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, <0.001) and had higher body mass index (44.06 [6.16] vs. 43.39 [5.80] kg m⁻², <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], <0.01) and higher odds of OSA (1.49 [1.16, 1.91], <0.01) in women, and the interaction was significant (<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 ≥ 40.00 kg m⁻² or BMI ≥ 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 ≥ 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 ≥ 140 mmHg and/or the diastolic blood pressure ≥ 90 mmHg (14) or if blood-pressure-lowering medication was used.

Dyslipidaemia

Patients were classified as having dyslipidaemia if low-density lipoprotein (LDL) cholesterol ≥ 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 (≥ 55.6 mg triglyceride per gram liver tissue or ≥ 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 χ² 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 men 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 obesity onset 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 [0.45, 1.00]).
[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,
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 2 Clinical characteristics of treatment-seeking men with severe obesity according to the time of obesity onseta

|                         | Childhood | Adolescent | Adult     | p-valueb |
|-------------------------|-----------|------------|-----------|----------|
| N (%)                   | 503 (35.55) | 263 (18.59) | 649 (45.87) | <0.001   |
| Age (years), mean (SD)  | 40.66 (12.08) | 40.23 (10.10) | 51.47 (10.10) | 0.16     |
| Ethnicity (non-Caucasian), n (%) | 11 (2.19) | 3 (1.14) | 21 (3.24) | 0.01     |
| Higher education, n (%)  | 84 (18.46) | 50 (20.83) | 162 (27.55) | <0.01    |
| Current employment, n (%) | 282 (61.30) | 148 (61.67) | 306 (51.43) | <0.01    |
| Disability benefits, n (%) | 59 (12.88) | 36 (15.06) | 172 (29.01) | <0.01    |
| Current smoker, 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 (82.72) | 225 (91.48) | 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 (7.88) | 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     |

aTime of obesity onset was categorized as childhood onset (age 0–11), adolescent onset (age 12–20) and adult onset (age > 20).
bComparing childhood, adolescence and adulthood. Continuous variables were compared using one-way ANOVA and categorical variables with χ2 test.
cOwing 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.
dCollege or university degree.
eCurrently 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 3 Clinical characteristics of treatment-seeking women with severe obesity according to the time of obesity onseta |
|---------------------------------------------------------------|
| N (%) | Childhood | Adolescent | Adult | p-valueb |
|-------|-----------|------------|-------|----------|
| 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, n (%) | 248 (25.57) | 189 (24.64) | 327 (28.34) | 0.15 |
| Current employment, n (%) | 532 (54.40) | 456 (59.14) | 565 (48.41) | <0.001 |
| Disability benefits, n (%) | 193 (19.94) | 145 (18.93) | 394 (33.99) | <0.001 |
| Current smoker, n (%) | 337 (31.58) | 236 (28.20) | 263 (20.84) | <0.001 |
| BMI (kg m\(^{-2}\)), mean (SD) | 5.13 (0.96) | 5.09 (0.94) | 5.21 (0.97) | 0.01 |
| 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) | <0.01 |
| DBP (mmHg), mean (SD) | 80 (10) | 81 (9) | 81 (9) | <0.01 |
| 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\(^{-1}\)) | 25 (10) | 25 (11) | 26 (14) | 0.03 |
| ASAT (U L\(^{-1}\)) | 132 (112) | 130 (111) | 131 (142) | 0.97 |
| ALAT (U L\(^{-1}\)) | 28 (16) | 29 (18) | 30 (22) | 0.05 |
| Hypertension, n (%) | 348 (32.61) | 269 (32.10) | 362 (50.08) | <0.001 |
| Type 2 diabetes | 229 (21.50) | 144 (17.20) | 234 (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 \(\chi^2\) 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.

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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 4  Odds ratios of comorbidities according to time of obesity onseta in treatment-seeking men with severe obesity

|                  | Childhood OR (95% CI) | p-value | Adolescent OR (95% CI) | p-value | Adult ORb |
|------------------|-----------------------|---------|------------------------|---------|-----------|
| **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      |
| **Multivariatec**|                       |         |                        |         |           |
| 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      |

aTime of obesity onset was categorized as childhood onset (age 0–11), adolescent onset (age 12–20) and adult onset (age > 20).
bReference category.
cAdjusted 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 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

| Table 5 | Odds ratios of comorbidities according to time of obesity onseta in treatment-seeking women with severe obesity |
|-----------|---------------------------------------------------------------|
|           | Childhood OR (95% CI) p-value | Adolescent OR (95% CI) p-value | Adult ORb |
| 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 |
| Multivariatec |                               |                               |           |
| 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 |

aTime of obesity onset was categorized as childhood onset (age 0–11), adolescent onset (age 12–20) and adult onset (age > 20).

bReference category.

cAdjusted for age and body mass index.

Abbreviation: NAFLD, non-alcoholic fatty liver disease.
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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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References

1. Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. Int J Obes (2005) 2011; 35: 891–898.
2. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. N Engl J Med 1992; 327: 1350–1355.
3. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. Obes Rev 2016; 17: 56–67.
4. Inge TH, King WC, Jenkins TM, et al. The effect of obesity in adolescence on adult health status. Pediatrics 2013; 132: 1098–1104.
5. Bazzano LA, Hu T, Bertisch SM, et al. Childhood obesity patterns and relation to middle-age sleep apnoea risk: the Bogalusa Heart Study. Pediatr Obes 2016; 11: 535–542.
6. Sanchez-Villegas A, Field AE, O’Reilly EJ, et al. Perceived and actual obesity in childhood and adolescence and risk of adult depression. J Epidemiol Community Health 2013; 67: 81–86.
7. Farinholt GN, Carr AD, Chang EJ, Ali MR. A call to arms: obese men with more severe comorbid disease and underutilization of bariatric operations. Surg Endosc 2013; 27: 4556–4563.
8. Dreyer N, Dixon JB, Okerson T, Finkelstein EA, Globe D. Prevalence of comorbidities and baseline characteristics of LAP-BAND AP® subjects in the Helping Evaluate Reduction in Obesity (HERO) study. PLoS One 2013; 8: e78971.
9. van Vliet-Ostaptchouk JV, Nuoto ML, Slagter SN, et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. BMC Endocr Disord 2014; 14: 9.
10. Must A, Spadano J, Coakley EH, Field AE, Colditz GA, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999; 282: 1523–1529.
11. Kochkodan J, Telem DA, Ghaferi AA. Physiologic and psychological gender differences in bariatric surgery. Surg Endosc 2017; 32: 1382–1388.
12. Tronieri JS, Wurst CM, Pearl RL, et al. Sex differences in obesity and mental health. Curr Psychiatry Rep 2017; 19: 29.
13. The NS, Richardson AS, Gordon-Larsen P. Timing and duration of obesity in relation to diabetes: findings from an ethnically diverse, nationally representative sample. Diabetes Care 2013; 36: 865–872.
14. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection,
Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42: 1206–1252.

15. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2016; 37: 2999–3058.

16. Kotronen A, Peltonen M, Hakkarainen A, et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. Gastroenterology 2009; 137: 865–872.

17. Bridger T. Childhood obesity and cardiovascular disease. Paediatr Child Health 2009; 14: 177–182.

18. Reis JP, Loria CM, Lewis CE, et al. Association between duration of overall and abdominal obesity beginning in young adulthood and coronary artery calcification in middle age. JAMA 2013; 310: 280–288.

19. Maas A, Appelman YEA. Gender differences in coronary heart disease. Neth Heart J 2010; 18: 596–602.

20. Shinohara E, Kihara S, Yamashita S, et al. Visceral fat accumulation as an important risk factor for obstructive sleep apnoea syndrome in obese subjects. J Intern Med 1997; 241: 11–18.

21. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000; 85: 1151–1158.

22. Saelens BE, Seeley RJ, van Schaick K, Donnelly LF, O’Brien KJ. Visceral abdominal fat is correlated with whole-body fat and physical activity among 8- to 10-year-old children at risk of obesity. Am J Clin Nutr 2007; 85: 46–53.

23. Goran MI. Visceral fat in prepubertal children: influence of obesity, anthropometry, ethnicity, gender, diet, and growth. Am J Hum Biol 1999; 11: 201–207.

24. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Am J Gastroenterol 2012; 107: 811–826.

25. Bays HE, Jones PH, Oram AE, et al. National Lipid Association annual summary of clinical lipidology 2016. J Clin Lipidol 2016; 10: S1–S43.

26. Perry GS, Byers TE, Mokdad AH, Serdula MK, Williamson DF. The validity of self-reports of past body weights by U.S. adults. Epidemiology 1995; 6: 61–66. published Online First: 1995/01/01.

27. Norgan NG, Cameron N. The accuracy of body weight and height recall in middle-aged men. Int J Obes Relat Metab Disord 2000; 24: 1695–1698.

28. Casey VA, Dwyer JT, Berkey CS, Coleman KA, Gardner J, Valadian I. Long-term memory of body weight and past weight satisfaction: a longitudinal follow-up study. Am J Clin Nutr 1991; 53: 1493–1498.

29. Must A, Willett WC, Dietz WH. Remote recall of childhood height, weight, and body build by elderly subjects. Am J Epidemiol 1993; 138: 56–64.

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 onset in treatment-seeking men and women with severe obesity.