Breast size and risk of type 2 diabetes mellitus

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ABSTRACT

Background: Elevated waist circumference and body mass index (BMI), both traditional measures of obesity, are accepted risk factors for type 2 diabetes mellitus. Girls who are obese experience earlier onset of puberty and possibly greater breast development. We sought to evaluate whether a woman's breast size in late adolescence is associated with an increased risk of type 2 diabetes mellitus in adulthood.

Methods: In conjunction with the ongoing Nurses' Health Study II, which began to study risk factors for breast cancer among women in 1989, we conducted a prospective cohort study involving 92 106 of the participants. We assessed the risk of type 2 diabetes mellitus in relation to self-reported bra cup sizes, categorized as \leq A, B, C and \geq D cups, among participants at age 20.

Results: The mean age of participants at baseline was 38.1 years. A total of 1844 new cases of type 2 diabetes mellitus arose at a mean age of 44.9 years during 886 443 personyears of follow-up. Relative to bra cup size \leq A, the respective age-adjusted hazard ratios (and 95% confidence intervals [CIs]) were 2.30 (1.99–2.66) for B cup, 4.32 (3.71–5.04) for C cup and 4.99 (4.12–6.05) for \geq D cup. Upon further adjustments for age at menarche, parity, physical activity, smoking status, diet, multivitamin use, family history of diabetes mellitus, BMI at age 18 and current BMI, the corresponding hazard ratios (and 95% CIs) were 1.37 (1.18–1.59) for B cup, 1.80 (1.53-2.11) for C cup and 1.64 (1.34–2.01) for \geq D cup. The addition of waist circumference to this model minimally changed the hazard ratios (and 95% CIs): 1.32 (1.14–1.53) for B cup, 1.71 (1.46–2.01) for C cup and 1.58 (1.29–1.94) for \geq D cup.

Interpretation: A large bra cup size at age 20 may be a predictor of type 2 diabetes mellitus in middle-aged women. Whether this relation is independent of traditional indicators of obesity remains to be determined.

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besity is an established risk factor for type 2 diabetes mellitus. 1,2 Affected individuals show signs of insulin resistance and hyperinsulinemia, a process that may begin in childhood. 3,4 Pre-adolescent obesity is also an important predictor of age of onset of

breast development in young women, and of breast size after puberty.^{5,6} Premature onset of puberty is preceded by childhood insulin resistance, hyperinsulinemia and hyperandrogenemia,⁷ which may persist after puberty⁸ and continue into early adulthood.⁹

Although an elevated body mass index (BMI)^{10,11} and central adiposity¹² are established risk factors for insulin resistance and the onset of type 2 diabetes mellitus, little is known about the contribution of extra-abdominal adipose tissue, including breast tissue, about 60% of which is fatty tissue, to this process.^{13,14} We hypothesized that a woman's breast size in late adolescence reflects her predisposition to insulin resistance and type 2 diabetes mellitus that is both additive to, and independent of, BMI. We explored this hypothesis in conjunction with the Nurses' Health Study II by relating bra cup size, a proxy for breast size, to the onset of type 2 diabetes mellitus.

Methods

Participants

The Nurses' Health Study II is a prospective cohort study, which was initiated in 1989 and is ongoing. The study involves 116 609 women, more than 90% of whom are white, from 14 US states. ¹⁵ At the time of enrolment, participants were between the ages of 25 and 42, and they completed a detailed baseline questionnaire about their health, lifestyles and anthrometric characteristics. They continue to complete follow-up questionnaires on a biennial basis. We included all women who had concomitant information about bra cup size at age 20 and BMI at age 18, for a total of 92 106 participants. We excluded women who had already received a diagnosis of diabetes mellitus or who had a history of gestational diabetes. Our study was approved by the Human Research Committees at the Harvard School of Public Health and the Brigham and Women's Hospital in Boston, Massachusetts.

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Assessment of bra cup size

Bra cup size is traditionally determined by measuring the horizontal chest circumference just under the breasts, adding 5 inches (12.7 cm) and subtracting the total from the horizontal chest circumference at the fullest part of the breasts. A net difference of 1 inch is equivalent to an A cup, 2 inches a B cup, 3 inches a C cup and 4 inches a D cup. 16 On the 1993 Nurses' Health Study II questionnaire, women were asked to recall their bra cup size at age 20 and indicate whether it was an A cup or smaller, B cup, C cup, or a D cup or larger. Those who did not wear a bra were asked to estimate their bra cup size. 17 Participants were not asked to formally measure their chest circumferences.

Assessment of type 2 diabetes mellitus

We assessed the incident onset of type 2 diabetes between 1993 (when the Nurses' Health Study II first recorded bra cup size) and 2003. We asked each woman who reported a diagnosis of diabetes on a biennial questionnaire during our study period to complete a supplemental form containing questions about symptoms, diagnostic tests and receipt of hypoglycemic therapy. We confirmed the diagnosis based on 1 or more of the following criteria: presence of 1 or more classic symptoms of diabetes (polydipsia, polyuria, weight loss or hunger) and either a fasting plasma glucose level of 7.8 mmol/L or more or a random plasma glucose level of 11.1 mmol/L or more; at least 2 instances of hyperglycemia (fasting plasma glucose level of ≥ 7.8 mmol/L, random plasma glucose level of ≥ 11.1 mmol/L or oral glucose tolerance test result of ≥ 11.1 mmol/L after 2 hours) on different occasions in the absence of symptoms; and treatment with insulin or an oral hypoglycemic medication.¹⁸ In 1997, in keeping with the revised American Diabetes Association criteria, the cutoff for fasting plasma glucose levels was lowered to 7.0 mmol/L.19 In a prior validation study of the Nurses' Health Study, an endocrinologist confirmed that the same supplementary questionnaire accurately ascertained 98% of cases of type 2 diabetes among study participants.²⁰

Assessment of other variables

At the time of enrolment in the Nurses' Health Study II, participants reported information on height and weight at age 18 and current weight. Information on current weight was updated every 2 years thereafter. Self-reported height and weight at age 18 were previously validated^{21,22} and were found to be reported with high accuracy (Pearson correlation coefficients 0.87 for height and 0.94 for weight).²¹ We obtained data on waist circumference, measured at the level of the umbilicus, from the 1993 survey; the Pearson correlation coefficient between self-reported and technician-measured waist circumference was 0.89.²²

Study participants completed a food frequency questionnaire every 4 years; its reproducibility and validity have been confirmed.²³ We calculated a dietary score for each woman based on her intake of trans fats and cereal fibre, the ratio of polyunsaturated fat to saturated fat and the glycemic load. The scores ranged from 1 to 5, with a higher score predicting a lower risk of diabetes.²⁴ The scores for the individual dietary factors were summed, and the mean composite score is presented herein. Participants reported multivitamin use as "yes" or "no." On the 1991 and 1999 questionnaires, the Nurses' Health Study II participants reported data on physical activity, which we assessed by calculating the total number of hours per week that participants engaged in moderate to vigorous activities from a specified list. The reproducibility and validity of this method have been confirmed.²⁵ Participants reported past and current smoking history on each biennial questionnaire.

Parity was based on the number of pregnancies that lasted longer than 6 months. Participants reported information about pregnancy at the time of enrolment and on each subsequent biennial questionnaire. They reported their age at menarche on the 1989 questionnaire. We determined the cumulative number of months of lactation using the total number of months from each delivery to cessation of breastfeeding, as reported on the 1993, 1997 and 2003 questionnaires. Finally, participants reported family history of diabetes mellitus on the 1989 and 1997 questionnaires.

Assessment of adiposity in childhood

A 9-level figure drawing in the 1989 survey allowed participants to report their body fat scores at ages 5 and 10. Scores for each age ranged from 1 to 5 or higher, with a score of 1 indicating little or no body fat, and higher scores indicating increasing leves of body fat.²⁶

Statistical analysis

We excluded participants who did not report bra cup size or BMI at age 18. We began our analysis of participants' data when they returned the 1993 questionnaire reporting bra cup size and ended the analysis for each participant upon diagnosis of type 2 diabetes, death or the end of the study period in 2003, whichever occurred first.

We used a Cox proportional hazards model to generate an age-adjusted hazard ratio and 95% confidence interval (CI) to determine the risk of type 2 diabetes in relation to BMI at age 18, using the lowest BMI quintile as the reference group. We then expanded our analysis to include age at menarche, parity, cumulative number of months of lactation, hours per week of physical activity, smoking status, mean dietary score, multivitamin use, family history of diabetes mellitus in 1989 and bra cup size at age 20.

We developed 5 models (models A to E) to determine the relation between bra cup size and risk of diabetes. We used a Cox proportional hazards model to generate an age-adjusted hazard ratio and 95% CI, comparing women who wore B cups or larger with women in the reference group (\leq A cup). In model A, we adjusted for current age, age at menarche, parity (0, 1, 2, \geq 3), cumulative number of months of lactation, hours per week of physical activity (< 1, 1 to < 2, 2 to < 4, 4 to \leq 7 and > 7), smoking status (never, past, 1-14 cigarettes/d, 15-24 cigarettes/d, ≥ 25 cigarettes/d), mean dietary score (1-5), multivitamin use (yes or no) and the presence of a family history of diabetes in 1989. Model B, the main analysis, expanded upon model A and included adjustment for BMI at age 18. In model B, we evaluated the relation between bra cup size and type 2 diabetes among each BMI quintile at age 18 years. We evaluated whether model B (the stratified model) better determined the

relation between BMI and bra cup size than model A (the nonstratified model) using a likelihood ratio test. Because of the broad range of BMI values within each quintile, it was necessary to adjust for BMI as a continuous variable among the groups to avoid within-group confounding. We adjusted model C to include participants' most recent BMI. Model D included an adjustment for change in weight (in kilograms) between age 18 and age at the time of completing the most recent biennial follow-up questionnaire; however, it did not include an adjustment for most recent BMI. Model E included both an adjustment for most recent BMI and waist circumference in 1993 in addition to the adjusted variables in model B.

Results

Of the original cohort of 116 609 women enrolled in the Nurses' Health Study II, we excluded 2032 women for whom there were a number of missing variables, and we excluded a

further 22 081 women because of a lack of information on bra cup size. We excluded an additional 300 women because of a history of gestational diabetes or because they had already received a diagnosis of diabetes. We included a total of 92 106 women in our analysis. The mean age at baseline (1993) was 38.1 years. BMI at age 18 years and in 1993, and waist circumference in 1993, increased in a linear fashion with larger bra cup size (Table 1). The mean score for body fat in childhood also increased with bra cup size at age 20 (Table 1). Conversely, women with a larger bra cup size were younger at menarche than women with the smallest cup size (reference group). Women in the largest bra cup size category were about 4.1% more likely to be nulliparous than women in the smallest category (Table 1). The proportion of participants with a family history of diabetes was higher among women with larger bra cup sizes than among those with the smallest cup size. Women with larger bra cup sizes were more likely than those in the smallest category to have smoked.

Table 1: Age-standardized characteristics of 92 106 participants of Nurses' Health Study II, at baseline (1993)

Characteristic	Bra cup size; no. (%) of participants*					
	≤ A n = 27 058	B n = 44 161	C n = 16 380	≥ D n = 4 507		
Age, yr, mean	38.3	38.1	37.8	38.4		
Body mass index, kg/m², mean						
At age 18	19.9	21.3	22.6	23.8		
In 1993	22.4	24.4	25.8	27.0		
Waist circumference in 1993, cm†, mean	74.8	78.7	81.3	83.5		
Body fat score‡, mean						
At age 5	2.2	2.5	2.6	2.7		
At age 10	2.4	2.8	3.0	3.1		
Age at menarche, yr, mean	12.6	12.4	12.1	12.2		
Parity						
0	6 196 (22.9)	9 804 (22.2)	3 800 (23.2)	1 217 (27.0)		
1	4 356 (16.1)	7 286 (16.5)	2 801 (17.1)	766 (17.0)		
2	10 147 (37.5)	16 693 (37.8)	6 061 (37.0)	1 537 (34.1)		
≥ 3	6 359 (23.5)	10 334 (23.4)	3 735 (22.8)	987 (21.9)		
Cumulative no. of months of lactation, mean	16.6	15.7	15.6	16.3		
Dietary score§, mean	2.7	2.7	2.7	2.7		
Multivitamin use	12 311 (45.5)	19 387 (43.9)	7 060 (43.1)	1 947 (43.2)		
Moderate to vigorous exercise, hours per week, mean	3.7	3.8	3.8	3.6		
Smoking history						
Never	18 508 (68.4)	28 793 (65.2)	10 172 (62.1)	2 767 (61.4)		
Past	5 980 (22.1)	10 337 (23.4)	4 079 (24.9)	1 118 (24.8)		
Current	2 543 (9.4)	4 990 (11.3)	2 113 (12.9)	613 (13.6)		
Family history of diabetes mellitus						
Maternal	1 678 (6.2)	3 135 (7.1)	1 228 (7.5)	374 (8.3)		
Paternal	2 219 (8.2)	3 974 (9.0)	1 572 (9.6)	487 (10.8)		

^{*}Unless stated otherwise.

[†]Information available for 49 003 (53.2%) of all participants.

[‡]Scores ranged from 1 to 5 or higher, with a score of 1 indicating little or no body fat, and higher scores indicating increasing levels of body fat.

Scores ranged from 1 to 5, with a score of 1 indicating a higher risk of type 2 diabetes, and higher scores indicating a lower risk.

During 886 443 person-years of follow-up, 1844 incident cases of type 2 diabetes were reported. Relative to the group with the lowest BMI at age 18 years (\leq 18.8), the age-adjusted hazard ratios (and 95% CIs) for type 2 diabetes mellitus were 0.94 (0.76-1.16) for the 18.9-20.1 BMI group, 1.33 (1.09–1.62) for the 20.2–21.2 BMI group, 2.14 (1.79–2.56) for the 21.3–23.0 BMI group and 5.05 (4.29–5.95) for the \geq 23.1 BMI group. After adjustment for age, age at menarche, parity, cumulative number of months of lactation, hours per week of physical activity, number of cigarettes smoked per day, mean dietary score, multivitamin use, family history of diabetes mellitus in 1989 and bra cup size at age 20, the covariableadjusted hazard ratios (and 95% CIs) were 0.88 (0.71–1.09) for the 18.9-20.1 BMI group, 1.15 (0.94-1.40) for the 20.2–21.2 BMI group, 1.64 (1.36–1.97) for the 21.3–23.0 BMI group and 2.94 (2.47–3.50) for the ≥ 23.1 BMI group.

The onset of diabetes was 2.1 years earlier among women who wore a D cup or larger (mean 43.7 years) compared with those who wore an A cup or smaller (mean 45.8 years). Relative to the smallest bra cup size, the age-adjusted hazard ratios were 2.30 for B cup, 4.32 for C cup and 4.99 for D cup or larger (Table 2). These risk estimates were slightly attenu-

ated after we adjusted for the covariables in model A. Additional adjustment for BMI at age 18 (model B) and current BMI (model C) attenuated the associations further, but the risk of diabetes mellitus remained significantly higher with increasing cup size (Table 2).

After adjusting for BMI at age 18 and weight change, we found that the relative risk of type 2 diabetes was 1.41 (95% CI 1.21–1.63) times higher among women who wore a B cup, 1.85 (1.58–2.18) times higher among women who wore a C cup and 1.71 (1.39–2.10) times higher among women who wore a D cup or larger, as compared with women who wore an A cup or smaller (model D, Table 2). Including the square of BMI at age 18 in model D did not alter these risk estimates (data not shown). When we adjusted for both waist circumference in 1993 and most recent BMI (model E), we found that the risk of type 2 diabetes changed minimally, with a hazard ratio (and 95% CIs) of 1.32 (1.14–1.53) for B cup, 1.71 (1.46–2.01) for C cup and 1.58 (1.29–1.94) for \geq D cup (Table 2).

Compared with women in the group with the lowest BMI at age 18 who wore an A cup or smaller, women who were in the 21.3–23.0 BMI group and wore a D cup or larger had about a 3 times higher risk of type 2 diabetes (hazard ratio

Table 2: Risk of type 2 diabetes mellitus in relation to bra cup size among 92 106 participants of Nurses' Health Study II

Assessment	Bra cup size				
	≤ A n = 27 058	B n = 44 161	C n = 16 380	≥ D n = 4 507	p value
No. of person-years of follow-up	261 877	425 178	156 572	42 816	_
No. of incident cases of type 2 diabetes mellitus	232	850	570	192	_
Age at onset of type 2 diabetes mellitus, yr, median	45.8	44.8	44.1	43.7	_
Age-adjusted hazard ratio (95% CI)	1.00¶	2.30 (1.99-2.66)	4.32 (3.71-5.04)	4.99 (4.12-6.05)	< 0.001
Model A: covariable adjusted hazard ratio (95% CI)*	1.00¶	2.14 (1.85-2.47)	3.80 (3.26-4.43)	4.12 (3.40-5.00)	< 0.001
Model B: covariable adjusted hazard ratio (95% CI), also adjusted for BMI at age 18†	1.00¶	1.75 (1.51-2.03)	2.60 (2.21-3.05)	2.37 (1.93-2.90)	< 0.001
Model C: covariable adjusted hazard ratio (95% CI), also adjusted for BMI at age 18 and current BMI†	1.00¶	1.37 (1.18-1.59)	1.80 (1.53-2.11)	1.64 (1.34-2.01)	< 0.001
Model D: covariable adjusted hazard ratio (95% CI), also adjusted for BMI at age 18† and weight change‡	1.00¶	1.41 (1.21-1.63)	1.85 (1.58-2.18)		< 0.001
Model E: covariable adjusted hazard ratio (95% CI), also adjusted for BMI at age 18, current BMI† and waist circumference in 1993§	1.00¶	1.32 (1.14-1.53)	1.71 (1.46-2.01)	1.58 (1.29-1.94)	< 0.001

Note: CI = confidence interval, BMI = body mass index.

¶Reference group.

^{*}Adjusted for age, age at menarche, parity, cumulative no. of months of lactation, hours per week of physical activity, no. of cigarettes smoked per day, mean dietary score, multivitamin use and family history of diabetes mellitus in 1989.
†Measured as a continuous variable.

[‡]Net weight change, in kilograms, between age 18 years and the last available weight measure before the end of the period of observation.

[§]Measured as a continuous variable.

3.14, 95% CI 2.11–4.68). Women who were in the ≥ 23.1 BMI group and wore a D cup or larger had a hazard ratio of 2.46 (95% CI 1.75–3.46) (Figure 1). We found that the interaction between BMI quintile at age 18 and bra cup size was not significant (p = 0.90).

Interpretation

In our prospective cohort study involving young and middle-aged women, we found that a larger bra cup size at age 20 predicted the onset of type 2 diabetes. Bra cup size, a simple, easily ascertained measure, explained the association beyond the well-established measure of BMI. The association held true within all BMI groups and also appeared to follow a dose–response relation. The association also persisted after we adjusted for other risk factors for type 2 diabetes, such as

family history of diabetes mellitus, diet and exercise. Furthermore, by developing 5 separate models to determine the relation between bra cup size and risk of diabetes, each model adjusting for different covariables, we found that the relative risk of diabetes was greater among women with larger bra cup sizes than among those in the reference group (≤ A cup size) in all models (Table 2). This finding illustrates that, whatever the approach to adjustment, there may be additional benefit to include breast size in the assessment of risk factors for type 2 diabetes.

Bra cup size, when properly determined, provides a reasonable cross-sectional estimate of overall breast volume. ¹⁶ Kusano and colleagues ¹⁷ have successfully studied the relation between breast size and breast cancer risk using cup size divisions similar to ours. Although better methods, including magnetic resonance imaging, exist for measuring

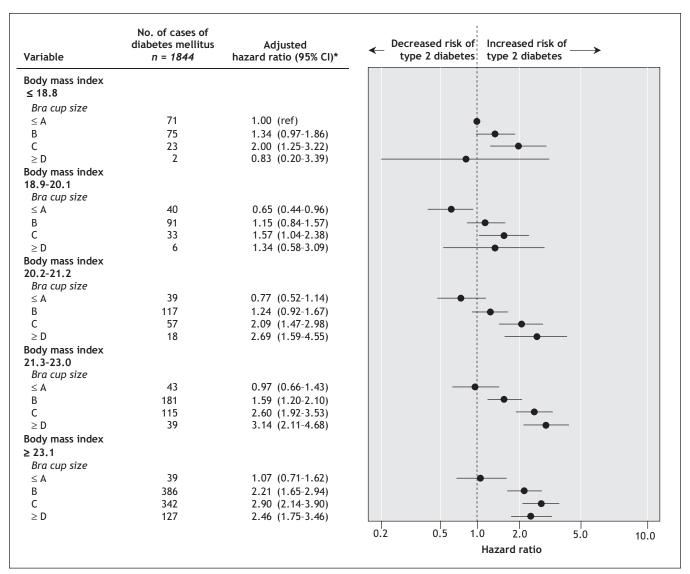


Figure 1: Forest plot showing risk of type 2 diabetes mellitus in relation to body mass index and bra cup size among 92 106 women involved in the Nurses' Health Study II. *Model B: adjusted for age, age at menarche, parity, cumulative no. of months of lactation, physical activity, smoking status, mean dietary score, multivitamin use, family history of diabetes and body mass index at age 18. CI = confidence interval, ref = reference group.

breast fat volume, they are expensive and time-consuming, and breast fat volume varies by about 15% across a woman's menstrual cycle.²⁷

If our findings prove to be true, they raise a number of new questions about the pathogenesis of type 2 diabetes. Although it is not known whether adipose tissue in the breast contributes to the pathogenesis of insulin resistance, posterior chest adiposity — marked by a high ratio of subscapular to triceps skinfold thickness — is positively correlated with insulin resistance and type 2 diabetes.28 The storage of steroid hormones within breast tissue, and the behaviour of breast tissue as a paracrine and autocrine organ, including expression of insulin-like growth factor-I by mammary adipocytes, has been widely discussed in relation to breast cancer, 29,30 but not in relation to diabetes. Adiponectin and leptin — hormones produced by adipose tissue that are responsible for regulation of glucose and fatty acid metabolism and appetite — have recently been found to be secreted in breast milk.31,32 Whether these hormones are expressed in breast tissue of nonlactating women remains unknown. Thus, while abdominal visceral obesity is known to contribute to the development of insulin resistance, 3,12 the additional action of hormonally active breast adipose tissue within this process requires elucidation.

We hypothesized that prepubertal obesity may accelerate and exaggerate the normal state of insulin resistance seen in puberty.³³ Although we did not directly test this hypothesis, the observed positive association between self-rated body fat in childhood (especially at age 10) and bra cup size, and the inverse association between age at menarche and bra cup size, is consistent with this concept.^{5,6} Breast size after puberty may also be a marker of postpubescent excessive insulin secretion and hyperandrogenemia.^{8,9} It is thus conceivable that breast size in early adulthood (e.g., at age 20) is a marker of childhood adiposity and peripubertal insulin resistance, which may continue into adulthood.

A cross-sectional study of the relation between breast volume determined by magnetic resonance imaging, markers of insulin resistance, and the metabolic syndrome among preand postpubertal women could clarify the mechanisms by which breast adiposity may predispose a young woman to type 2 diabetes.³⁴ In addition, an accurate evaluation of chest adiposity in men and women may help decipher the degree to which breast fat tissue²⁸ versus extra-abdominal fat contributes to the overall risk of insulin resistance and type 2 diabetes. Consideration of ethnic background and socioeconomic status in each of these studies is also recommended.

Our study had several strengths: a large sample, near complete prospective long-term follow-up and the use of a standard definition for type 2 diabetes. Other variables potentially associated with the development of diabetes, such as self-reported height, weight and waist circumference, have been previously validated. ^{21,22} Our study has a number of limitations. One limitation was that we relied on the women's recall of their bra cup size at age 20, which was a key variable in the study. If underweight and obese women over- and underestimated their bra cup size at age 20, respectively, then the true relation between breast size and risk of diabetes may have

been underestimated. Direct measurement of breast size and adiposity by physical examination or magnetic resonance imaging would have been useful herein. Another potential limitation was that we did not ask about breast augmentation, in part because cosmetic breast surgery was uncommon at the time that the study was initiated. Another limitation relates to the individuals enrolled in the study. The majority of our study participants were white; therefore, we are unsure whether our results would hold true for women of other ethnic backgrounds.28 A fair number of participants did not report bra cup size at age 20. Only about 18% of the Nurses' Health Study II participants included in this study wore a C cup bra at age 20, and only 5% wore a D cup or larger. Moreover, the risk of type 2 diabetes in relation to larger bra cup size was only modest. On the other hand, we found BMI at age 18 to be a strong independent predictor of diabetes, a finding that is consistent with results from other studies. 1-3,9 Hence, BMI appears to be a stronger predictor of risk of type 2 diabetes than bra cup size and should remain an established measure in clinical practice. Recent Canadian guidelines also recommend measuring the waist circumference of adults when assessing obesity-related health risks.35

In summary, we documented a statistically significant association between bra cup size and the development of type 2 diabetes. We believe that our findings should be reproduced in other settings, and in studies involving women of different ethnic backgrounds. Finally, the mechanisms underlying the potential risks and health consequences of obesity in the upper and lower torso require additional research.

This article has been peer reviewed.

Competing interests: None declared.

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