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Duration of obesity and overweight and risk of type 2 diabetes among US women

Yang Hu¹, Shilpa N Bhupathiraju², Lawrence de Koning³, and Frank B Hu⁴

¹Brigham and Women's Hospital, Boston, MA

²Departments of Nutrition, Harvard School of Public Health, Boston, MA

³Departments of Pathology and Laboratory Medicine, Pediatrics, and Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

⁴Departments of Nutrition and Epidemiology, Harvard School of Public Health and the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Abstract

Objective—The purpose of this study was to examine the association between duration of adiposity and risk of type 2 diabetes (T2D) in US women.

Methods—We prospectively followed 61,821 participants from the Nurses' Health Study (1984-2008) and 63,653 participants from Nurses' Health Study II (1991-2011). Participants were considered overweight (BMI 25-30 kg/m²) or obese (BMI \geq 30 kg/m²) if their BMI was above the cutoffs for two successive assessments. We used time-dependent Cox proportional hazard models to assess associations between excess weight duration and T2D risk.

Results—In pooled multivariable analyses of the two cohorts, each two extra years of being overweight was associated with 9% (RR=1.09, 95% CI 1.08 - 1.09) increased risk of developing T2D. For each 2-year increment in obesity duration, the risk of T2D was increased by 14% (RR=1.14, 95% CI 1.14 - 1.15). Adjustment for current BMI greatly attenuated the association for obesity duration (RR =1.02, 95% CI 1.01 - 1.03), although the attenuation was less for overweight duration (RR =1.04, 95% CI 1.04 - 1.05).

Conclusions—Both overweight and obesity duration were associated with a significantly higher risk of T2D, and these associations were mainly explained by current BMI, especially for obesity duration.

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Corresponding author: Frank B. Hu, Address: 655 Huntington Avenue, Building II, 3rd floor. Boston, MA, 02115, USA., Telephone: 617-432-0113, Fax: 617-432-3435, frank.hu@channing.harvard.edu.

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Author contributions: FBH designed the study, obtaining funding, supervised the study and edited the manuscript. LDK designed the study, interpreted the results and edited the manuscript. SNB provided statistical advice, reviewed and edited the manuscript. YH researched the data, interpreted the results and drafted the manuscript. All authors contributed to discussion of the analysis and approved the final version of the manuscript for submission.

Keywords

Type 2 diabetes; Obesity duration; Overweight duration

Introduction

Both overweight and obesity have become critical public health issues in the United States. Nationally representative survey data have shown that the prevalence of obesity and overweight has steadily increased over the past three decades. More than 35% of US men and women were obese in 2009–2010 (1). If current trends continue and no effective measures are adopted to stop the trend, it is estimated that by the year of 2030, 86.3% of the US adults will be overweight or obese (2). Numerous studies have demonstrated that obesity is a powerful risk factor for many health outcomes including T2D, cardiovascular diseases and all-cause mortality (3–7). Most studies have put emphasis on quantifying the association between the degree of adiposity and chronic diseases, but few studies have examined the influence of the duration of adiposity on the health outcomes. Clinically, failing to consider excess weight duration might underestimate risk of T2D, because it is likely that those are overweight or obese for a longer duration of time are more likely to be in a chronic state of inflammation and metabolic dysregulation and, therefore, more predisposed to develop T2D (8).

To our knowledge, few studies have examined the relationship between obesity/overweight duration and incidence of T2D (9–15) and some of them did not assess body weight prospectively. Only one study analyzed overweight duration, but it was not specifically designed to investigate the association between overweight duration and risk of T2D (12). Moreover, it remains unclear if excess weight duration is predictive of diabetes risk after accounting for current adiposity levels. Most recently, in the Framingham Heart Study, each two additional years of obesity duration was associated with 13% and 12% increased T2D risk for men and women respectively, and these associations were independent of the degree of BMI (15). However, it remains unclear if these results are readily generalizable to the current population because the study population was followed up from 1950s when the prevalence of obesity and diabetes was much lower. Further, this study failed to adjust for several important dietary factors such as sugar-sweetened beverages, red meat, and fiber that have been associated with both obesity and T2D (16–20). A recently study found that longer duration of abdominal obesity was significantly associated with increased T2D risk, but a dose-response relationship was not observed (21).

Therefore, the aim of the present study was to examine whether the duration of overweight and obesity were independent risk factors of type2 diabetes after adjusting for lifestyle and dietary risk factors and current BMI in two large well-established cohorts of US women.

Methods

Data sources

The Nurses' Health Study (NHS) was initiated in 1976 and comprised of 121,700 female registered nurses, aged 30-55 years. The NHS II was established in 1989 and consisted of 116,671 female registered nurses, aged 25-42 years. Participants in both cohorts were followed biennially through validated questionnaires that obtained updated information on their medical history, lifestyle, and occurrence of chronic diseases. All participants were expected to attend all biennial follow-up although they were censored if developing type 2 diabetes, lost to follow-up, death or the end of study. The follow-up rates exceeded 90% in each 2-year cycle for both cohorts. Detailed descriptions of the cohort design are provided elsewhere (22, 23).

In the present analysis, we used 1984 as baseline for NHS and 1991 for NHS II when all the important covariates were comprehensively measured. We included participants who were free from diabetes, cancer or cardiovascular disease at baseline. We excluded participants with missing values on height because their BMI could not be determined. We also excluded participants with a BMI $\geq 25\text{kg/m}^2$ in 1976 (NHS) and 1991 (NHS II) in order to reduce the possibility of miscalculating the excess weight duration for people with overweight or obese long before the enrollment of the cohort. After exclusion, 62,167 participants from NHS and 64,038 participants from NHS II were included in the analysis.

Definition of cumulative excess weight duration

Cumulative overweight and obesity duration was calculated from 1976 in NHS and 1989 in NHS II when information on height and weight were first collected. Body weight and height were self-reported by the participants. We calculated body mass index (BMI) as weight in kilograms divided by squared height in meters. Self-reported measures of body weight are highly correlated with measured weights ($r=0.96$) in the NHS (24). Overweight was defined as $25 \leq \text{BMI} < 30\text{kg/m}^2$ and obesity was defined as $\text{BMI} \geq 30\text{kg/m}^2$. To reduce potential overestimation of excess weight duration, the beginning of an individual's obesity/overweight duration was the first examination of the two consecutive occurrences of obesity and an individual was considered to be continuously obese until the first of two consecutive examinations when the participant was no longer obese/overweight, death, lost-to-follow-up, diagnosis with T2D or the end of study (June 30, 2008 in NHS and June 30, 2009 in NHS II), whichever occurred earlier. According to this definition, the maximum obesity/overweight duration in the study was 28 years for NHS and 18 years for NHS II.

Diagnosis of type 2 diabetes

Participants with self-reported diagnoses of diabetes on the main questionnaire were mailed a supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy (25). We used the National Diabetes Data Group criteria (26) for defining cases before 1998. For cases diagnosed after 1998, we used the American Diabetes Association criteria (27). The validity of the self-reported questionnaire was verified by reviewing medical records, and the diagnosis of T2D was confirmed in $>98\%$ of the cases in NHS (28, 29). Only clinically confirmed diabetes cases were considered as the outcome.

Assessment of diet and covariates

Since 1980 and 1991, a validated FFQ was administered to NHS and NHS II participants to collect information on their usual intakes of foods and beverages over the previous year. Participants were asked how often on average during the previous year they consumed certain food by using standard portion sizes (one standard serving, cup, glass, can, or bottle). There were 9 possible responses that ranged from never or, 1 time/month to ≥ 6 times/day. Nutrient intakes were computed by multiplying the frequency of consumption of each food or beverage by the nutrient content of the specified portion and summing the contributions from all items.

In the biennial follow-up questionnaires, we updated information on a participant's age, weight, smoking status, family history of diabetes, menopausal status, and use of postmenopausal hormone therapy. Alcohol consumption status was measured from 1980 for NHS and from 1989 for NHS II and was updated every 4 years. Physical activity information was collected biennially since 1986 for NHS and from 1991 for NHS II using a validated questionnaire. Participants were asked to report the average time spent on 10 common activities. The information was then summed and calculated as metabolic equivalent hours per week (30). The presence or absence of a family history of diabetes (in first-degree relatives) was assessed in 1982 and 1988 in NHS, in 1989, 1997, 2001, and 2005 in NHS II. Diet quality was assessed using the alternative healthy eating index that measures adherence to a healthy diet pattern based on 11 dietary components that were found to be highly predictive of disease risk in the literature (20).

Statistical analysis

The association between excess weight duration and incidence of T2D was analyzed using time-dependent Cox proportional hazard models. Our main exposures, cumulative duration of overweight and obesity were included in the model as time-dependent variables. Similarly, age, smoking status, physical activity, alcohol consumption, postmenopausal hormone use, dietary variables, and BMI were included in the multivariable model as time-varying covariates. Missing data of the exposure and covariates were carried forward one cycle.

Cumulative overweight and obesity duration were treated as both continuous and categorical (0, 1-4, 5-8, 9 years) variables in our regression models. In multivariable model 1, we adjusted for age, smoking status (never, past, current 1-14 cigarettes/day, current 15-24 cigarettes/day, current ≥ 25 cigarettes/day), physical activity level (<3.0 , 3.0-8.9, 9.0-17.9, 18.0-26.9, ≥ 27.0 hrs of metabolic equivalent tasks per wk), alcohol consumption (0, 0.1-4.9, 5-14.9, 15-29.9, ≥ 30.0 g/day), coffee intake (<1 cup/week, 2-4 cups/week, 5-7 cups/week, 2-3 cups/day, 4 cups/day), alternate healthy eating index (quintiles), total energy (kcal/day), family history of diabetes and menopausal status and postmenopausal hormone use (premenopausal, never use, current use, past use). To examine if observed associations were independent of current BMI, in multivariable model 2 we further adjusted for time-varying BMI. For the continuous excess weight duration, obesity and overweight duration were mutually adjusted in all models. To examine whether the associations were independent of weight gain, we further adjusted for weight change between each cycle (quintiles). We also

conducted an analysis to quantify the relative risk for each combination of current BMI (25-29.9, 30-35, 35) and overweight or obesity duration (4 categories) using normal weight as the reference group and adjusted for the covariates described above. The interactions between obesity and overweight duration and current BMI were tested by including the product of obesity/overweight duration and current BMI in the model and the Wald test was used to calculate p value for interactions.

A sensitivity analysis was performed to assess the influence of comorbidities especially cardiovascular disease (coronary heart disease and stroke) on the risk of T2D by additionally censoring the cardiovascular cases during the follow up. We also conducted another sensitivity analysis that did not carry forward missing BMI values to assess the influence of missing data. All statistical tests were 2-sided and performed using SAS version 9.2 for UNIX (SAS Institute Inc, NC).

Results

After exclusions, 61,821 participants from NHS and 63,653 participants from NHS II were included in the analysis. During 2,469,671 person-years of follow-up, we documented 4,835 cases of incident T2D. Nearly 13% of NHS participants and 11% of NHS II participants developed obesity. On the other hand, over half of NHS participants (51 %) and 44.3% of NHS II participants became overweight during follow-up. The average duration of obesity and overweight were 6.5 y and 7.6 y in NHS and 5.0 y and 2.9 y in NHS II, respectively. NHS participants were on average 53 years when they became obese and they were on average 51 years when they became overweight. The mean age at initiation of obesity and overweight was 43 for participants in NHS II.

Table 1 shows the characteristics of participants from 2 cohorts by categories of obesity duration. In both cohorts, women with longer obesity duration tended to be younger at baseline, have a higher baseline BMI, current BMI, less physical activity and less alcohol consumption. Those with more obesity years also had higher prevalence of current hypertension and hypercholesterolemia, higher proportion of ever cigarette smoking, family history of diabetes, and postmenopausal. Also, women exposed to obesity for longer time had modestly less coffee and higher total energy intake. Although it appeared people with longer obesity duration were more likely to have poorer diet quality and current hormone use in NHS I, the opposite relationship was observed in NHS II.

In both cohorts, after adjustment for age, lifestyle, and other dietary factors, participants who were overweight or obese for a longer duration had a significantly higher risk for T2D compared to those who were normal weight (Table 2). The pooled relative risk for T2D was 1.09 (95% CI 1.08-1.09) and 1.14 (95% CI 1.14-1.15) for each 2-year increment in overweight and obese duration, respectively. In pooled results, women exposed to more than 9 years of obesity had a nearly 5-fold (pooled RR 4.82 [95% CI 4.31-5.38]) increased risk of developing T2D than those who were never obese (included overweight people). Likewise, women who were overweight for more than 10 consecutive years had nearly a 3-fold higher risk of T2D than their normal weight counterparts (pooled RR 3.44 [95% CI 3.17-3.73]). When current BMI was controlled for, the association between obesity duration of 9 years

and T2D was no longer significant (pooled RR 0.96 [95% CI 0.83-1.11]) although the association for continuous duration of obesity remained significant but largely attenuated (for each 2-year increment: RR=1.02, 95% CI 1.01-1.03). Adjustment for current BMI also substantially attenuated the association for overweight duration (for each 2-year increment: RR=1.04, 95% CI 1.04-1.05). Additional adjustment for weight change (quintiles) between cycles attenuated the estimates for each category modestly (multivariable-adjusted pooled RR for obesity duration ≥ 9 years 4.40 [95% CI 3.94-4.92]); multivariable-adjusted pooled RR for overweight duration ≥ 9 years 3.25 [95% CI 2.99-3.52]), but for continuous overweight and obesity duration, the estimates remained unchanged.

Figure 1 shows the relative risk for each combination of BMI category and duration of obesity or overweight. The reference group includes normal weight participants. Within each category of duration, a higher BMI was associated with a higher risk for T2D. In panel A, participants who were overweight for over 9 years had a nearly 4-fold higher risk (RR 3.91, [95% CI 3.57-4.28]) of T2D, while those who were obese for the same duration had a 10-fold higher risk (RR 10.10 [95% CI 8.93-11.43]) of developing T2D compared to those who were normal weight. In panel B, after adjusting for current BMI, all the RRs were substantially attenuated, especially for obesity duration. However, the increasing trend of diabetes with longer duration of being overweight persisted. The interaction term between obesity duration and current BMI was highly significant ($p < 0.001$) in both cohorts while the p value did not reach significant level for the interaction between overweight duration and current BMI in either cohort.

In sensitivity analyses, when we censored cases of cardiovascular diseases including myocardial infarction, stroke and coronary artery bypass graft, the associations in general, became stronger across adiposity categories but the higher risk for each additional 2 years of obesity duration (pooled RR 1.15 [95% CI 1.14-1.16]) and overweight duration (pooled RR 1.09 [95% CI 1.09-1.10]) remained unchanged (Supplemental table 1). In addition, not carrying forward missing BMI did not change the results substantially (pooled RR for obesity duration 1.15 [95% CI 1.14-1.16]; pooled RR for overweight duration 1.09 [95% CI 1.08-1.10]). (Supplemental table 2)

Discussion

In these 2 large cohorts of US women with more than 2 decades of follow-up, we found that both overweight and obesity durations were significantly associated with a higher risk for T2D. Each two-year increase in overweight duration was associated with 1.09 fold higher risk of diabetes and for each two additional years of obesity duration, the risk was increased by 14%. Adjustment for current BMI greatly attenuated the association for obesity duration, although the attenuation was less for overweight duration.

Few studies have explored the association between excess weight duration and risk of T2D, and most of the previous studies have some methodological limitations. First, several studies (10, 11, 13) relied on retrospective recalls of body weight, which is susceptible to recall bias and measurement error. Second, although diet is an important confounder of the association between adiposity and T2D, none of the studies adjusted for dietary confounders, such as

coffee consumption, sugar-sweetened beverage consumption, and red meat intake which were associated with both body weight and T2D (22, 25, 31). Third, only one study assessed whether the obesity duration – diabetes risk association was independent of degree of adiposity (15). This additional adjustment for current BMI is important because individuals with longer duration of overweight or obesity tend to have greater BMI, and thus the observed positive association could be due to the degree of BMI instead of the duration of adiposity.

Our findings are in agreement with results from a previous study using the Framingham Heart Study (FHS) cohort. In FHS, an 11% increased risk of T2D was observed for each 2 additional years of obesity in the multivariable-adjusted model and the increased risk was attenuated to 6% after further adjustment for current BMI in women. The difference between our findings and their results was that the association between obesity duration and risk of T2D was greatly attenuated after additionally controlling for current BMI in our study. We found a 2% increased risk of T2D when taking the current BMI into account. Because our two cohorts were initiated in 1976 (NHS) and 1989 (NHS 2), whereas the FHS was started in the 1950s, this discrepancy could be attributed to the different characteristics between the study populations. The BMI of obese participants in the FHS cohort was likely to be lower than that in our cohorts, and thus the impact of further adjustment for current BMI was much less in the FHS compared to that in our cohorts.

It was interesting to note that the association for people with long obesity years (over 9 years) was attenuated to null after adjustment for current BMI, while each 2 additional obesity years as a continuous variable was still marginally associated with elevated diabetes risk, but the similar association was not observed for overweight duration. This finding suggests that for people with long obesity duration, their risk of developing T2D was largely determined by their current BMI rather than the duration of obesity. In contrast, for people with long overweight duration, both current BMI and overweight years may play important roles in T2D risk. This interpretation is supported by the finding that the interaction between excess weight duration and current BMI was only statistically significant for obesity duration, but not for overweight duration. In addition, there was a positive correlation between obesity duration and current BMI in our cohorts, and the mean BMIs for those being obese over 9 years reached the Class II obesity (35 kg/m² in NHS and 36 kg/m² in NHS II). Among individuals with class II or class III obesity, the degree of adiposity might be more important because people with very large BMI tend to have higher rates of hypertension, dyslipidemia, insulin resistance, be in chronic oxidative stress, and have higher circulating concentrations of inflammatory markers (32) all of which are important predictors for development of T2D. Accordingly, our results suggest that people could still lower their T2D risk by losing weight immediately even if they have been exposed to obesity for long time. It was also interesting to note that the overweight duration was negatively correlated with current BMI and this might suggest that it was easier for overweight people to lose weight than obese people.

In our analysis, cumulative overweight and obesity duration were mutually adjusted, but the estimates changed very modestly when they were put into the model individually, suggesting the effects of overweight duration and obesity duration on T2D risk were

independent of each other. They were actually weakly correlated and the age-standardized Pearson correlation coefficient between overweight and obesity duration was only -0.36. Moreover, individuals with longer excess weight duration are less likely to maintain their body weight but more likely to gain weight, which is an independent risk factor for diabetes. However, further adjustment for weight change did not alter the association between excess weight duration and risk of diabetes, suggesting that the observed association could not be explained by weight gain.

Our study had several strengths. First, NHS and NHS II are prospective cohorts with the exposure measured before the outcome, which minimized the possibility of reverse causation. Second, both exposure and covariate information was updated every 2 or 4 years, ensuring a relatively accurate calculation of overweight and obesity duration and appropriate adjustment for time-varying confounders. Third, we had a very large sample size that included more than 120,000 women, which provided us with ample power to detect small but potentially important associations.

There were also several limitations to this study. First, generalizability might be an issue in our study, because participants in our study were female health care professionals, the vast majority of whom were of European ancestry. However, because similar associations were observed from studies in men and other ethnic groups (15), we believe that our results can be generalized to the US population. Second, unmeasured and residual confounding is inevitable in any observational studies. However we carefully adjusted for a very wide range of lifestyle and dietary variables with repeated measurement during follow-up to minimize the impact of residual confounding. Finally, since the assessment of T2D cases was based on self-report and subsequent medical record review, we might have missed some true cases. However, given the high follow-up rate and highly-motivated participants with medical knowledge in our cohorts, we believe that the likelihood of false negative cases is relatively low.

In conclusion, the present analysis shows that both overweight and obesity duration are important risk factors for T2D in a cohort of US women. Their effects were independent of each other and the weight gain. When current BMI was taken into account, obesity duration was only marginally associated with risk of T2D but longer duration of being overweight was still associated with substantially elevated risk of diabetes. Given these findings, public health efforts should focus on prevention early onset of overweight and obesity and the importance of losing body weight to reduce risk of T2D.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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What is already known about this subject: Obesity is a strong risk factor for type 2 diabetes.

What this study adds: Both obesity duration and overweight duration were associated with a significantly higher risk of type 2 diabetes, and these associations were mainly explained by current BMI, especially for obesity duration.

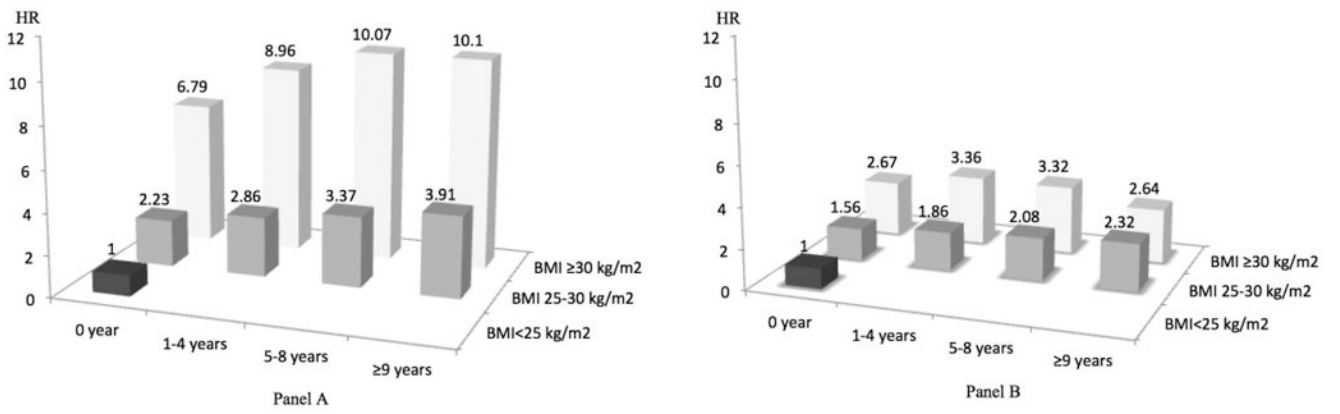


Figure 1.

Table 1
Characteristics of NHS (n=61,821) and NHS II (n=63,653) participants by obesity duration categories

Characteristic	NHS					NHS II						
	0 years ^a	1-4 years	5-8 years	9 years	0 years	1-4 years	5-8 years	9 years	0 years	1-4 years	5-8 years	9 years
No. of participants	53,984	2,758	1,910	3,169	56,640	3,510	1,879	1,624				
Age at baseline (years)	50.1(7.2)	47.1(6.5)	46.3(6.2)	46.2(6.2)	36.3(4.6)	36.0(4.6)	35.8(4.6)	36.2(4.6)				
Baseline body mass index (kg/m ²)	22.5(2.2)	25.2(2.3)	25.7(2.3)	27.9(3.4)	21.7(2.1)	24.2(2.0)	24.8(2.2)	26.5(3.2)				
Current body mass index (kg/m ²)	23.9(3.1)	29.8(2.7)	31.3(2.9)	33.8(4.0)	24.2(3.1)	31.0(2.7)	32.7(3.0)	35.1(4.1)				
Physical activity (MET-h/week)	19.3(23.8)	15.4(23.1)	14.8(20.2)	13.3(20.9)	23.5(28.6)	18.4(23.9)	17.4(22.3)	16.2(22.8)				
Alternate healthy eating index	53.9(11.4)	52.7(11.0)	52.5(10.8)	51.8(10.8)	53.3(12.7)	51.4(11.7)	50.8(11.5)	50.8(11.8)				
Alcohol use (g/day)	7.0(9.6)	5.5(8.4)	5.5(8.6)	4.7(7.9)	3.9(5.8)	3.5(5.6)	3.4(5.6)	2.9(5.3)				
Coffee consumption (servings/day)	2.3(1.6)	2.4(1.6)	2.4(1.6)	2.3(1.6)	1.4(1.4)	1.5(1.5)	1.4(1.5)	1.4(1.5)				
Total energy intake (kcal/day)	1710(421)	1707(429)	1714(425)	1739(440)	1806(478)	1784(485)	1811(483)	1805(497)				
Ever smoker (%)	56.2	60.3	57.1	59.7	33.6	36.2	36.6	36.0				
Ever hypertension (%)	54.5	64.5	69.1	74.5	21.5	38.5	44.1	51.9				
Ever high cholesterol (%)	67.5	75.6	76.8	75.2	40.6	56.6	57.5	61.2				
Postmenopausal (%)	79.6	70.8	69.0	68.4	23.7	23.4	24.0	25.2				
Current hormone use (%)	16.9	11.7	11.5	10.7	9.3	9.4	9.5	9.0				
Family history of diabetes (%)	25.9	28.0	30.3	31.0	30.7	37.2	38.9	40.8				

Data are means (standard error) unless otherwise indicated.

^aIncludes people who were overweight.

Table 2
Association of obesity and overweight duration with risk of type 2 diabetes in NHS (1984-2008) and NHS II (1991-2011)

	0 years	1-4 years	5-8 years	9 years	Risk for Each additional 2 years ^a
NHS					
Obesity duration					
Cases/person-years	2,563/1,226,119	387/37,118	267/19,539	314/18,540	
Age-adjusted	1.00	4.19(3.76,4.67)	5.02(4.41,5.71)	5.57(4.93,6.29)	1.14(1.13,1.15)
Model1	1.00	3.64(3.26,4.07)	4.24(3.72,4.82)	4.47(3.95,5.05)	1.13(1.12,1.13)
Model2	1.00	1.62(1.44,1.83)	1.48(1.28,1.71)	1.01(0.86,1.18)	1.02(1.01,1.03)
Overweight duration					
Cases/person-years	1,028/844,001	694/174,003	751/132,528	1,058/150,784	
Age-adjusted	1.00	3.06(2.78,3.37)	3.86(3.51,4.25)	3.81(3.48,4.17)	1.09(1.08,1.09)
Model1	1.00	2.76(2.51,3.05)	3.42(3.11,3.77)	3.33(3.04,3.64)	1.08(1.07,1.09)
Model2	1.00	1.59(1.43,1.76)	1.84(1.66,2.03)	1.85(1.68,2.03)	1.04(1.03,1.05)
NHS II					
Obesity duration					
Cases/person-years	908/1,124,291	203/27,484	117/11,056	76/5,523	
Age-adjusted	1.00	6.04(5.16,7.06)	7.82(6.40,9.54)	8.84(6.92,11.29)	1.27(1.25,1.29)
Model1	1.00	4.89(4.17,5.73)	6.03(4.92,7.38)	6.54(5.10,8.38)	1.24(1.22,1.26)
Model2	1.00	1.48(1.22,1.78)	1.31(1.03,1.67)	0.82(0.60,1.13)	1.03(1.00,1.06)
Overweight duration					
Cases/person-years	451/894,381	389/154,323	269/78,920	195/40,731	
Age-adjusted	1.00	3.77(3.28,4.33)	3.98(3.40,4.66)	4.63(3.87,5.54)	1.16(1.14,1.17)
Model1	1.00	3.24(2.82,3.73)	3.34(2.85,3.92)	3.90(3.26,4.68)	1.14(1.13,1.16)
Model2	1.00	1.60(1.38,1.85)	1.67(1.42,1.96)	2.08(1.74,2.50)	1.07(1.05,1.08)
NHS and NHS II Pooled					
Obesity duration					
Age-adjusted	1.00	4.72(4.32,5.16)	5.72(5.13,6.37)	6.11(5.48,6.81)	1.16(1.15,1.17)
Model1	1.00	4.00(3.66,4.38)	4.69(4.21,5.23)	4.82(4.31,5.38)	1.14(1.14,1.15)
Model2	1.00	1.58(1.43,1.75)	1.43(1.27,1.62)	0.96(0.83,1.11)	1.02(1.01,1.03)

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	0 years	1-4 years	5-8 years	9 years	Risk for Each additional 2 years ^a
Overweight duration					
Age-adjusted	1.00	3.28 (3.03, 3.55)	3.89 (3.58, 4.22)	3.97 (3.66, 4.30)	1.10 (1.09, 1.10)
Model1	1.00	2.91 (2.69, 3.15)	3.40 (3.13, 3.69)	3.44 (3.17, 3.73)	1.09 (1.08, 1.09)
Model2	1.00	1.59 (1.46, 1.73)	1.79 (1.64, 1.95)	1.89 (1.74, 2.06)	1.04 (1.04, 1.05)

Data are HR (95% CI).

Model 1 was adjusted for age (continuous), smoking status (never smoker, past smoker, current 1-14 cigarettes/day, current 15-24 cigarettes/day, current more or equal than 25 cigarettes/day), physical activity (<3 mets/week, 3-9 mets/week, 9-18 mets/week, 18-27 mets/week, 27 mets/week), alcohol consumption (0g/day, 0.1-4.9g/day, 5.0-14.9g/day, 15-29.9g/day, 30g/day), coffee intake (<1/week, 2-4 times/week, 5-7 times/week, 2-3 times/day, 4 times/day), alternate healthy eating index (quintiles), total energy (quintiles), family history of diabetes and hormone use (premenopause, never use, current use, past use).

Model 2 was adjusted for variables in Model1 plus current BMI (time-varying, continuous).

^aContinuous overweight and obesity duration were mutually adjusted in the model.