.94)	3.89 (0.96)	0.20
Triglycerides (mmol L^{-1})	1.80 (1.68)	1.75 (1.08)	1.77 (0.92)	0.69
Fasting glucose (mmol L^{-1})	5.90 (2.37)	5.60 (1.70)	6.06 (2.20)	<0.001
Fasting insulin (pmol L^{-1})	132 (112)	130 (111)	131 (142)	0.97
ASAT (U L^{-1})	25 (10)	25 (11)	26 (14)	0.03
ALAT (U L^{-1})	28 (16)	29 (18)	30 (22)	0.05
Comorbidity, *n* (%)				
Hypertension	348 (32.61)	269 (32.10)	632 (50.08)	<0.001
Type 2 diabetes	229 (21.50)	144 (17.20)	334 (26.47)	<0.001
Dyslipidaemia	837 (80.25)	636 (77.47)	1,049 (84.26)	<0.001
Coronary heart disease	15 (1.41)	6 (0.72)	35 (2.77)	<0.01
Obstructive sleep apnoea	155 (14.53)	100 (11.93)	207 (16.39)	0.02
Asthma	211 (19.78)	175 (20.88)	298 (23.59)	0.07
NAFLD	752 (74.83)	559 (70.58)	879 (74.74)	0.07
Gall bladder disease	143 (13.40)	116 (13.84)	201 (15.93)	0.18
Reflux	159 (14.92)	115 (13.72)	271 (21.46)	<0.001
Gout	35 (3.28)	25 (2.99)	68 (5.39)	0.01
Joint pain	590 (55.30)	500 (59.74)	844 (66.83)	<0.001
Anxiety and/or depression	522 (48.97)	417 (49.82)	622 (49.25)	0.93

[a]Time of obesity onset was categorized as childhood onset (age 0–11), adolescent onset (age 12–20) and adult onset (age > 20).
[b]Comparing childhood, adolescence and adulthood. Continuous variables were compared using one-way ANOVA and categorical variables with χ^2 test.
[c]Owing to missing values, the total number of participants varied for each of the following variables: higher education, *n* = 2,891; current employment, *n* = 2,916; disability benefits, *n* = 2,893; and current smoker, *n* = 3,165.
[d]College or university degree.
[e]Currently receiving disability benefits.
Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; SBP, systolic blood pressure; SD, standard deviation.

coronary heart disease (18). Of note, although earlier onset of obesity may imply longer duration of obesity, men and women with obesity onset in childhood in the current cohort were more than 10 years younger than those with obesity onset in adulthood. Also, the mean age of the participants with adult obesity onset was relatively low (52 and 49 years for men and women, respectively). Thus, the duration of obesity between those who had childhood, adolescent or adult onset of obesity did not necessarily substantially differ. This implies that the specific time of obesity onset, and not only the duration of obesity, may be important when estimating risk of comorbidities later in life. The non-significant association between time of obesity onset and odds of coronary heart disease among women may be a consequence of the very low prevalence (1.77%) of female participants having verified coronary heart disease. Heart disease is often under-recognized in women because of the differences

Table 4 Odds ratios of comorbidities according to time of obesity onset[a] in treatment-seeking men with severe obesity

	Childhood		Adolescent		Adult
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR[b]
Univariate					
Hypertension	0.46 (0.36, 0.59)	<0.001	0.42 (0.31, 0.56)	<0.001	1.00
Type 2 diabetes	0.57 (0.44, 0.73)	<0.001	0.57 (0.43, 0.80)	<0.01	1.00
Dyslipidaemia	0.73 (0.54, 1.00)	0.05	0.73 (0.50, 1.06)	0.10	1.00
Coronary heart disease	0.72 (0.48, 1.07)	0.11	0.36 (0.19, 0.69)	<0.01	1.00
Obstructive sleep apnoea	0.52 (0.40, 0.66)	<0.001	0.57 (0.42, 0.77)	<0.001	1.00
Asthma	0.91 (0.65, 1.29)	0.61	0.98 (0.64, 1.29)	0.92	1.00
NAFLD	0.63 (0.38, 1.05)	0.08	0.53 (0.30, 0.95)	0.03	1.00
Gall bladder disease	0.92 (0.53, 1.60)	0.78	0.92 (0.47, 1.82)	0.81	1.00
Reflux	0.81 (0.58, 1.12)	0.21	0.79 (0.53, 1.19)	0.27	1.00
Gout	0.61 (0.41, 0.92)	0.02	0.62 (0.37, 1.02)	0.06	1.00
Joint pain	0.75 (0.59, 0.95)	<0.001	0.73 (0.55, 0.98)	<0.01	1.00
Anxiety and/or depression	0.98 (0.77, 1.26)	0.89	0.91 (0.67, 1.24)	0.56	1.00
Multivariate[c]					
Hypertension	1.14 (0.85, 1.52)	0.39	1.05 (0.75, 1.47)	0.79	1.00
Type 2 diabetes	1.14 (0.86, 1.51)	0.37	1.25 (0.89, 1.77)	0.20	1.00
Dyslipidaemia	1.04 (0.73, 1.47)	0.84	1.02 (0.68, 1.52)	0.94	1.00
Coronary heart disease	1.82 (1.15, 2.89)	0.01	1.04 (0.51, 2.11)	0.92	1.00
Obstructive sleep apnoea	0.69 (0.53, 0.91)	<0.01	0.79 (0.57, 1.09)	0.15	1.00
Asthma	0.97 (0.66, 1.42)	0.87	1.05 (0.67, 1.65)	0.83	1.00
NAFLD	0.76 (0.43, 1.34)	0.34	0.67 (0.36, 1.26)	0.21	1.00
Gall bladder disease	1.16 (0.64, 2.11)	0.62	1.19 (0.58, 2.47)	0.64	1.00
Reflux	1.10 (0.77, 1.57)	0.60	1.09 (0.71, 1.68)	0.72	1.00
Gout	1.00 (0.65, 1.54)	0.99	1.07 (0.62, 1.83)	0.82	1.00
Joint pain	1.11 (0.85, 1.45)	0.46	1.10 (0.80, 1.51)	0.56	1.00
Anxiety and/or depression	0.89 (0.68, 1.17)	0.40	0.82 (0.59, 1.14)	0.24	1.00

[a]Time of obesity onset was categorized as childhood onset (age 0–11), adolescent onset (age 12–20) and adult onset (age > 20).
[b]Reference category.
[c]Adjusted for age and body mass index.
Abbreviation: NAFLD, non-alcoholic fatty liver disease.

in clinical presentation and the misperception that women are protected against cardiovascular disease (19). Women are consequently less likely to be referred for diagnostic procedures than are men; thus, the prevalence of coronary heart disease among women is possibly underestimated (19).

On the other hand, women with obesity onset in childhood had higher odds of type 2 diabetes than had women who had onset of obesity in adulthood, and this association was not observed among men. In accordance with the results of the present study, The *et al*. found obesity onset before the age of 16, as compared with obesity onset after 18 years of age, to be associated with increased odds of type 2 diabetes in women, but not in men (13). The authors speculated that the association was a consequence of the changes in insulin sensitivity and increased insulin resistance during puberty, which is especially pronounced in women. However, the result should be interpreted with caution as the effect size was moderate and the *p*-value close to non-significant. Also, women with childhood onset of obesity had larger WC than had those with adult onset of obesity, and when including current WC in the multivariate model, there was no longer a significant association between time of obesity onset and type 2 diabetes.

Unexpectedly, men with childhood onset of obesity had lower odds of OSA than had men who developed obesity as adults, while women with childhood-onset obesity had increased odds of OSA than had women who developed obesity in adulthood. As visceral adipose tissue, and not subcutaneous abdominal adipose tissue, is associated with increased risk of OSA (20,21), differences in fat deposition between men and women across the lifespan may serve as an explanation to this interaction. Increasing adiposity in childhood is related to increased deposition of visceral fat (22), but in women, during and after puberty, oestrogen influences fat storage in hips and thighs (23). Thus, women who develop obesity during childhood years may gain more visceral fat than do women who develop obesity as adults. In contrast,

Table 5 Odds ratios of comorbidities according to time of obesity onset[a] in treatment-seeking women with severe obesity

	Childhood		Adolescent		Adult
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR[b]
Univariate					
Hypertension	0.48 (0.41, 0.57)	<0.001	0.47 (0.39, 0.57)	<0.001	1.00
Type 2 diabetes	0.76 (0.63, 0.92)	<0.01	0.58 (0.46, 0.72)	<0.001	1.00
Dyslipidaemia	0.76 (0.61, 0.94)	0.01	0.64 (0.51, 0.80)	<0.001	1.00
Coronary heart disease	0.50 (0.27, 0.92)	0.03	0.25 (0.12, 0.60)	<0.01	1.00
Obstructive sleep apnoea	0.87 (0.69, 1.09)	0.22	0.69 (0.54, 0.89)	<0.01	1.00
Asthma	0.80 (0.65, 0.97)	0.03	0.86 (0.69, 1.06)	0.15	1.00
NAFLD	1.00 (0.83, 1.22)	0.97	0.81 (0.66, 0.99)	0.04	1.00
Gall bladder disease	0.82 (0.65, 1.03)	0.09	0.85 (0.66, 1.09)	0.19	1.00
Reflux	0.64 (0.52, 0.80)	<0.001	0.58 (0.46, 0.74)	<0.001	1.00
Gout	0.60 (0.39, 0.92)	0.02	0.54 (0.34, 0.86)	0.01	1.00
Joint pain	0.61 (0.52, 0.73)	0.02	0.74 (0.62, 0.88)	0.04	1.00
Anxiety and/or depression	0.99 (0.84, 1.16)	0.89	1.02 (0.86, 1.22)	0.80	1.00
Multivariate[c]					
Hypertension	1.11 (0.91, 1.36)	0.30	1,04 (0.84, 1.28)	0.73	1.00
Type 2 diabetes	1.25 (1.01, 1.54)	0.04	0.90 (0.71.1.14)	0.37	1.00
Dyslipidaemia	1.16 (0.91, 1.47)	0.24	0.91 (0.72, 1.16)	0.46	1.00
Coronary heart disease	0.96 (0.51, 1.82)	0.90	0.49 (0.20, 1.19)	0.12	1.00
Obstructive sleep apnoea	1.49 (1.16, 1.91)	<0.01	1.17 (0.89, 1.53)	0.28	1.00
Asthma	0.98 (0.79, 1.21)	0.84	1.03 (0.82, 1.29)	0.79	1.00
NAFLD	1.08 (0.87, 1.33)	0.51	0.88 (0.71, 1.10)	0.27	1.00
Gall bladder disease	1.03 (0.80, 1.32)	0.84	1.05 (0.81, 1.37)	0.69	1.00
Reflux	0.97 (0.77, 1.22)	0.77	0.84 (0.65, 1.08)	0.17	1.00
Gout	0.95 (0.61, 1.48)	0.82	0.89 (0.54, 1.45)	0.63	1.00
Joint pain	0.86 (0.71, 1.04)	0.11	1.01 (0.83, 1.22)	0.95	1.00
Anxiety and/or depression	0.96 (0.80, 1.15)	0.64	1.00 (0.83, 1.20)	0.97	1.00

[a]Time of obesity onset was categorized as childhood onset (age 0–11), adolescent onset (age 12–20) and adult onset (age > 20).
[b]Reference category.
[c]Adjusted for age and body mass index.
Abbreviation: NAFLD, non-alcoholic fatty liver disease.

visceral adipose tissue has been found to grow larger in men after age 12 as the influence of testosterone favours central deposition of fat (23). Thus, in men, development of obesity after puberty may be especially unfavourable with respect to central adiposity.

In accordance with earlier studies of men and women with obesity (4,7,10), almost all men and women in the present cohort suffered from one or more obesity-related comorbidities. The prevalence of NAFLD has been reported to exceed 90% in patients with severe obesity undergoing bariatric surgery (24), and accordingly, the prevalence of NAFLD is 93.67% among men and 73.66% among women in the current study. However, the NAFLD liver fat score is only a surrogate marker of NAFLD, and there is a possibility that the prevalence has been overestimated owing to the low cut-off value for NAFLD diagnosis (≥55.6 mg triglyceride per gram liver tissue or ≥5.56% of liver tissue weight). Increased LDL cholesterol is an established causal risk factor for cardiovascular disease, and in the current study, dyslipidaemia (LDL cholesterol ≥ 2.6 mmol L^{-1} and/or use of lipid-lowering agents) was the second most prevalent comorbidity among men (81.82%). Notably, serum levels of non-high-density-lipoprotein cholesterol, which contains all the atherogenic lipids and may be a superior marker for cardiovascular disease risk among men and women with obesity (25), were also similar in men and women. The present results also confirm previous findings of comorbidities such as type 2 diabetes and hypertension, NAFLD, OSA and coronary heart disease being more common among men (7–9), and anxiety and/or depression, asthma and gallbladder disease being more frequently observed among women (11).

A major strength of the present study is the large cohort of consecutively included treatment-seeking men and women with severe obesity. Also, this study is strengthened in that demographic data, obesity-related comorbidities and data on relevant current medication use were obtained in a clinical setting by a trained physician as opposed to patient-reported data only. This study

does also have several limitations. First, the study participants were referred to a tertiary care centre for evaluation and treatment with bariatric surgery, medical therapy or long-term lifestyle rehabilitation for severe obesity; thus, the results cannot be generalized to the general population of men and women with obesity (i.e. non-treatment-seeking men and women). Second, the majority was of Caucasian ethnicity, and as such, the results may not be applicable to other ethnicities. Third, given the cross-sectional design, conclusions on causality or causal directions between obesity and comorbidities cannot be made. Fourth, although medical history was retrieved in a clinical setting, we cannot exclude the possibility of recall bias especially with respect to time of obesity onset. However, previous studies have reported measured and recalled weights to be highly correlated, with men tending to slightly overestimate their earlier weight and women to underestimate it (26–29). Recalls of previous weights have also been found not to be significantly influenced by the passage of time, education or accuracy of current weight reports (28). Fifth, as the patients did not go through extensive diagnostic procedures of all the obesity-related comorbidities such as sleep registrations or coronary angiography, prevalence of several comorbidities may be underestimated. Finally, there is always a risk of false-positive findings in studies including multiple outcome measures. The effect sizes should be taken into account when interpreting significance of associations, paying particular attention to associations with p-values < 0.01.

Conclusion

Early obesity onset was associated with increased odds of coronary heart disease in adult men and type 2 diabetes in adult women. Surprisingly, early obesity onset was associated with decreased odds of OSA in men and increased odds of OSA in women. If the results are confirmed, clinicians may use information on obesity debut to identify patients with severe obesity who should be screened for undiagnosed coronary heart disease, OSA and type 2 diabetes.

Conflict of interest statement

The authors declare no conflicts of interest.

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Author Contributions

H. B. and L. H. B. analysed data. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Odds ratios of comorbidities according to time of obesity onset1 in treatment-seeking men and women with severe obesity.