Eur Respir J 2010; 35: 1235–1242
DOI: 10.1183/09031936.00192408

Body mass index as predictor for asthma: a cohort study of 118,723 males and females

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ABSTRACT: The objective of the present study was to quantify the relationship between body mass index (BMI; in kilogrammes per metre squared) and asthma in middle-aged males and females, and to evaluate change in BMI as a risk factor for asthma.

Asthma incidence was estimated from data on redeemed prescriptions of anti-asthmatic drugs during the period 2004–2007, retrieved from the nationwide Norwegian Prescription Database. BMI was measured during health surveys in 1994–1999 in >100,000 individuals born during 1952–1959. Change in BMI was based on self-report. Relative risks were estimated using Poisson regression.

The relative risk associated with a 3-unit increase in BMI ranged from 1.14 (95% confidence interval 1.10–1.18) in current smokers to 1.27 (1.22–1.32) in never-smokers after adjusting for confounders. The relative risk associated with a 3-unit increase in BMI was 1.21 (1.16–1.26) after adjusting for confounders, including sex, smoking and BMI.

Asthma incidence, as measured by anti-asthmatic drug use, was positively related to both BMI and change in BMI. For BMI, the association was stronger for never-smokers than for ex-smokers and current smokers.

KEYWORDS: Anti-asthmatic drugs, asthma, body mass index, body weight changes, smoking

Many studies have shown obesity to be a risk factor for asthma [1, 2], especially in females [3, 4]. The findings have been concordant in adolescents and adults [5]. One study also reported a positive relationship between hip/waist ratio and asthma incidence [6], and another found an inverse relationship between body height and asthma incidence [7]. Furthermore, one study found the body mass index (BMI)–asthma relationship only in non-atopic disease [6]. A recent meta-analysis of prospective studies concluded that asthma incidence increased by 50% in overweight/obese individuals [8]. It also concluded that there was a dose–response relationship, and that sex does not disproportionately affect the obesity–asthma relationship [8].

Fewer studies have investigated the relationship between change in BMI (ΔBMI) and subsequent asthma, but, in a prospective study of 85,911 female nurses, weight gain after the age of 18 yrs was strongly associated with an increased risk of adult-onset asthma [9]. ROMIEU *et al.* [10] found that both weight loss and weight gain were associated with an increased risk of asthma in a middle-aged French female population. However, other studies suggest that weight loss seems to reduce symptoms in individuals who have asthma [11, 12].

Assessing the asthma prevalence in a population is challenging as no single instrument can be used to identify asthma with certainty. The use of self-reported asthma or asthma symptoms as a measure of asthma has been questioned by several studies [13, 14]. Using data on prescriptions of anti-asthmatic medications provides an alternative method [15]. A number of healthcare databases of prescriptions have shown the feasibility of using this kind of data to identify individuals with asthma [16–18]. A study from a prescribing database in general practice in the Netherlands found that a prescription of one or more anti-asthmatics identified 95% of adults with an asthma diagnosis [19]. In the present study, therefore, asthma incidence was estimated on the basis of data on redeemed prescriptions of anti-asthmatic drugs retrieved from the nationwide Norwegian Prescription Database (NorPD).

The objective of the present study was to quantify the relationship between BMI and asthma in middle-aged males and females, and to evaluate ΔBMI as a risk factor for asthma.

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Received:
Dec 19 2008
Accepted after revision:
Nov 27 2009
First published online:
Jan 14 2010

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

This article has supplementary material accessible from www.erj.ersjournals.com

MATERIALS AND METHODS

Study population

Data from health surveys conducted by the Norwegian government during 1994–1999 were linked to information from the NorPD, which includes all drug prescriptions dispensed at pharmacies in Norway since 2004 [20]. The health surveys were performed partly by means of questionnaires (*e.g.* on smoking, exercise habits, level of education and history of asthma, heart infarction, angina pectoris, stroke and diabetes) and partly by physical measurements (*e.g.* height and weight). The questionnaires were filled in at home and delivered at the screening.

Altogether 107,001 males and 102,911 females born during 1952–1959 were invited to participate in the health surveys. A total of 159,331 (70 and 82% of the invited males and females, respectively) attended, and 132,924 answered the question about asthma history (''do you have, or have you had, asthma?'' (yes/no)). The 8,638 who answered ''yes'' were excluded, together with 4,325 who were excluded for other reasons (fig. 1), leaving 118,723 (55,940 males and 62,783 females) for analysis. BMI was calculated as weight in kilogrammes divided by height in metres squared.

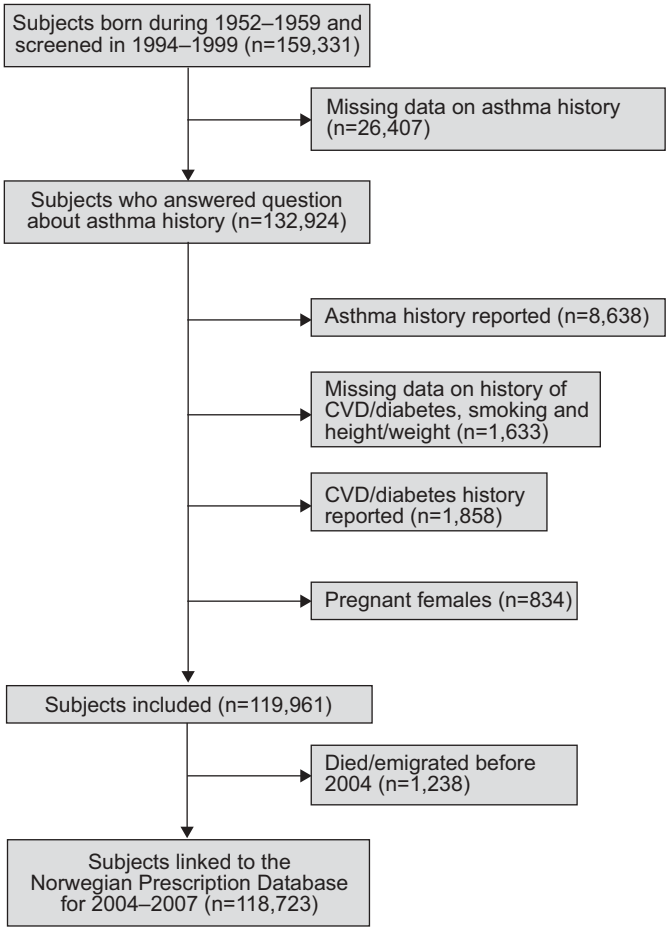

FIGURE 1. Flow chart showing the study population. Norwegian health survey results during 1994–1999 were linked to the nationwide Norwegian Prescription Database for 2004–2007. CVD: cardiovascular disease.

A total of 114,577 subjects also reported their minimum (w_{min}) and maximum weight (w_{max}) during the 5 yrs before screening. Females were asked not to report weight during pregnancy. ΔBMI was calculated from the measured height and the reported w_{min} and w_{max} as $\Delta BMI=(w_{max} - w_{min})\cdot height^{-2}$. Relative ΔBMI was calculated as $\Delta BMI/BMI \times 100\%$, where BMI is the measured BMI.

In addition, the following variables from the health surveys were included: smoking (never-, ex- and current), physical activity (low, medium and high), education (five levels), year of birth, urban/rural residence and receipt of disability pension (yes/no).

Physical activity was addressed by asking about the time spent on light (no sweating or heavy breathing) and hard activity. The alternatives in both categories were 0, <1, 1–2 and $\geqslant$3 h·week^{-1}, averaged over the year. The two questions were joined in a new variable with three levels: 1) <1 h with light activity and 0 h with hard activity, 2) <3 h with hard activity, and 3) $\geqslant$3 h with hard activity.

Educational level was given as one of five categories: 1) elementary school (to an age of 16 yrs), 2) technical college or similar (for 1–2 yrs), 3) further education/high school or similar (for 3 yrs), 4) university/college for <4 yrs, and 5) university/college for $\geqslant$4 yrs.

Subjects living in municipalities with >50,000 inhabitants were classified as urban, and others as rural. However, the two largest cities in Norway were not screened during 1994–1999.

Measuring asthma incidence

Asthma incidence (new cases of asthma occurring between screening and 2007) was estimated from data on redeemed prescriptions of inhaled anti-asthmatic drugs during 2004–2007 retrieved from NorPD. Since January 1, 2004, all pharmacies in Norway have been obliged by law to send electronic data on all prescriptions to the Norwegian Institute of Public Health [20]. The NorPD contains information on all individuals who have received prescription drugs dispensed at pharmacies. All prescriptions, whether reimbursed or not, are stored in the database. The drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system [21]. Among the data collected are the patient's unique identification number (encrypted), sex and age, the date of dispensing, detailed information on the drug (brand name, package size, number of packages, ATC code, defined daily dose and price) and the reimbursement code if relevant.

An end-point was used of at least two prescriptions, with the last one being dispensed $\geqslant$6 months after the first one, of reimbursed inhaled anti-asthmatic drugs, *i.e.* drugs with ATC code R03AC (selective β_2-agonists), R03BA (glucocorticoids) and/or R03AK (long-acting β_2-agonists/glucocorticoids combined in one inhaler). The system for general reimbursement in Norway is basically a positive-list system, based on a list of diseases or conditions for which pharmaceutical treatment can be reimbursed. Reimbursement is granted only under the condition that the patient has a chronic disease (*e.g.* asthma) for which long-term medication (>3 months) is necessary [22].

Use of glucocorticoids indicates more persistent asthma than use of β_2-agonists alone. An analysis was also performed in

which the end-point was defined as at least two prescriptions, with the last one being dispensed ⩾6 months after the first one, of reimbursed glucocorticoids (ATC code R03BA or R03AK).

The drug prescription data were linked to the health survey data using the unique personal identification number assigned to every Norwegian citizen at birth or immigration (encrypted). Permission for the linkage was given by the Norwegian Data Inspectorate (Oslo, Norway) and the Regional Committees for Medical Research Ethics.

Statistical methods

Poisson regression was used to estimate associations (expressed as relative risks (RRs)) between effect variables (BMI and ΔBMI) and the outcome variable (incident asthma) for never-smokers, ex-smokers and current smokers separately [23]. The estimation was carried out using the glm (generalised linear model) function in the statistical package R [24]. The effect variables were entered as categorical as well as continuous. RR estimates are presented adjusted for age (year of birth; continuous variable) and sex, physical activity, education, urban/rural residence and disability pension (categorical variables). In the analyses with ΔBMI as effect variable, BMI (continuous variable) was also adjusted for.

Interactions between sex and the effect variables (BMI and ΔBMI), and between smoking and the effect variables, were tested for by including the relevant interaction terms in the model in addition to sex, smoking category and the potential confounders listed above. The effect variables were entered as continuous.

Trends in the potential confounders as a function of BMI were tested for at baseline using linear regression for continuous variables and logistic regression for yes/no variables, with BMI entered as a continuous variable. Individuals with a BMI of <20 kg·m^{-2} were not included in the trend tests.

RESULTS

The mean BMI at baseline was higher in males (26.2 kg·m^{-2}) than in females (24.7 kg·m^{-2}), but severe obesity (BMI of ⩾35 kg·m^{-2}) was more common in females than in males (tables 1 and 2). Females also reported a larger ΔBMI than males, in both absolute and relative terms. Smoking habits and education were comparable for males and females, but more males were physically active and more females received disability pension (tables 1 and 2). Overweight at baseline was associated with low educational level, low physical activity, rural residence, high prevalence of disability pension, low prevalence of smoking, later year of birth and large ΔBMI (tables 1 and 2). Incident asthma was typically associated with the same baseline characteristics as was overweight, except that smoking and high physical activity (for males) were more common at screening among the incident asthma cases than among the others (tables 1 and 2). The incident asthma cases were also born and screened slightly earlier than the others.

BMI and asthma incidence

The total asthma incidence was 3.4%. Incidence was highest in current smokers and lowest in never-smokers, higher in females than in males (table 3; fig. 2) and positively related to BMI (table 3; fig. 2). There was no significant interaction between BMI and sex ($p=0.25$), but the BMI–asthma relationship was significantly weaker in current smokers than in never-smokers ($p<0.001$ for interaction). As measured by the risk difference, the three smoking groups were more similar (fig. 2; parallel curves would indicate an equal risk difference). The prescription rate was more than three times higher for very obese (BMI of ⩾35) never-smokers than for normal-weight (20⩽BMI<25) never-smokers. Treating BMI as a continuous variable, the RR associated with an increase of 3 kg·m^{-2} in BMI ranged from 1.14 in current smokers to 1.27 in never-smokers when adjusting for confounders. The RRs

TABLE 1 Baseline characteristics at screening in males in different body mass index (BMI) groups and in those who were and were not incident asthma cases

	<20	20–24.9	25–29.9	30–34.9	⩾35	ptrend#	Incident asthma¶	
							No	Yes
Subjects n	700	20382	28241	5722	895		54493	1447
ΔBMI kg·m^{-2}	1.2	1.6	2.3	3.5	5.2	<0.001	2.2	2.6
ΔBMI %	6.3	6.8	8.4	11.1	13.8	<0.001	8.1	9.6
Year of birth	1955.5	1955.5	1955.6	1955.8	1955.9	<0.001	1955.6	1955.4
Never-smokers	28.3	39.1	40.2	38.3	39.2	0.463	39.7	30.0
Ex-smokers	9.7	19.7	26.4	29.7	29.1	<0.001	24.1	24.0
Current smokers	62.0	41.2	33.4	32.0	31.7	<0.001	36.2	46.0
High education+	28.5	36.1	32.7	26.6	20.2	<0.001	33.2	28.8
Physically active§	14.0	19.3	17.0	13.3	11.0	<0.001	17.3	20.0
Disability pension	7.5	2.5	2.2	3.5	7.0	<0.001	2.5	5.0
Urban residence	18.3	18.2	16.8	14.9	15.0	<0.001	17.2	15.0

Data are presented as means for continuous variables and percentages for dichotomous variables; BMI group ranges are shown in kilogrammes per metre squared. ptrend: p-value for trend; Δ: change. #: calculated for subjects with a BMI of ⩾20 kg·m^{-2}; ¶: received at least two prescriptions of reimbursed inhaled anti-asthmatic drugs during 2004–2007, with the last one being dispensed ⩾6 months after the first one; +: university/college or higher (level 4 or 5); §: ⩾3 h·week^{-1} with hard activity (level 3).

TABLE 2 Baseline characteristics at screening in females in different body mass index (BMI) groups and in those who were and were not incident asthma cases

	<20	20–24.9	25–29.9	30–34.9	⩾35	ptrend#	Incident asthma¶	
							No	Yes
Subjects n	3493	34688	18559	4688	1355		60181	2602
ΔBMI kg·m^{-2}	1.5	2.1	3.2	4.7	6.5	<0.001	2.6	3.3
ΔBMI %	8.0	9.2	11.9	14.8	16.9	<0.001	10.4	12.5
Year of birth	1955.5	1955.6	1955.6	1955.8	1955.9	<0.001	1955.6	1955.5
Never-smokers	35.9	36.9	38.1	40.1	43.6	<0.001	38.0	27.4
Ex-smokers	13.8	24.1	26.3	26.0	26.7	<0.001	24.5	20.4
Current smokers	50.3	39.0	35.6	33.9	29.7	<0.001	37.5	52.2
High education+	33.3	33.6	27.7	22.1	19.6	<0.001	30.9	24.8
Physically active§	9.0	10.7	9.3	7.6	4.7	<0.001	9.8	9.7
Disability pension	5.4	3.5	4.9	7.1	11.4	<0.001	4.2	9.3
Urban residence	19.9	18.2	15.7	14.2	12.3	<0.001	17.2	15.1

Data are presented as means for continuous variables and percentages for dichotomous variables; BMI group ranges are shown in kilogrammes per metre squared. ptrend: p-value for trend; Δ: change. #: calculated for subjects with a BMI of ⩾20 kg·m^{-2}; ¶: received at least two prescriptions of reimbursed inhaled anti-asthmatic drugs during 2004–2007, with the last one being dispensed ⩾6 months after the first one; +: university/college or higher (level 4 or 5); §: ⩾3 h·week^{-1} with hard activity (level 3).

obtained by adjusting for sex and age alone were very similar to those shown in table 3.

The overall incidence of persistent asthma, as defined by use of corticoids, was 2.7%, and the association with BMI was typically marginally stronger for incident persistent asthma than for incident asthma (see Section S1 of online supplementary material).

ΔBMI and asthma incidence

The direction of the ΔBMI was not known, but, assuming a weight gain in subjects whose measured weight at screening was closer to the reported wmax than to the reported wmin, and a weight loss in the other subjects, the direction of the change had a minor impact (table S2.1 of online supplementary material). Thus it seems reasonable to use absolute (direction-free) ΔBMI as an effect variable. There was no significant interaction between self-reported ΔBMI during the last 5 yrs before screening and sex ($p=0.97$) or smoking ($p>0.47$). ΔBMI was positively associated with incident asthma. A 3-kg·m^{-2} increase in the ΔBMI during the 5 yrs before screening was associated with a 35% increase in the risk of asthma incidence after adjusting for sex, age and smoking category (table 4). After adjustment for all confounders, including BMI, the RR (95% confidence interval (CI)) remained as high as 1.21 (1.16–1.26).

Within each category of BMI, in the range $20 \leqslant BMI < 35$, the RR of being prescribed anti-asthmatic drugs was higher in individuals who reported a relative ΔBMI of ⩾10% of their screening BMI than in those with a smaller ΔBMI (table S2.2 of online supplementary material). This was true for all smoking categories.

DISCUSSION

The risk of developing asthma in middle age, as estimated by use of reimbursed inhaled anti-asthmatic drugs, increased with

TABLE 3 Number of incident asthma cases and adjusted relative risk (RR) for incident asthma by body mass index (BMI) group and for three-unit increase in BMI, stratified by smoking#

	<20		20–24.9		25–29.9		30–34.9		⩾35		Increase in BMI	
	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
Never-smokers¶	28 (2.0)	0.9 (0.6–1.4)	390 (1.9)	Ref	456 (2.6)	1.5 (1.3–1.7)	153 (4.0)	2.2 (1.8–2.7)	61 (7.0)	3.5 (2.6–4.5)	1088 (2.5)	1.27 (1.22–1.32)
Ex-smokers¶	11 (2.1)	0.7 (0.4–1.3)	313 (2.6)	Ref	346 (2.9)	1.2 (1.0–1.4)	127 (4.6)	1.9 (1.6–2.4)	39 (6.7)	2.6 (1.9–3.7)	836 (3.0)	1.22 (1.16–1.28)
Current smokers¶	102 (5.0)	1.1 (0.9–1.3)	840 (4.0)	Ref	710 (4.7)	1.3 (1.2–1.4)	196 (6.1)	1.6 (1.4–1.9)	47 (7.5)	1.7 (1.3–2.3)	1895 (4.5)	1.14 (1.10–1.18)
All+	141 (3.6)	1.0 (0.9–1.2)	1543 (2.9)	Ref	1512 (3.4)	1.3 (1.2–1.4)	476 (4.9)	1.8 (1.6–2.0)	147 (7.1)	2.4 (2.0–2.9)	3819 (3.4)	1.19 (1.17–1.22)

BMI group ranges are shown in kilogrammes per metre squared. CI: confidence interval; Ref: reference group. #: 5,491 individuals were excluded because of missing data for one or more of the variables adjusted for; ¶: adjusted for sex, age (year of birth), education, physical activity, disability pension and rural/urban status; +: additionally adjusted for smoking category.

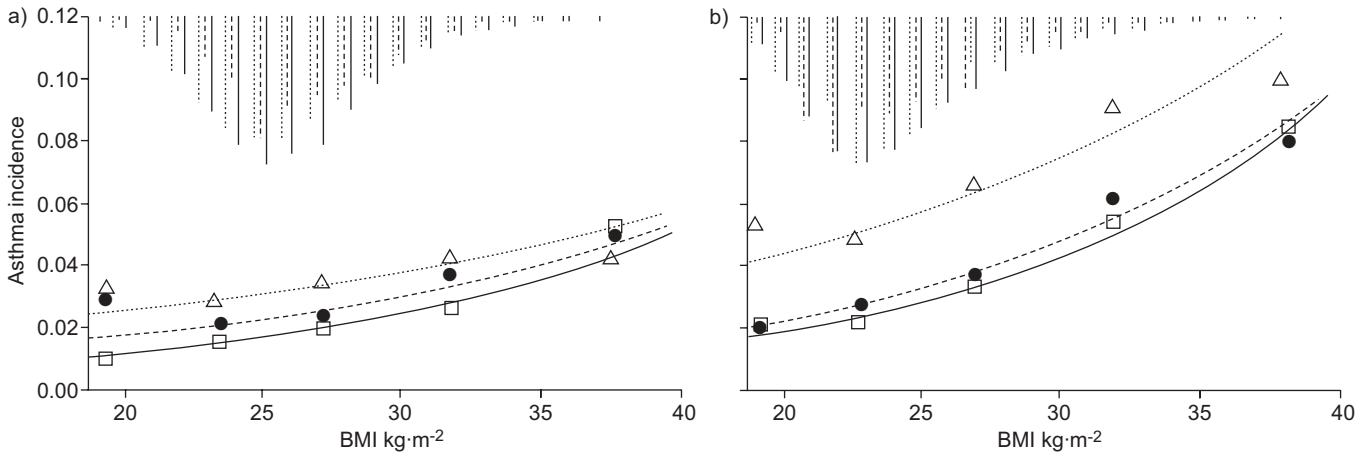

FIGURE 2. Asthma incidence (number of new asthma cases divided by number of subjects at risk) as a function of body mass index (BMI) in: a) males; and b) females (△; · · · · ·: current smokers; ●; -------: ex-smokers; □; ——: never-smokers). The mean BMI for each category (<20, 20–24.9, 25–29.9, 30–34.9 and ⩾35 kg·m^{-2}) was used as × coordinate for the points. The curves are fitted Poisson regression curves from univariate models with BMI as a continuous variable. The histograms represent the relative distribution of BMI.

increasing BMI. The relationship was strongest in never-smokers and weakest in current smokers, as measured by the RR. The risk of incident asthma in very obese (BMI of ⩾35) never-smokers was 3.5 times higher than for normal-weight (20⩽BMI<25) never-smokers, after adjusting for confounders. The risk of incident asthma in individuals with a self reported ΔBMI of ⩾10 kg·m^{-2} during the last 5 yrs before screening was twice as high as in those with a ΔBMI of ⩽2.5 kg·m^{-2}, after adjusting for BMI and other confounders.

Strengths and limitations

The main strength of the present study is that it was based on information on measured BMI and several important confounders in >100,000 healthy individuals within a narrow age range, as well as on all dispensed prescriptions of inhaled anti-asthmatic drugs between January 1, 2004 and January 1, 2008 for the same individuals. This approach eliminates the problem of recall bias as regards incident asthma, and attenuates any effect of the seasonal variation in asthma, which may affect prevalence estimates based on cross-sectional surveys with self-reported asthma symptoms and/or doctor-diagnosed asthma.

The main limitations of the present study are (see discussion below) the possibility of false negatives (undetected cases of mild asthma) and false positives (asthma medication may have been prescribed for COPD, especially in smokers, or for other diseases) and the use of self-reported data to calculate ΔBMI. In addition, ~25% of those who were invited to the health surveys did not attend. If the association between BMI and asthma were to differ between non-attenders and attenders, the effect estimates would be biased, but we believe that the participation rate is more likely to influence prevalence estimates than effect estimates. Further, individuals with a self-reported asthma history were excluded, and the self-reports might have been hampered by recall bias, but, again, the effect estimates are only biased to the extent that the association between asthma and BMI differed between those who recalled their asthma history correctly and those who did not.

Use of drug prescriptions as a proxy for asthma

False positives

In Norway, anti-asthmatic drugs are prescribed by doctors after they have recognised a patient's symptoms as being asthma-like. We believe that using a minimum of two such

TABLE 4 Number of incident asthma cases and adjusted relative risk (RR) for incident asthma by self-reported change in body mass index (ΔBMI)[#] and for three-unit increase in ΔBMI[¶]

	<2.5	2.5–4.9	5.0–7.4	7.5–9.9	⩾10	Increase in ΔBMI
Incident asthma n (%)	1903 (2.7)	1235 (4.1)	377 (5.6)	119 (7.5)	72 (9.8)	3706 (3.4)
RR[+]	Ref	1.5 (1.4–1.6)	1.9 (1.7–2.1)	2.5 (2.1–3.0)	3.3 (2.6–4.1)	1.35 (1.31–1.39)
RR[§]	Ref	1.4 (1.3–1.6)	1.8 (1.6–2.0)	2.3 (1.9–2.7)	2.9 (2.2–3.6)	1.31 (1.27–1.35)
RR[ƒ]	Ref	1.3 (1.2–1.4)	1.5 (1.3–1.7)	1.7 (1.4–2.1)	2.0 (1.5–2.5)	1.21 (1.16–1.26)

Relative risk data are presented with 95% confidence interval in parentheses; ΔBMI are shown in kilogrammes per metre squared. Ref: reference group. [#]: the direction of the change was ignored; [¶]: 8,861 individuals were excluded because of missing data for ΔBMI or for one or more of the variables adjusted for; [+]: adjusted for sex, age (year of birth) and smoking category; [§]: additionally adjusted for education, physical activity, disability pension and rural/urban status; [ƒ]: additionally adjusted for BMI.

prescriptions separated by an interval of $\geqslant$6 months as a proxy for having asthma should minimise the number of false positives. A formal validation of this approach has not been performed, but a study from the Netherlands found that, in the age group 18–49 yrs, asthma patients could be identified reliably from a prescribing database in general practice (with a positive predictive value of 0.79 when using at least two anti-asthmatic medications in 12 months as definition criterion) [19]. The present study population was older (48–56 yrs in 2007), and may include non-asthma patients treated with anti-asthmatics. The most relevant example is patients with chronic obstructive pulmonary disease (COPD), which is strongly related to smoking. A study of an adult Norwegian study population found adjusted odds ratios for current smokers and ex-smokers of 9.6 (95% CI 3.6–25.2) and 5.0 (95% CI 1.8–13.8), respectively, compared to never-smokers [25]. We, therefore, believe that the number of COPD patients was small in the present group of never-smokers (aged 48–56 yrs in 2007), but, in the groups of ex-smokers and current smokers, it was probably higher. However, in a study of 485 males aged 40–75 yrs without COPD at baseline, 13.1% of those with a BMI of $\leqslant$24.3 kg·m^{-2} (tertile 1) developed COPD over a 10-yr period, compared to only 4.6% of those with a BMI of $>$26.6 kg·m^{-2} (tertile 3) [26, 27]. This suggests that the proportion of COPD patients was probably also lower among the obese than among those of normal weight in the present population, and that the relationship between asthma and BMI would have been stronger than the observed relationship had it been possible to eliminate the COPD patients.

False negatives

The definition criterion of two prescriptions with an interval of $\geqslant$6 months may have led to a loss of some cases of mild asthma. Some of these were probably undiagnosed and not prescribed any anti-asthmatic drugs during 2004–2007. The chance of a mild asthma case being diagnosed would increase if a person visited a doctor for any reason, and the general medication prevalence increased with BMI. The percentage of males who received at least one prescription for any drug during 2004–2007 was 86% in the normal-weight group and 96% in the $\geqslant$35-kg·m^{-2} group. For females, the corresponding percentages were 94 and 98. Only 12% of the males and 5% of the females did not receive any prescription during 2004–2007, and a relatively high proportion of these would need to have had undetected asthma in order to influence the results of the present study significantly.

Some individuals had probably received an asthma diagnosis before 2004, without any need for anti-asthmatic drugs during 2004–2007. Among those who reported an asthma history in the health survey, and were excluded from this study, only 44% would have been defined as asthma patients using the present criterion. For those who were aged $>$20 yrs at the first asthma incidence (self-reported age), the percentage was 52, and relatively independent of BMI at screening. This indicates that not all of the subjects who developed asthma before screening were in need of anti-asthmatic drugs during 2004–2007. Thus it is also possible that some subjects may have developed asthma after the screening without any need for anti-asthmatic drugs during 2004–2007. Among the subjects without an asthma history at screening who redeemed anti-asthmatic drugs and got the first prescription in 2004, 12% did not receive any prescription during 2006 and 2007, the proportion being approximately the same in the various BMI groups. In conclusion, there might have been some cases of incident asthma that were not identified in the present study, but, as the probability of not being identified seems to be relatively independent of BMI, the observed relationship between BMI and adult-onset asthma should remain valid.

Use of self-reported maximum weight as basis for ΔBMI

ΔBMI was calculated from self-reported w_{min} and w_{max} during the last 5 yrs before screening, and was thus less accurate than measurements of BMI *per se*. It is known that self-reported weights and heights tend to be too low and too high, respectively, and thus the corresponding BMI too low [28, 29]. Whether there was a systematic under- or over-reporting of ΔBMI with increasing BMI is not known, but the fact that the relative ΔBMI increased with increasing BMI may indicate an over-reporting of ΔBMI with increasing BMI. However, the association between ΔBMI and asthma remained significant after adjusting for BMI.

The direction of the ΔBMI was not known, but, assuming a weight gain in subjects whose measured weight at screening was closer to the reported w_{max} than to the reported w_{min}, and a weight loss in the other subjects, the direction of the ΔBMI had a minor impact (table S2.1 of online supplementary material). Thus, although the means of defining weight loss and weight gain were imprecise, they were both associated with increased asthma incidence, which is in agreement with the results of ROMIEU *et al.* [10]. Conversely, weight loss studies on the basis of behavioural change and bariatric studies have shown substantial improvements in the clinical status of many obese patients with asthma who lost weight [11, 12].

BMI versus *waist-to-hip ratio and waist circumference*

Waist circumference and waist-to-hip ratio have been suggested as being better screening tools than BMI for cardiovascular risk factors [30]. In a subsample of 71,424 subjects, for whom measurements of waist and hip were available, the waist-to-hip ratio and the waist circumference were associated with asthma in roughly the same way as was BMI. They were both significantly associated with incident asthma, after adjustment for confounders, including BMI (see section S3 of online supplementary material).

Obesity and asthma: possible mechanisms

Many authors have found an association between obesity and asthma incidence, but it is not clear whether the association is causal or whether the two conditions share the same environmental, behavioural or genetic influences. Although the exact mechanisms responsible for the relationship between obesity and asthma incidence remain unknown, some possible explanations have been put forward [31]. These include the effect of obesity on lung mechanics, systemic inflammation and comorbid conditions [32]. The comorbid conditions include dyslipidaemia, type 2 diabetes, gastro-oesophageal reflux disease and hypertension. Excluding the 23,141 individuals who, during 2004–2007, were dispensed antihypertensives (ATC group C02), lipid-modifying agents (C10), drugs for gastro-oesophageal reflux disease (A02B) or drugs used in

diabetes (A10), the RR associated with a 3-kg·m^{-2} increase in BMI in table 3 changed by <0.02 in all smoking categories. This shows that these comorbid conditions do not explain the association between BMI and asthma found in the present study.

Enhancement of pro-inflammatory cytokines and the effect of oestrogens have also been mentioned [33]. However, the literature is ambiguous. BARR *et al.* [34] found that post-menopausal hormone use was associated with an increased rate of newly diagnosed asthma. Conversely, CARLSON *et al.* [35] found that post-menopausal females who used hormone replacement therapy had higher forced expiratory volumes in 1 s, which, again, is expected to give a lower risk of asthma. In a mouse asthma model, MATSUBARA *et al.* [36] characterised how oestrogens can suppress airway hyperresponsiveness. In the present population, the proportion that used oestrogens decreased with increasing BMI, but excluding the 7,000 females who were dispensed oestrogens (ATC group G03C) during 2004–2007 did not change the BMI–asthma association in table 3. However, the possibility cannot be excluded that some females used oestrogens during the interval from screening to the start of the NorPD. Both the timing and duration of use, as well as the dose, seem to be very important when assessing the potential effects of hormones. This was clearly demonstrated in the Women's Health Initiative study regarding the effect on coronary heart disease [37].

STATEMENT OF INTEREST

None declared.

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