# Age of onset of obesity and risk of type 2 diabetes

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## Abstract

**Objective**: To compare a simple measure – age of onset of obesity – to an obese-years construct (a product of duration and magnitude of obesity) as risk factors for type 2 diabetes.

**Method**: Participants from the Framingham Heart Study who were not obese and did not have diabetes at baseline were included (n=4,320). The Akaike Information Criterion (AIC) was computed to compare four Cox proportional hazards models with incident diabetes as the outcome and: (i) obese-years; (ii) age of onset of obesity; (iii) body mass index (BMI); and (iv) age of onset of obesity plus magnitude of BMI combined, as exposures.

**Results**: AIC indicated that the model with obese-years provided a more effective explanation of incidence of type 2 diabetes compared to the remaining three models. Models including age of onset of obesity plus BMI were not appreciably different from the model with BMI alone, except in those aged ≥60.

**Conclusions**: While obese-years was the optimal obesity construct to explain risk of type 2 diabetes, age of onset may be a useful, practical addition to current BMI in the elderly.

**Implications**: Where computation of obese-years is not possible or impractical, age of onset of obesity combined with BMI may provide a useful alternative.

**Key words**: obesity, body mass index, obese-years, age of onset, type 2 diabetes

It is well accepted that obesity increases the risk of type 2 diabetes.[1] Risk of diabetes may be influenced by the severity of obesity, duration of obesity, and magnitude and rate of weight gain.[1,2] It is unclear what level of detail is required to best capture the health risks associated with obesity in a clinically practical and meaningful way. It has been argued that examination of duration of obesity is important as, unlike measurements of body mass index (BMI) at one point in time, it takes into account any cumulative effect of obesity. Being obese for longer is associated with an increased risk of type 2 diabetes.[2] More recently, a construct known as obese-years, which takes into account both how long a person has been obese and their magnitude of obesity, was shown to be a better predictor of diabetes risk than duration of obesity or level of BMI alone.[3] However, the computation of obese-years requires knowledge of BMI regularly throughout life, and is therefore less straightforward than measures such as BMI at a single point in time or duration of obesity alone. This potentially limits the use of the obese-years metric in practical situations.

There is limited data on the relationship between age of onset of obesity and risk of diabetes. There is evidence that men who were overweight in early adulthood were more likely to develop type 2 diabetes in middle-to-older age.[4,5] Age of onset may represent a crude marker for duration of obesity, particularly in settings where people rarely revert from an obese state to a non-obese state. Age of onset of obesity, alone or combined with current BMI, may provide sufficient information on health risks associated with obesity and represent a simpler alternative to the obese-years metric as a predictor of type 2 diabetes. The aim of this study was to compare age of onset of obesity with the obese-years construct as predictors of risk of type 2 diabetes.

## Method

### *Study population*

The Framingham Heart Study (FHS), established in 1948, followed 5,209 adults aged 30–62 years over about 60 years. Participants had repeat biennial examinations during which data on cardiovascular risk factors and health outcomes were collected. The current study included participants without diabetes and obesity at baseline (n=4,320). Individuals who were obese at baseline were excluded as their age of onset of obesity was unknown (n=666).

### *Measurement of body mass index*

Height was measured to the nearest 0.25 inches and weight to the nearest 0.5 lbs. BMI was calculated as weight/height$^2$ (kg/m$^2$).

### *Obese-years*

The obese-years construct was calculated as the product of duration and degree of obesity as described previously.[3] Individuals without at least two consecutive obesity (BMI ≥30 kg/m$^2$) occurrences were assigned a value of zero for their obesity duration. For others, the beginning of their obesity duration interval was defined as the date of the first of the consecutive examinations at which they were obese. They were considered to be continuously obese until either the first of at least two consecutive examinations at which they were non-obese, death, or the end of follow-up. Duration of obesity could increase

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incrementally at each examination and hence varied over time.[2,6] Degree of obesity was defined as: 1) zero if BMI <30 kg/m$^2$; and 2) BMI minus 29 kg/m$^2$ if BMI ≥30 kg/m$^2$. For example, a person with BMI 33 kg/m$^2$ had a degree of 4 (33 kg/m$^2$ minus 29 kg/m$^2$).

### Age of onset of obesity

Age of onset of obesity was zero up to the first of at least two consecutive examinations with obesity upon which it was the age at the first of those two examinations. Age of onset was zero for all examinations for participants that never become obese.

### Ascertainment of diabetes status

An individual was defined as having type 2 diabetes if the participant was on insulin and/or an oral hypoglycaemic agent, or if their fasting plasma glucose was ≥200 mg/dl at a given examination. An individual was considered to have incident diabetes if they developed diabetes during the follow-up. Time at risk was defined as time between baseline and the first examination at which the participant had diabetes, death, censoring due to missing data, or end of follow-up at examination 24, whichever came first.

### Measurement of covariates

Information on marital status, smoking status, education, country of birth, family history of diabetes and menopause status were collected using questionnaires at each examination.

### Imputation for missing values

If diabetes was missing at a single isolated examination then its value at that examination was imputed by carrying the last observation forward. Values for BMI and smoking status were imputed if missing for ≤2 consecutive examinations. Where only one examination was missed, the last observation was carried forward. In the instance that two consecutive examinations were missing, the first was imputed using the last observation carried forward and the second was imputed using the next observation carried backward. Where more than two consecutive BMI or smoking status values were missing, or two or more consecutive diabetes values were missing, no imputation was performed, and participants were censored from analysis at the occurrence of the first missing value. Marital status and menopause status were imputed by carrying the last observation forward.

### Statistical analysis

Cox proportional hazards regression was used with calendar time as the underlying time metric and our chosen obesity indicators as time-varying covariates. Adjustments were made for education, country of birth, family history of diabetes and for the time-varying values of marital status, smoking, and menopause. For model comparison, the Akaike Information Criterion (AIC) was computed for the Cox proportional hazards models defined by inclusion of one of: (i) obese-years; (ii) age of onset of obesity; (iii) BMI; and (iv) age of onset of obesity plus BMI combined as exposures. The formula for AIC is as follows, with a lower AIC indicating a more parsimonious fit of the model to the observed times to diabetes incident events:[7]

> -2(log-*likelihood)*+2*(n)*, where n=number of estimated parameters in the model relating exposure and adjustment variables to diabetes incidence.

Each exposure variable was divided into an equal number of categories: those who were not obese were categorised as 'zero' (used as the reference category); and for those with obesity, ten categories (1-10) were created on the basis of deciles.

In exploratory analysis interaction terms were included between sex and age with obese-years and age of onset of obesity. Effect modification by sex and by age was found for the relationship between obese-years and incident diabetes. Hence subsequent analyses were stratified by sex and by age (dichotomised as <60 years and ≥60 years).

## Results

The characteristics of the study population are presented in Table 1. The mean age of the study population at baseline was 44 years (SD 9) and 45% were men. The median follow-up time was 26 years for men and 32 years for women. Men were more likely to be smokers and had a younger median age of onset of obesity.

When comparing those with a younger age of onset of obesity (<60 years) to those with an older age of onset of obesity (≥60 years), those with a younger age of onset of obesity were more likely to be born in the US (90% *vs.* 79%, *p* for difference <0.001) and had a lower mean BMI at baseline (26.0 *vs.* 27.4 kg/m$^2$, *p* for difference <0.001). They did not differ in terms of marital status, education or smoking.

The incidence rates for diabetes were the same for men and women (3.4 per 100 person-years, 95%CI 3.0, 4.0) (Table 1). In all subgroups, the model with obese-years performed best in predicting incident diabetes. AIC was lowest (optimal) for the model with obese-years, compared to the models with BMI alone, age of onset of obesity alone or age of onset of obesity plus BMI (Table 2). However, AIC for the model with age of onset of obesity plus BMI was not appreciably different from the model with BMI alone, except in those aged ≥60 where it was lower.

## Discussion

In this large cohort, the obese-years construct performed better than BMI alone and age of onset of obesity plus BMI in explaining the observed information on risk of incident type 2 diabetes. In contrast to our expectations a model with current BMI and age of onset of obesity did not appear to improve prediction of type 2 diabetes compared to a model with BMI alone, except in the elderly.

This study is novel in that no previous study has examined age of onset of obesity in relation to risk of type 2 diabetes. Our findings indicate that while obese-years was the optimal construct to predict risk of type 2 diabetes, age of onset of obesity in combination with current BMI might be better than BMI alone in the elderly. As the calculation of obese-years is less straight forward than age of onset of obesity, the latter may be a useful practical alternative although at the cost of reduced ability to explain diabetes incidence.

The strengths of this study include a long period of follow-up with biennial examinations and measured height and weight. The study was limited by the modest number of participants who developed obesity over the follow-up period (n=590 (14%)). Additionally, as it was not possible to include any obesity duration prior to the commencement of the study, total obesity duration may be underestimated.

In conclusion, this study demonstrated that the obese-years construct was the optimal construct to predict risk of type 2 diabetes, indicating the importance of both duration of obesity and the level of obesity in the risk of developing diabetes.

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**Table 1. Characteristics of the study population.**

| | Men (n=1978) | Women (n=2342) |
|---|---|---|
| **Baseline characteristics** | | |
| Age ( years) | 44 (37 – 51) | 42 (36 – 50) |
| Education, n (%) | | |
| Did not graduate high school | 832 (43.9) | 827 (36.7) |
| Graduated high school | 679 (42.4) | 924 (57.6) |
| Graduated college | 189 (10.0) | 153 (6.8) |
| Post-graduate, business college, nursing | 194 (10.2) | 351 (15.6) |
| Born in the United States, n (%) | 1615 (81.7) | 1932 (82.5) |
| Body Mass Index (kg/m$^2$) | 24.9 (2.8) | 24.0 (3.0) |
| Current smokers, n (%) | 1547 (78.8) | 1035 (44.5) |
| Marital status, n (%) | | |
| Single | 110 (5.6) | 279 (11.9) |
| Married | 1823 (92.2) | 1844 (78.7) |
| Widowed | 23 (1.2) | 137 (5.9) |
| Divorced/separated | 22(1.1) | 82 (3.5) |
| **Other characteristics** | | |
| Follow-up time | 25.7 (16.2 – 36.4) | 31.6 (19.9 – 43.1) |
| Age of onset of obesity[a] | 56 (50 – 65) | 60 (51 – 68) |
| Obese-years[a] | 18.2 (9.2 – 41.8) | 24.4 (10.4 – 56.0) |
| Diabetes incidence rate[b] (95% CI) | 3.4 (3.0, 4.0) | 3.4 (3.0, 4.0) |

*a: for those ever obese*

*b: per 100 person-years*

*Data presented as mean (SD) or median (25th – 75th percentile), unless indicated otherwise*

**Table 2. Akaike Information Criterion (AIC) for time-varying Cox proportional hazards models with obese-years, age of onset of obesity and BMI in relation to risk of type 2 diabetes.**

| | Men | Women | <60 years | ≥60 years |
|---|---|---|---|---|
| BMI | 2,761 | 2,616 | 1,312 | 4,289 |
| Obese-years | 2,743 | 2,604 | 1,301 | 4,268 |
| Age of onset of obesity | 2,770 | 2,631 | 1,325 | 4,294 |
| Age of onset of obesity + BMI | 2,760 | 2,616 | 1,316 | 4,285 |

*Analyses were adjusted for country of birth, marital status, education, family history of diabetes and smoking; analysis for women further adjusted for menopause status. A lower AIC indicates a more parsimonious fit of the model to the observed times to diabetes incident events.*

*BMI = body mass index*