

**Birth weight, body silhouette over the life course and incident diabetes in 91,453 middle-aged women from the French E3N cohort**

Running title: Body silhouette history and incident diabetes

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## **ABSTRACT**

**OBJECTIVE**— Obesity and increases in body weight in adults are considered to be among the most important risk factors for type 2 diabetes. Low birth weight is also associated with a higher diabetes incidence. We aimed to examine to what extent the evolution of body shape, from childhood to adulthood is related to incident diabetes in late adulthood.

**RESEARCH DESIGN AND METHODS**— E3N is a cohort study of French women born 1925-1950 and followed by questionnaire every 2 years. At baseline, in 1990, women were asked to report their current weight, height and body silhouette at various ages. Birth weight was recorded in 2002. Cases of diabetes were self-reported or obtained by drug reimbursement record linkage, and further validated.

**RESULTS**— Of the 91,453 women non-diabetic at baseline, 2534 developed diabetes over the 15 years of follow-up. Birth weight, and body silhouette at 8 years, at menarche and in young adulthood (20-25 years) were inversely associated with the risk of diabetes, independently of adult BMI during follow-up (all *P* trends <0.001). In mid-adulthood (35-40 years), the association was reversed, with an increase in risk related to a larger body silhouette. An increase in body silhouette from childhood to mid-adulthood amplified the risk of diabetes.

**CONCLUSIONS**— Low birth weight and thinness until young adulthood may increase the risk of diabetes, independently of adult BMI during follow-up. Young women who were thin children should be especially warned against weight gain.

There are well-established associations between overweight or obesity and type 2 diabetes (1,2). There is also accumulating evidence indicating that high weight in adolescence and early adult life may affect later adult-onset diabetes (3,4). Conversely, many studies have demonstrated associations between low birth weight, a proxy for reduced fetal growth, and diabetes or impaired glucose tolerance in adult life (5,6). Hales and Barker suggested that diabetes was a consequence of poor nutrition during critical periods in foetal life and infancy with consequent impaired development of  $\beta$  cell function; a reduced ability to secrete insulin would become a disadvantage if nutrition became abundant (7). Eriksson et al. (8) showed two different growth pathways leading to type 2 diabetes: in babies with below-average birth weight, although there was an initial catch-up growth after birth, the BMI of those who later develop type 2 diabetes remained below that of their peers until the age of 7. Babies with above-average birth weight were at higher risk for type 2 diabetes if they had a more profound catch-down growth after birth followed by a rapid increase in weight and BMI after two years. Moreover, an early adiposity rebound appears to be associated with a higher risk for later type 2 diabetes (9).

Despite this apparent paradox of an association of type 2 diabetes with both low birth weight and adult obesity, few studies have investigated the impact of body shape throughout life. In terms of public health, it may be critical to determine at which period of life the association between body shape and diabetes risk reverses, in order to tailor prevention recommendations for diabetes to patients' body shape histories.

This study examines the influence of birth weight and body silhouette, from childhood to middle age, on incident diabetes in a cohort of middle-aged French women born between 1925 and 1950.

## **RESEARCH DESIGN AND METHODS**

### **Participants**

The E3N (Etude Epidemiologique de Femmes de la Mutuelle Générale de l'Education Nationale, MGEN) prospective cohort was initiated in France in 1990 to investigate risk factors for cancer in women (10). The cohort included 98,995 women living in France, aged 40-65 years at baseline, who were covered by the MGEN, a National Health Insurance Plan for teachers and co-workers. All women signed an informed consent, in compliance with the rules of the French National Commission for Computed Data and Individual Freedom (Commission National Informatique et Libertés) from which approval was obtained. Women completed baseline and biennial self-administered questionnaires with demographic and anthropometric characteristics, reproductive history, health status, lifetime use of hormonal treatment, parental diabetes, and smoking status. Follow-up questionnaires updated information, especially on medication use and menopausal status, and to record occurrence of major health events, among which, diabetes.

### **Identification and validation of diabetes cases**

A first set of potential cases of diabetes included women who had self-reported either diabetes, a diet to manage diabetes, use of diabetic drugs, or a hospitalization for diabetes in at least one of the eight questionnaires up until July 2005. A total of 4289 self-reported potential cases were thus identified. Among them, 2315 cases were validated when women were identified from a drug reimbursement file provided by the health insurance, as having been reimbursed for a diabetic drug between January 1st, 2004 (date when the file became available) and June 30th, 2007 (endpoint in the present study). Among the 1974 women without diabetic drug reimbursement, women alive and with an accurate address (n=1735) were mailed a questionnaire specifically designed to validate diabetes. It included questions on the circumstances of diagnosis (date of diagnosis, symptoms, and biological data including

fasting or random glucose concentrations at diagnosis), the current therapy (prescription of diet and/or physical activity, list of diabetes drugs) and on monitoring of diabetes (last values of fasting glucose and glycated hemoglobin levels). Among the 1480 women who completed this questionnaire (response rate: 84 %), 342 potential cases were confirmed, as glucose at diagnosis was reported to comply with WHO recommendations (fasting glucose  $\geq 7.0$  mmol/l or random glucose  $\geq 11.1$  mmol/l), and/or when women reported taking diabetic drugs, and/or their last values of fasting glucose or glycated hemoglobin levels were reported to be  $\geq 7.0$  mmol/l and/or  $\geq 7\%$  respectively. In this first set of potential cases, a total of 2657 diabetes cases were thus validated. Among the 1632 non-validated cases, 1144 women reported diabetes only once during the follow-up.

A second set of potential cases of diabetes was identified exclusively from the drug reimbursement file (n=1216) without prior report of diabetes in any of the eight study questionnaires. We mailed the diabetes specific questionnaire detailed above to 1139 of them and 734 women completed it. We considered as non-cases, women who reported to be non-diabetic and who had been reimbursed for diabetic drugs only once before June 30th, 2007 (n=233); we validated as diabetic cases, women who confirmed diabetes in the diabetes specific questionnaire (n=458) as well as those who did not answer the diabetes specific questionnaire but who had diabetic drugs reimbursed at least twice (n=381). Other potential cases were considered as non-validated (n=144).

Altogether, 3496 diabetes cases were validated up until June 30th, 2007.

Although this procedure did not systematically allow differentiation between type 1 and type 2 diabetes, very few incident cases with type 1 diabetes were expected considering the age-range. Prevalent diabetes cases were excluded from analyses (see below).

### **Body shape history.**

*Birth weight.* Women were asked about their birth weight in the 2002 questionnaire. They could report their exact birth weight and we subsequently categorized it as low (<2500g), medium (2500-4000g) or high (>4000g). Women were also asked whether they had been told they had a low, medium, or high birth weight as a newborn (we used this information when birth weight was missing, n=40,817) and whether their birth was premature.

*Body silhouette (see Online Appendix Figure 1).* At baseline, women provided information on their body silhouette (11) at different ages (around 8 years, menarche, age 20-25, and age 35-40). A four level categorical variable was used with values from 1 (leanest silhouette) to 4 and over (the four largest silhouettes were grouped together due to small numbers), except at age 35-40, where categories were ranked from  $\leq 2$  to 5 or more. Silhouette 3 appeared as the best choice for a common reference category at all ages given the corresponding number of subjects at each age.

*Body mass index.* BMI was computed at each follow-up (8 biannual questionnaires) from self-reported weight and height.

### **Population for analysis and follow-up**

We excluded women who declared themselves diabetic on the first questionnaire (n=715) as well as those with non-validated incident diabetes or with unknown date of diagnosis (n=1968), those with no follow-up after baseline (n=2714), and those with missing baseline BMI (n=2145), leaving 91,453 women for analysis.

Follow-up started at the date of return of the baseline questionnaire. Women contributed person-time until the date of diagnosis of diabetes, date of last completed questionnaire if the 2005 questionnaire was not completed, or June 30th 2007, whichever occurred first.

## Statistical analysis

We used Cox proportional hazards regression models with age as the timescale, to estimate the hazards ratios (HR) for diabetes and 95% confidence intervals (CI) associated with birth weight categories or silhouettes at different ages in separate models. In a more global analysis of weight history over the life-course, subjects were categorised according to birth category (low, medium, high), silhouette at 8 years (1, 2,  $\geq 3$ ) and baseline BMI (overweight or not) in a 18-level class variable. Hazard ratio for each category of this variable was estimated in reference to women with birth weight in medium class, silhouette 2 at 8 years and baseline BMI  $< 25 \text{ kg/m}^2$ . This analysis was restricted to subjects without missing values for any of the three variables. To respect the proportional hazards assumption, analyses were performed according to 5-year interval birth cohorts, using the STRATA option of SAS PHREG procedure (SAS 9.1.3, SAS Institute, Cary, NC). We controlled for potential confounders by adjusting models for education level, baseline physical activity, prematurity, parental history of diabetes, high cholesterol level, age at menarche, parity, and ever use of oral contraceptive pills. Data on smoking, menopausal status, use of menopause hormonal therapy, hypertension, and BMI were also considered as potential confounders and analyzed as time-dependent variables. Cutoffs for these variables are indicated in the footnotes of Tables 2 and 3.

We replaced missing values by the modal value (all were categorical variables) when data was missing in fewer than 5% of women, or else by a “missing” category. We performed sensitivity analyses that also included all non-validated incident diabetes as diabetic cases, and as well, all prevalent cases of diabetes.

All analyses were performed with SAS statistical software (version 9.1; SAS Institute Inc, Cary, North Carolina).

## RESULTS

Among the 91,453 women studied, 2534 cases of incident diabetes were ascertained during a median follow-up of 15.1 years. Characteristics of the study population according to diabetes status at the end of the follow-up, are presented in Table 1.

The relationship between body weight or silhouette at various ages and diabetes risk was investigated (Table 2).

After adjustment for confounders, the risk of diabetes decreased with increasing birth weight ( $P_{\text{trend}} < 0.001$ ). This result remained statistically significant after additional adjustment for adult BMI during follow-up.

At 8 years, both a lean and a large silhouette were associated with an increased risk of incident diabetes. After controlling for potential confounders, only the association with the leanest silhouette remained statistically significant. This association was enhanced after controlling for adult BMI during follow-up. Body silhouette at menarche was inversely associated with the risk of incident diabetes ( $P_{\text{trend}} < 0.001$ ) and the association was enhanced after full adjustment.

Body silhouette at age 20-25 was positively associated with the risk of diabetes ( $P_{\text{trend}} < 0.001$ ), even after adjustment for potential confounders. However, the association reversed after additional adjustment for adult BMI during follow-up, with a decrease in risk among women with a large silhouette and an increased risk in lean women ( $P_{\text{trend}} < 0.001$ ). A significantly increased risk of diabetes was associated with the larger silhouettes at age 35-40. After controlling for potential confounders and additionally for adult BMI during follow-up, HRs were of a lower magnitude, but the relationship remained statistically significant.

Adjustment for birth weight did not substantially modify the above findings (data not tabulated). Interactions between birth weight and body silhouettes were also tested in the model adjusted for confounders but none was statistically significant. Missing values on



silhouettes were associated with a significantly increased diabetes risk and they were more frequent both among overweight or obese women ( $P<0.001$  for birth weight and each body silhouette, except at age 20-25 years,  $P=0.012$ ), and among older women ( $P<0.001$  for birth weight and each body silhouette) independently.

Since self-reported birth weight and body silhouette may be influenced by baseline body weight, we investigated a potential interaction between these variables and baseline BMI. A statistically significant interaction was found for birth weight or body silhouettes (all  $P<0.001$ ). However, analyses stratified on baseline overweight status (see Online Appendix Table 1) displayed associations between diabetes risk and birth weight or body silhouette until early adulthood similar to those presented in Table 2. Only the positive association between body silhouette at 35-40 years and new-onset diabetes in each sub-group was no longer significant after adjustment for BMI during follow-up (all  $P>0,2$ ).

In a more global analysis of weight history over the life-course (Table 3), as compared to non-overweight women with medium birth weight and silhouette 2 at 8 years, women who were thin in childhood were at higher risk for new-onset diabetes. The highest risk for new-onset diabetes was found for overweight women who had low birth weight and were thin in childhood. Finally, normal weight women who reported a larger silhouette in childhood, tended to have a lower risk of diabetes. The only situation where a large silhouette in childhood was not associated with a lower risk for diabetes compared to thinner silhouette was in overweight women with a high birth weight.

When validated and non-validated cases of incident diabetes were included in the analysis ( $n=3867$ ), the results remained similar to those presented above (data not tabulated). In a sensitivity analysis, we also included prevalent diabetes cases and estimates were consistent with the main results presented (data not shown).

## CONCLUSIONS

In this large cohort study of French women, we described a complex relationship between body shape throughout life and adult-onset diabetes. Low birth weight and thinness from childhood to early adulthood increased the risk of diabetes, independently of adult BMI. The association between body silhouette from childhood to adulthood and diabetes risk was not modified by birth weight. As compared to having a medium silhouette both as a child and as a middle-aged adult, an evolution from a lean to a large silhouette conferred the highest risk, while evolution from medium to lean conferred the lowest risk. Early adulthood, 20 to 25 years, appeared to be a critical period when the relationship between body silhouette and diabetes reversed.

As there is no birth weight registry for the whole French population, we used self-reported birth weight, as in other large studies (12-14). Potential non-differential misclassification may occur and reduce the association, thus the actual association between low birth weight and diabetes might be even stronger than that reported here. A recent systematic review suggested that the association between birth weight and type 2 diabetes decreased linearly (15), except in native North American populations, where there is a high prevalence of maternal diabetes. Low birth weight may be due to the duration of gestation. Although we lacked information on duration of their mothers' gestation, adjustment for having been a premature baby did not modify our results. This is consistent with previous studies which have shown, using precise information on the length of gestation, that the relationship between small birth weight and incidence of type 2 diabetes was not explained by prematurity.

A recent paper showed that a genetic locus previously identified as a marker of type 2 diabetes could also influence birth weight, suggesting that the association between low birth weight and type 2 diabetes could be genetically mediated (16).

In addition to low birth weight, thinness in childhood and adolescence was associated with later diabetes risk. This association with thinness in childhood has already been shown by Eriksson et al. (8). They speculated that the association between low weight gain between 6 months and 1 year and the risk of later type 2 diabetes may be due to impaired development of the endocrine pancreas, since islet development continues from late gestation until adolescence (17,18). However, high BMI in childhood or adolescence has also been associated with impaired glucose tolerance (19) and even type 2 diabetes (20) in early adulthood. A rapid increase in BMI during childhood was also found to be related with a higher plasma insulin levels (21). In our study, few women reported either of the two largest silhouettes (silhouettes numbers 7 or 8) at 8 years or at menarche (n=94 and 177 respectively), and we may have lacked power to detect associations with a larger silhouette in early life. However, a thin silhouette in childhood was not associated with the risk of diabetes in overweight adult women with a large birth weight. As pointed out by Eriksson (8), the pathway leading to diabetes appears different in subjects with low and high birth weight. It is also noteworthy that the adjustment for adult BMI, by inclusion as a time-dependant variable, reinforced the associations between thinness in childhood and adolescence and diabetes risk. In our study, after thus controlling for BMI in middle-age, the body silhouette at age 20-25 was inversely associated with the risk of incident diabetes in middle age. This is the first cohort indicating that the relationship between body silhouette and risk of later onset diabetes could reverse so late in life.

Our results are consistent with previous observations that increases in BMI from childhood to adulthood are an important risk factor for adult-onset diabetes (1). Although

increased adiposity is the strongest risk factor for type 2 diabetes (8,14), our results add evidence that increased adiposity is particularly detrimental for those who have experienced a slow growth in-utero but also throughout childhood. In our cohort, the adjustment for BMI in middle age increases the risk associated with body silhouette in childhood but not with birth weight. Differences between studies for the latter point may be related to the period in life when overweight developed. In our sample of French women born between 1925 and 1950, it occurred more often in early adulthood.

A strength of our study is the large number of participants and the large number of incident cases of diabetes from whom we were able to obtain data on body silhouette from childhood to middle age. The exclusion of non-validated cases of diabetes limited misclassification errors, while sensitivity analyses suggested the absence of major selection bias. Analyses were replicated with all potential cases of diabetes and the results were similar. A limitation is the use of recalled body silhouette to estimate corpulence over the life course. However, a validation study to determine the accuracy of reported anthropometric measurements and perceived body silhouettes showed a correlation of 0.78 between BMI measured by technicians and the current self-reported silhouette, with no significant differences between self-reported and technician-measured mean BMI (22). Body shape has been evaluated by recall in other studies and found to be reliable (23,24) providing a good ranking of past corpulence and changes in corpulence over time. Must et al. (23) reported that the BMI percentile at menarche was well correlated with recalled body size at this period, after a recall time ranging from 23 to 33 years. The ability to recall events around menarche appeared to be good in that study, probably because the occurrence of the first menstrual period is usually a disrupting event. Must et al. (23) also described systematic recall biases, with the thinnest girls overestimating their body size, while normal and heavier girls underestimated it. Such a pattern was also observed among adult women in the validation

study conducted in our population (22). However, this type of bias would tend to underestimate any association between body silhouette and incident diabetes. In addition, our results were robust when we stratified analyses by overweight status at baseline (Online Appendix Table 1). Finally, an increased risk of incident diabetes was observed in the missing value category for all body silhouette measurements, a result which could be partially explained by the lower response rate among overweight or obese women and among older women. The prevalence of diabetes assessed in French women, aged 60-69 years was about 8% in 2005 (25). In our cohort the prevalence of diabetes in women of similar age at the end of the follow-up was lower (around 3%). This difference may in part be explained by a low prevalence of obesity in our cohort (around 3% at inclusion). Our results could thus be very different in a younger cohort, born from an increasing number of overweight mothers with glucose intolerance, and experiencing overweight throughout childhood.

In summary, among women born in 1925-1950, both low birth weight and thinness in childhood and early adulthood were found to be associated with the risk of diabetes in middle age, independently of adult BMI. An increase in body silhouette from childhood to mid-adulthood increased diabetes risk. Weight gain prevention programs need to be implemented in order to prevent diabetes in young adult women, especially among those who were thin in childhood.

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Table 1— Characteristics (Mean  $\pm$  SD or %) of the E3N study population, according to diabetes status at the end of the 17 years follow-up

	No diabetes n=88919	New-onset diabetes n=2534
Age (y)	49.3 $\pm$ 6.6	51.3 $\pm$ 6.7
Body mass index (kg/m <sup>2</sup> )	22.5 $\pm$ 3.0	26.9 $\pm$ 4.7
Physical activity (MET-h/wk)	52.3 $\pm$ 38.0	44.3 $\pm$ 35.8
At least one parent with diabète (%)	9.6	23.7
Current smoker (%)	13.3	13.2
University degree (%)	35.2	24.4
Hypercholesterolemia (%)	8.2	15.2
Hypertension (%)	8.6	25.4
Menopause (%)	40.5	53.7
Low birth weight (%)	7.2	9.6
Body silhouette (1-8 scale)		
- at 8 years	1.8 $\pm$ 1.1	1.8 $\pm$ 1.2
- at menarche	2.5 $\pm$ 1.2	2.4 $\pm$ 1.2
- at 20-25 y	2.5 $\pm$ 0.9	2.7 $\pm$ 1.1
- at 35-40 y	3.0 $\pm$ 1.0	3.7 $\pm$ 1.2

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\* Birth weight in grams categorized as low (<2500g), or women's self-classification as newborn of low birth weight (when birth weight in grams was missing).

Table 2— Hazards ratio [95% CI] for incident diabetes in relation to body silhouette history in the E3N cohort (1990-2007, n=91,453)

		Hazards Ratio [95% CI]			
		Cases diabetes / person-years (2534/1,381,311)	Model 1 : Adjusted for year of birth	Model 2 : Adjusted for confounders*	Model 3 : Adjusted for confounders* and BMI <sup>†</sup>
<b>Birth weight</b>					
	Low	242 / 106,584	1.47 [1.29 - 1.69]	1.31 [1.13 - 1.53]	1.40 [1.20 - 1.62]
	Medium	1,469 / 945,893	1	1	1
	High	160 / 118,033	0.87 [0.74 - 1.03]	0.82 [0.70 - 0.97]	0.72 [0.61 - 0.85]
	<i>Missing</i>	<i>663 / 210,802</i>	<i>2.27 [2.07 - 2.49]</i>	<i>1.21 [1.04 - 1.41]</i>	<i>1.19 [1.02 - 1.39]</i>
			<i>P<sub>trend</sub>&lt;0.001</i>	<i>P<sub>trend</sub>&lt;.0001</i>	<i>P<sub>trend</sub>&lt;.0001</i>
<b>Body silhouette</b>					
<b>- at 8 years</b>					
	1	1,440 / 711,442	1.35 [1.18 - 1.54]	1.35 [1.18 - 1.54]	1.66 [1.45 - 1.9]
	2	423 / 276,290	1.06 [0.91 - 1.24]	1.10 [0.95 - 1.29]	1.28 [1.10 - 1.5]
	3	260 / 178,920	1	1	1
	≥ 4	255 / 144,255	1.22 [1.03 - 1.45]	1.15 [0.96 - 1.36]	1.09 [0.92 - 1.30]
	<i>Missing</i>	<i>156 / 70,404</i>	<i>1.46 [1.20 - 1.78]</i>	<i>1.21 [0.99 - 1.48]</i>	<i>1.45 [1.19 - 1.77]</i>
			<i>P<sub>trend</sub>&lt;0.0001</i>	<i>P<sub>trend</sub>&lt;0.0001</i>	<i>P<sub>trend</sub>&lt;0.0001</i>
<b>- at puberty</b>					
	1	599 / 296,009	1.14 [1.02 - 1.28]	1.16 [1.03 - 1.31]	1.48 [1.32 - 1.67]
	2	808 / 430,164	1.09 [0.98 - 1.22]	1.08 [0.97 - 1.20]	1.23 [1.10 - 1.37]
	3	545 / 320,388	1	1	1
	≥ 4	449 / 285,608	0.93 [0.82 - 1.06]	0.90 [0.79 - 1.02]	0.81 [0.71 - 0.92]
	<i>Missing</i>	<i>133 / 49143</i>	<i>1.51 [1.25 - 1.82]</i>	<i>1.15 [0.95 - 1.39]</i>	<i>1.26 [1.04 - 1.53]</i>
			<i>P<sub>trend</sub>&lt;0.0001</i>	<i>P<sub>trend</sub>&lt;0.0001</i>	<i>P<sub>trend</sub>&lt;0.0001</i>
<b>- at 20-25 years</b>					

1	250 / 139,062	0.94 [0.81 - 1.08]	0.99 [0.86 - 1.14]	1.43 [1.23 - 1.65]
2	894 / 564,902	0.85 [0.78 - 0.94]	0.90 [0.82 - 0.99]	1.13 [1.03 - 1.25]
3	840 / 454,936	1	1	1
≥ 4	454 / 188,665	1.29 [1.15 - 1.45]	1.15 [1.03 - 1.29]	0.84 [0.75 - 0.95]
<i>Missing</i>	<i>96 / 33,746</i>	<i>1.48 [1.20 - 1.83]</i>	<i>1.10 [0.89 - 1.36]</i>	<i>1.22 [0.98 - 1.51]</i>
		$P_{\text{trend}} < 0.0001$	$P_{\text{trend}} = 0.001$	$P_{\text{trend}} < 0.0001$
- at 35-40 years				
≤ 2	352 / 439,332	0.52 [0.46 - 0.59]	0.59 [0.52 - 0.66]	0.78 [0.69 - 0.88]
3	861 / 572,537	1	1	1
4	706 / 251,002	1.87 [1.69 - 2.06]	1.55 [1.40 - 1.71]	1.17 [1.05 - 1.29]
≥ 5	516 / 82,573	4.22 [3.78 - 4.71]	2.72 [2.43 - 3.05]	1.17 [1.03 - 1.32]
<i>Missing</i>	<i>99 / 35,868</i>	<i>1.76 [1.43 - 2.16]</i>	<i>1.32 [1.07 - 1.63]</i>	<i>1.15 [0.93 - 1.42]</i>
		$P_{\text{trend}} < 0.0001$	$P_{\text{trend}} < 0.0001$	$P_{\text{trend}} < 0.0001$

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\* Model 2: Includes physical activity (<34 / 34-47 / 47-62 / ≥ 62 MET-h/week), education (≤ 9 / 10-11 / 12-14 / 15-16 / ≥ 17 y), prematurity (no / yes), family history of diabetes (none / only one parent / both parents), smoking (never / former / current smoker, time-dependent variable), high cholesterol level (no / yes), hypertension (no / yes, time-dependant variable), menopausal status (no / yes, time-dependent variable), hormone replacement therapy (never / ever, time-dependent variable), oral contraceptive pills (never / ever), parity and age at 1<sup>st</sup> child (nulliparous / 1st child before 30 y, 1-2 children / 1<sup>st</sup> child before 30 y, 3+ children / 1<sup>st</sup> child at 30 y or more), age at menarche (≤12 / 13 / ≥14 years old), according to birth cohort (1925–1930 / 1930–1935 / 1935–1940 / 1940–1945 / 1945–1950).

† Model 3: Confounders as above and further adjustment for adult BMI as a time-dependent variable

Table 3— Fully adjusted hazards ratio [95% CI] for incident diabetes in relation to body shape history over the life-course, from birth to middle age, in the E3N cohort (1990-2007)

	BMI < 25		BMI ≥25	
	kg/m <sup>2</sup> at		kg/m <sup>2</sup> at	
	baseline		baseline	
	Cases / total	HR [95% CI] *	Cases / total	HR [95% CI] *
	person-years		person-years	
Low birth weight				
- Silhouette 1 at 8 y	71 / 63,063	1.78 [1.31 - 2.43]	22 / 9,232	4.83 [3.62 - 6.45]
- Silhouette 2 at 8 y	426 / 13,127	1.35 [0.72 - 2.53]	174 / 1,968	3.12 [1.77 - 5.50]
- Silhouette ≥3 at 8 y	29 / 11,005	1.48 [0.79 - 2.77]	22 / 3,368	3.11 [1.99 - 4.87]
Medium birth weight				
- Silhouette 1 at 8 y	71 / 428,348	1.64 [1.32 - 2.05]	25 / 60,075	3.45 [2.75 - 4.33]
- Silhouette 2 at 8 y	297 / 169,633	1	208 / 29,037	2.80 [2.16 - 3.61]
- Silhouette ≥3 at 8 y	13 / 171,261	0.72 [0.53 - 0.97]	42 / 43,203	2.05 [1.59 - 2.63]
Large birth weight				
- Silhouette 1 at 8 y	29 / 35,825	1.34 [0.88 - 2.03]	15 / 6,227	1.43 [0.89 - 2.30]
- Silhouette 2 at 8 y	138 / 19,044	0.67 [0.33 - 1.38]	150 / 4,155	2.22 [1.41 - 3.52]
- Silhouette ≥3 at 8 y	8 / 34,896	0.63 [0.36 - 1.10]	31 / 11,933	1.77 [1.25 - 2.50]

\* adjusted for physical activity (<34 / 34-47 / 47-62 / ≥ 62 MET-h/week), education (≤ 9 / 10-11 / 12-14 / 15-16 / ≥ 17 y), prematurity (no / yes), family history of diabetes (none / only one parent / both parents), smoking (never / former / current smoker, time-dependent variable), high cholesterol level (no / yes), hypertension (no / yes, time-dependant variable), menopausal status (no / yes, time-dependent variable), hormone replacement therapy (never / ever, time-dependent variable), oral contraceptive pills (never / ever), parity and age at 1<sup>st</sup> child (nulliparous / 1st child before 30 y, 1-2 children / 1<sup>st</sup> child before 30 y, 3+ children / 1<sup>st</sup>

child at 30 y or more), age at menarche ( $\leq 12$  / 13 /  $\geq 14$  years old), and adult BMI as a time-dependent variable, according to birth cohort (1925–1930 / 1930–1935 / 1935–1940 / 1940–1945 / 1945–1950).