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Title:

Estimating the risk of cardiovascular disease using an obese-years metric

Running title:

Obese-years and cardiovascular disease

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ABSTRACT:

Objective: To examine the association between obese-years and the risk of cardiovascular disease.

Study design: Prospective cohort study for approximately 50 years of follow-up.

Setting: Boston, USA

Participants: 5036 participants of the original Framingham Heart Study were examined.

Methods: The variable of obese-years was calculated by multiplying for each participant the number of BMI units above 30 kg/m^2 by the number of years lived at that BMI during approximately 50 years of follow-up. The association between obese-years and the outcome was analyzed by using time-dependent Cox regression adjusted for potential confounders and compared with the current models using the Akaike Information Criterion (AIC)

Primary outcome: Cardiovascular diseases.

The Results: The average cumulative obese-years was 63 (range, 2–556 obese-years). During 138,918 person-years of follow-up, 2753 (55%) participants were diagnosed with cardiovascular disease. The incidence rates and adjusted hazards ratios (AOR) for CVD increased with an increase in the number of obese-years. AOR for the categories 1–24.9, 25–49.9, 50–74.9, and ≥75 obese-years was 1.31 (95% CI: 1.15-1.48), 1.37 (95% CI: 1.14-1.65), 1.62 (95% CI: 1.32-1.99), and 1.80 (95% CI: 1.54-2.10) compared with those who never-obese (zero obese-years) respectively. A dose-response relationship (across the 5 categories) was significant (*P* trend= 0.001). Effect of obese-years was higher in males than females. For every 10 unit increase in obese-years, the AOR of CVD increased by 6% (95% CI 4% to 8%) for males and 3% (95% CI 2% to 4%) for females. The AIC was lowest in the model containing obese-years compared with models containing either the level of BMI or the duration of obesity alone.

Conclusions: This study confirm that the obese-years construct is an independent risk factor for CVD. Obese-years metric is a better predictor the risk of CVD although it shows similar risk estimation to other two models.

Key Words:

Obesity, BMI, the duration of obesity, obese-years, risk factor, cardiovascular disease

Strengths and limitations of this study

- Examining the total effect of obesity by combining the number years lived with obesity and the level of BMI into a single measurement of obese-years
- A long term prospective cohort study - approximately 50 years followed-up with biennial measurements of body weight, covariates and health outcomes.
- The analysis takes into account changes in covariates during study follow-up and adjusted for a large number of potential confounding variables.
- The obese-years construct was developed based on the measurement of BMI. It is unclear whether using anthropometric measures other than BMI would produce different results.
- Data used for this study was from a relatively old cohort study, baseline of the study began in 1948

Background

Obesity has been associated with an increased risk of cardiovascular disease (CVD)[1 2]. In addition, we have recently demonstrated that the duration of obesity is also risk factor for type-2 diabetes, independent of level of body mass index (BMI) [3]. However, the quantification of these association by only analysing the level of BMI [4] or the duration lived with obesity [5 6]; this approach may not reflect the total effect of obesity and may underestimated the risk of CVD associated with obesity.

We recently demonstrated the additional benefit of constructs combining the level of obesity with the number of years lived with obesity into a single measure of an obese-years construct is a better predictor the risk of type-2 diabetes than level of BMI or duration of obesity alone [7]. A similar approach that has been used in smoking studies, examining the adverse health effects associated with the combination of number of cigarettes or packs smoked per day (degree) and duration of smoking as a cigarette-years or pack-years [8-10].

The use of a similar construct for body weight, to estimate the risk of CVD has not been investigated yet. We hypothesized that the obese-years construct is likely a similar independent risk factor for CVD and would provide an improved estimation of the risk of future CVD. This study aimed to examine the association between obese-years and risk of CVD and to examine whether the obese-years construct was a better predictor for risk of CVD than current BMI or duration of obesity alone. We investigated these objectives using the original Framingham Heart Study, a long term prospective cohort study where body weight, health outcomes and other covariates were measured regularly for almost 50 years [11].

METHODS

Data source

We used data from the original Framingham Heart Study (FHS) [12]. In this prospective cohort study, 5,209 participants (aged 28–62 years at the time of enrollment) were examined regularly at 2-years interval for approximately 50 years from 1948. For the purpose of this study, only participants who were free from CVD (any types), cancer and type-2 diabetes at baseline included in the analysis (n = 5,036).

Variables: measurement, missing and imputation

Most of variables in the FHS was measured regularly at every two-years interval, including body weight, height, demographic variables, health behaviors, and health outcomes (including cardiovascular disease) [11]. However some values are missing by design where variables were not collected at every examination. For example the variables of current smoking status was not recorded at four examinations (2, 3, 6 and 17), cholesterol was not measured at seven examinations (11, 12, 17-20 and 22), alcohol consumption was measured only in eight examinations (2, 4, 7, 19, 20–23), and physical activity was measured only at four examinations (4, 11, 12, and 19). For this circumstance, the nearest measured value of the covariate was used in our analysis. Another circumstance, the missing values occur intermittently missing one or more values during study follow-up; for example body weight and hence BMI. In this case missing values for BMI were imputed with a conditional mean estimated by a multiple linear regression model using age at prior exam, sex and several transformations of the previously measured BMI (BMI, log BMI, BMI squared and BMI as a categorical variable). Methods of measurement of these variables have been described in detail elsewhere [5 7].

The level of obesity, duration and obese-years measurement

A participant was considered obese at a given examination if their BMI was greater than or equal to 30 kg/m^2. The level of obesity was defined as follows: (1) if BMI < 30 kg/m^2, the level was zero; and (2) if BMI ≥ 30 kg/m^2, the level was BMI minus 29 kg/m^2. For example, if BMI was 35 kg/m^2, the level was 6 (35 – 29) obese units.

The duration of obesity was defined using a similar definition as has been described previously [5]. The duration of obesity was calculated for those individuals with at least two consecutive occurrences of obesity (which implies at least two years of being continuously obese), to avoid the potential misclassification of body weight, either due to measurement error or fluctuations between the borderline of the 'overweight' category or the 'obese' category. For those individuals without two consecutive obesity occurrences, duration was considered to be zero at all exams. For those individuals with two consecutive obesity occurrences the beginning of their obesity duration interval was defined as the date of the first of these two examinations and from that time, the individual was considered to be continuously obese until either the first of two consecutive non-obese examinations, or death, or the end of follow-up at examination 24. The duration increased incrementally at each exam according to the time (in years) between the current exam and the first obese examination. Individuals could have multiple periods of obesity duration during follow-up.

The level of obesity and the duration of obesity then was combined into a single variable called obese-years. The variable was calculated at each examination as the defined level of obesity (in "obese units") multiplied by the defined duration of obesity (in years). The cumulative number of obese-years was calculated at each examination as a sum of all obese-year "exposures" up to and including that examination as has been illustrated in the previous paper[7]

Measurement of the outcome and time to event

The main outcome of interest in this study was CVD incident (the first event of any type of CVD; defined as a composite of coronary heart disease (CHD), cerebrovascular accident (CVA), peripheral artery disease, and congestive heart failure (CHF)[13]. Additional outcomes are individual types of CVD: hard CVD, CHD, CVA, and CHF. Hard CVD defined as a composite of hard CHD (coronary death, myocardial infarction), stroke (fatal and nonfatal), peripheral artery disease and heart failure. In the FHS, the criteria for each cardiovascular outcome during follow-up were standardized [14] and a panel of Framingham investigators made the decision regarding diagnosis. CHD includes the diagnoses of (1) angina pectoris, evidenced by a typical history of chest pain on a physician-administered questionnaire; (2) myocardial infarction, determined by specified electrocardiographic changes, diagnostic elevation of serum enzymes with prolonged ischemic chest pain, or autopsy; (3) coronary insufficiency, defined as prolonged ischemic chest pain accompanied by transient ischemic abnormalities on the ECG; and (4) sudden (in less than 1 hour) or non-sudden coronary death. CHF was indicated when at least two major or one major and two minor diagnostic conditions existed concurrently upon examination.

Time to event was measured as the time until the date a participant was diagnosed as having cardiovascular disease. Individuals who died or reached the end of the follow-up (examination 24) before developing CVD were censored at date of death or examination 24, respectively.

Data analysis

To model the relationship between the various measures of obesity and risk of CVD, a dynamic survival model[4] (time-dependent Cox regression model)[15 16] was used. The demographic and health behavior variables included in the analysis were age, sex, education level, country of birth, marital status, smoking status, alcohol consumption (ounces/month), and physical activity. Most of these variables included in the model were time-varying, except for sex, age (at baseline) and country of birth.

The obese-years construct was analysed both as a continuous and as a categorical variable using a similar categories as using in the previous study [7] for comparison purpose. For continuous analyses, hazard ratios were presented per 10 obese-years. For categorical, those who never obese during study follow-up (zero obese-years) was assigned as a comparator. Those who values of obese-years within the study follow-up period, then obese-years was grouped into short, medium and long periods representing 1-24.9, 25-49.9, 50-74.9 and >=75 obese-years. Hazard ratios were presented, both as crude hazard ratios and as multivariate-adjusted hazard ratios for both continuous and categorical variable. Three models of analysis were used to examine the change in hazard ratios associated with the addition of different confounding variables. Model 1 adjusted for age. Model 2 adjusted for age, sex, marital status, educational level and country of birth. Model 3 includes all variables in model 2 plus health behavior variables of smoking status, alcohol consumption and physical activity and this model was considered the primary model of the study. The analyses were additionally stratified by sex and a test for interaction between sex and obese-years was performed for all models.

To compare the predictive value of obesity level, obesity duration and obese-years construct, each of these three variables were divided into an equal number of categories. One group was created for those who were never obese (BMI less than 30 kg/m^2) as a reference. For those with obesity, ten deciles categories were created. The goodness of fit of the models incorporating each of the three variables was compared using Akaike's information criterion (AIC), computed as −2(log-likelihood) + 2 (number of estimated parameters); with a lower AIC indicating a better fit [17]. All analyses were performed using the Stata statistical software package version 11.0 (StataCorp, College Station, TX, USA) [18].

Sensitivity analyses

A sensitivity analysis was performed to examine whether the association might be influenced by the imputation method for missing BMI; specifically, an analysis was performed that included only participants with no missing values of BMI in any examinations. The effect of the duration of obesity prior to baseline was tested by performing extra analyses that excluded those who were obese at baseline (no = 576).

RESULTS

Characteristics of the Respondents

Of the 5,036 eligible study participants, 1230 (24%) participants were obese for at least 2 consecutive examinations during the study follow-up. Mean cumulative duration of obesity was approximately 16 years (range, 2–46 years), and the mean cumulative obese-years was 63 (range, 2–556 obese-years). 2753 (55%) participants were diagnosed with cardiovascular disease over approximately during 138,918 person-years of follow-up (Table 1).

Incidence and Hazards Ratios of Cardiovascular Disease

The incidence rates and adjusted hazards ratios for CVD increased with an increase in the number of obese-years (Table 2 and Table 3). In the primary model (Model 3) for total population, the adjusted hazard ratios for the categories 1–24.9, 25–49.9, 50–74.9, and ≥75 obese-years for total population was 1.31 (95% CI: 1.15-1.48), 1.37 (95% CI: 1.14-1.65), 1.62 (95% CI: 1.32-1.99), and 1.80 (95% CI: 1.54-2.10) compared with those who never-obese (zero obese-years) respectively. A dose-response relationship (across the 5 categories) was significant (*P* trend= 0.001). For continues analysis, every 10 unit increase in obese-years, the adjusted hazard ratios for CVD in the total population increased by 4% (95% CI 3% - 4%) (Table 4). There were no significant interactions between obese-years categories and sex and smoking status but there was evidence of an interaction between obese-years as a continuous variable and each of sex (*P* value = 0.01). Effect of obese-years was higher in males than females.

Comparing obesity constructs and Akaike's Information Criterion (AIC),

Table 5 demonstrates the risk of CVD for each of the three different constructs for obesity: level of obesity (based on BMI), duration of obesity, and the obese-years construct as additive effects. Each construct was analysed in a separate model and the strength of association was compared using the Akaike Information Criterion (AIC). In all outcomes, the AIC was lowest in the construct of obese-years compared with the other two constructs both in analysis by total population and by sex.

Sensitivity analysis

The sensitivity analyses showed that the association between obese-years and risk of CVD was similar between a complete case analysis and the analysis using imputed missing values for BMI. Exclusion of participants who had no record of body mass index at baseline has no change in adjusted hazard ratio, but exclusion of those who were obese at baseline showed only a slightly lower adjusted hazard ratio: 1.03 (95% CI: 1.01-1.05)

DISCUSSION

This study found that the approach of measuring the total effect of obesity by combining the level and the duration of obesity into a single metric of obese-years, is a stronger predictor of the risk of CVD than using the duration of obesity or the intensity of obesity alone. A clear dose-response relation between obese-years and the risk of CVD was observed. The stronger effect was found in males than females

Although the hazard ratios were very similar between three different constructs and it is not possible to perform a statistical comparison of discrimination between the models due to the fact that they are non-nested, the AIC does tell us that combining level of obesity and the duration into a single construct of obese-years provides us with more discriminative power than a model with level of obesity based on BMI or obesity duration alone. This finding has important implications for future studies of the total health impact associated with obesity that should be taken into account both the impact of obesity level and changes in the duration of obesity.

There are different ways to operationalize the impact of excess weight over time. A recent systematic review identified at least four models: additive models, duration-of-obesity model, additive-weight-change model and interactive model [19]. In addition to these models, the obese-year model confirms that analyzing the combined effect of the duration and the level of obesity as a predictor of the cardiovascular is worthwhile. Such approaches add information over and above simply the level of excess weight or length of time with obesity. As has been argued previously [7] other potential additions to this analysis is examining the excess body weight as higher than 25 kg/m^2.

The finding is derived from analysis of a long term prospective cohort study with biennial measurements of body weight, covariates and health outcomes which enabled us to analyze change in level of obesity and the duration of obesity over long term period. The analysis take into account changes in covariates, such as smoking status, alcohol consumption and physical activity and adjusted for a large number of potential confounding variables. However, some potential confounders, such as diet, were not collected consistently in the original Framingham Heart Study and therefore have not been adjusted for in this study.

As has been described elsewhere [7], the limitation of this analysis might related the population of study using a relatively old cohort study of the original Framingham Heart Study that began in 1948, and the prevalence rates of obesity and cardiovascular disease were relatively low at that time (in the 1950s was below 10%)[20]. Therefore some people argued the results of this study might not reflect the current population, where the prevalence of obesity is markedly higher than 50 years ago. In 2008 alone, the prevalence of obesity among adults in the United States was more than 30%[21]. Moreover, the contemporary obesity epidemic is also characterized by a much earlier onset of obesity, which should result in even longer exposure by the time today's obese generation of children reach the age of our studied cohort. In our study, the average age at onset of obesity was approximately 50 years, and the average number of years lived with obesity was approximately 13 years but, in today's society, the average age at onset of obesity is likely to be more than 10 years earlier than in previous decades [22]. However, our results indicate that obese-years is still valid and is a better tool than level of BMI or duration alone. If further analysis is conducted, the association between obese-years and CVD could be even stronger today since the exposure to obesity is now greater than it was.

The obese-years construct in this study was based on the measurement of BMI. It is unclear whether using anthropometric measures other than BMI would produce different results. Although a recent meta-analysis study has showed that BMI, waist circumference (WC), and the waist/hip ratio (WHR) to each estimate a similar risk, particularly type-2 diabetes [23]; it is still worthy to explore the relationship between obese-years and risk of CVD using WC or WHR.

As discussed in our previous study [7], the obese-years metric was developed based on assumption that level and duration have a similar impact, an assumption that has been used for the concept of pack-years in smoking studies. In some smoking studies it was highlighted that for certain health outcomes, the effect of the duration was more important than intensity [24], while in others, duration was not significant after adjustment for intensity [25]. As this is a new concept in obesity studies, it requires further exploration. The notion that obese-years is only “switched on” when BMI reaches 30 kg/m^2 is crude, although it does find a parallel in pack-years for smoking which is a construct that ignores any effects of passive smoking.

This findings demonstrate one again that it is important to consider not only the level of obesity but also the duration of obesity and its combination when examining the association between obesity and the risk of chronic disease. This effect is likely to be because account is taken of the cumulative damage of obesity on body systems, and consequently is likely to be applicable to other chronic diseases. However, further investigations are recommended to undertaken, of other possible intensity/duration constructs of obesity such as considering the effect of BMI above 25 kg/m^2, and of relationships between obese-years and other chronic diseases and mortality.

CONCLUSION

This study demonstrates the importance of measuring total effect of obesity combining both the level and the duration of obesity when estimating the risk of cardiovascular disease associated with obesity. The obese-years construct might takes into account of the cumulative damage of obesity on body systems, therefore provides better estimation the risk of CVD than level or the duration of obesity alone. This approach of examining total effect of obesity is suggested to use in measuring the burden of obesity related diseases in the community.

CONFLICT OF INTEREST:

None declared.

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CONTRIBUTORS

Author AA developed the analytical techniques of study, performed data analysis, interpretation, drafting of the article and prepared the final version for publication; FAA performed data analysis and interpretation of data; JS, ST, and JB helped review the data analysis and reviewed the article; RW contributed to the study design and reviewing of the article; and AP supervised the implementation of the study, designed the study's analytic strategy, and reviewing of the article.

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COMPETING INTERESTS

None

DATA SHARING STATEMENT

No additional data available

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Table 1: Characteristics of the study population [a]

Participant Characteristics	No.	%	Mean	Range
Eligible sample	5,036			
Obese participants during study follow-up	1,230	24		
Age at baseline (years)			44	28–62
Female	2,799	56		
Born in the United States	4,082	81		
Marital status				
Single	452	9		
Married	4,269	85		
Widowed, divorced, or separated	315	6		
Educational level				
Eighth grade or less	1,374	27		
High school	2,306	46		
College	752	15		
Graduate school	604	12		
Health behavior				
Current smoker at baseline	2,893	58		
Ever-smoker during study follow-up period	3,178	63		
Physical activity score at examination 4			32	25–83
Alcohol drinking at examination 2, ounces/month[b]			14	0–360
Blood pressure at baseline				
Systolic (mm Hg)			132	85–270
Diastolic (mm Hg)			84	52–150
Hypertension at baseline	843	17		
Biochemical characteristics at baseline (mg/100 mL)				
Serum cholesterol			226	96–586
Blood glucose			80	40–197
Body weight characteristics				
Body mass index at baseline (kg/m^2)[c]			25.5	16.2–46.3
Underweight (<18.5)	67	1		
Normal weight (18.5–24.9)	2,408	48		
Overweight (25–29.9)	1,992	40		
Obese (≥30)	569	11		
Cumulative obesity duration (years)[d]			16	2–46
Cumulative obese-years[d]			63	2–556
1–24.9	515	42		
25–49.9	232	19		
50–74.9	139	11		
≥75	344	28		
Cardiovascular disease	2753			
Coronary heart disease events	1890			
Heart attack	1538			
Myocardial infarction	1104			
Coronary insufficiency	259			
Angina pectoris	945			
Cerebrovascular accident	946			
Congestive heart failure	876			

[a] Participants were free from existing diabetes, cardiovascular disease, and cancer at baseline.
[b] One ounce ≈ 28.35 g. [c] Body mass index: weight (kg)/height $(m)^2$. [d] For those who were obese during study follow-up.

Table 2: Incidence of Cardiovascular Disease (Events/1,000 Person-Years) According to Categories of Cumulative Obese-Years

	Obese-Years	Events	PYFU	Incident Rate
Total population				
	0 year	2,177	116,681	18.66 (17.89-19.46)
	1-25 years	276	10,846	25.45 (22.62-28.63)
	25-50 years	124	4,509	27.50 (23.06-32.80)
	50-75 years	78	2,365	32.98 (26.42-41.18)
	>=75years	186	4,517	41.17 (35.66-47.54)
Males				
	0 year	1,138	46,950	24.24 (22.87-25.69)
	1-25 years	134	4,669	28.70 (24.23-34.00)
	25-50 years	56	1,710	32.75 (25.21-42.56)
	50-75 years	36	720	50.02 (36.08-69.34)
	>=75years	49	951	51.51 (38.93-68.16)
Females				
	0 year	1,039	69,731	14.90 (14.02-15.83)
	1-25 years	142	6,177	22.99 (19.50-27.10)
	25-50 years	68	2,799	24.30 (19.16-30.81)
	50-75 years	42	1,645	25.53 (18.87-34.54)
	>=75years	137	3,566	38.42 (32.49-45.42)

PYFU = Persons years of follow-up

Table 3: Risk of Cardiovascular disease According to Obese-Years Category

	Hazard Ratio (95% Confidence Interval)		
	Total population*	Males	Females
Model 1			
0 obese-years	1	1	1
1-25 obese-years	1.28 (1.13-1.45)	1.18 (0.99-1.41)	1.37 (1.15-1.64)
25-50 obese-years	1.31 (1.09-1.57)	1.28 (0.97-1.67)	1.40 (1.09-1.79)
50-75 obese-years	1.50 (1.21-1.85)	1.78 (1.35-2.36)	1.46 (1.08-1.96)
>=75 obese-years	1.59 (1.36-1.85)	1.72 (1.33-2.22)	1.78 (1.48-2.15)
Dose-response *P* value	0.0001	0.0001	0.0001
Model 2			
0 obese-years	1	1	1
1-25 obese-years	1.26 (1.11-1.43)	1.18 (0.99-1.41)	1.33 (1.11-1.60)
25-50 obese-years	1.32 (1.10-1.59)	1.29 (0.99-1.70)	1.35 (1.05-1.74)
50-75 obese-years	1.55 (1.27-1.91)	1.80 (1.36-2.38)	1.40 (1.04-1.88)
>=75 obese-years	1.74 (1.50-2.03)	1.71 (1.32-2.21)	1.71 (1.42-2.07)
Dose-response *P* value	0.0001	0.0001	0.0001
Model 3			
0 obese-years	1	1	1
1-25 obese-years	1.31 (1.15-1.48)	1.22 (1.02-1.45)	1.37 (1.14-1.65)
25-50 obese-years	1.37 (1.14-1.65)	1.39 (1.05-1.83)	1.36 (1.05-1.76)
50-75 obese-years	1.62 (1.32-1.99)	1.89 (1.42-2.51)	1.44 (1.08-1.94)
>=75 obese-years	1.80 (1.54-2.10)	1.81 (1.39-2.36)	1.74 (1.44-2.10)
Dose-response *P* value	0.0001	0.0001	0.0001

Model 1 adjusted for age.
Model 2 adjusted for age, marital status, education, country of birth.
Model 3 adjusted for age, marital status, education, country of birth, smoking status, alcohol consumption, physical activity
* Analyses for total population were adjusted for sex.

Table 4: The Hazard Ratio of Cardiovascular per 10 Obese-Years

CVD	Hazard Ratio per additional 10 Obese-Years (95% Confidence Interval)		
	Total population*	Males	Females
Cardiovascular diseases (all types CVD)			
Model 1	1.03 (95% CI 1.02-1.04)	1.05 (95% CI 1.03-1.07)	1.03 (95% CI 1.02-1.04)
Model 2	1.03 (95% CI 1.02-1.04)	1.05 (95% CI 1.03-1.07)	1.03 (95% CI 1.02-1.04)
Model 3	1.04 (95% CI 1.03-1.05)	1.06 (95% CI 1.04-1.08)	1.03 (95% CI 1.02-1.04)
Hard Cardiovascular diseases (Hard CVD)			
Model 1	1.03 (95% CI 1.02-1.04)	1.06 (95% CI 1.04-1.08)	1.03 (95% CI 1.02-1.05)
Model 2	1.04 (95% CI 1.03-1.05)	1.06 (95% CI 1.04-1.08)	1.03 (95% CI 1.02-1.04)
Model 3	1.04 (95% CI 1.03-1.05)	1.06 (95% CI 1.04-1.08)	1.03 (95% CI 1.02-1.04)
Coronary heart disease (CHD)			
Model 1	1.02 (95% CI 1.01-1.03)	1.03 (95% CI 1.01-1.06)	1.03 (95% CI 1.02-1.04)
Model 2	1.03 (95% CI 1.02-1.04)	1.03 (95% CI 1.01-1.06)	1.03 (95% CI 1.02-1.04)
Model 3	1.03 (95% CI 1.02-1.04)	1.04 (95% CI 1.02-1.06)	1.03 (95% CI 1.02-1.04)
Cerebrovascular accident (CVA)			
Model 1	1.03 (95% CI 1.02-1.04)	1.06 (95% CI 1.04-1.09)	1.03 (95% CI 1.01-1.04)
Model 2	1.03 (95% CI 1.02-1.04)	1.06 (95% CI 1.04-1.09)	1.02 (95% CI 1.01-1.04)
Model 3	1.03 (95% CI 1.02-1.04)	1.06 (95% CI 1.04-1.09)	1.02 (95% CI 1.01-1.04)
Congestive health failure (CHF)			
Model 1	1.05 (95% CI 1.03-1.06)	1.06 (95% CI 1.04-1.09)	1.05 (95% CI 1.03-1.06)
Model 2	1.05 (95% CI 1.04-1.06)	1.06 (95% CI 1.04-1.09)	1.04 (95% CI 1.03-1.06)
Model 3	1.05 (95% CI 1.04-1.06)	1.06 (95% CI 1.04-1.09)	1.04 (95% CI 1.03-1.06)

Model 1 adjusted for age.
Model 2 adjusted for age, marital status, education, country of birth.
Model 3 adjusted for age, marital status, education, country of birth, smoking status, alcohol consumption, physical activity
* For total population also adjusted for sex

Table 5: Comparison of the Obese-years construct, Body Mass Index and Obesity Duration as predictors of the Risk of CVD

Constructs	**Akaike Information Criterion (AIC)**		
	Total population	**Males**	**Females**
Cardiovascular diseases (all types CVD)			
Construct 1: Level of BMI	43390	19227	20307
Construct 2: Duration of obesity	43379	19221	20306
Construct 3: Obese-Years	43368	19209	20294
Hard Cardiovascular diseases (Hard CVD)			
Construct 1: Level of BMI	34069	15102	15976
Construct 2: Duration of obesity	34065	15099	15968
Construct 3: Obese-Years	34050	15096	15955
Coronary heart disease (CHD)			
Construct 1: Level of BMI	29038	14355	12156
Construct 2: Duration of obesity	29039	14354	12162
Construct 3: Obese-Years	29028	14351	12152
Cerebrovascular accident (CVA)			
Construct 1: Level of BMI	13575	5211	7147
Construct 2: Duration of obesity	13577	5208	7141
Construct 3: Obese-Years	13573	5208	7136
Congestive health failure (CHF)			
Construct 1: Level of BMI	13141	5275	6667
Construct 2: Duration of obesity	13122	5263	6663
Construct 3: Obese-Years	13104	5255	6649

Each construct was split into 11 categories; 1 represents "not obese" and 2-11 represent deciles of obesity exposure (intensity, duration and obese-years)

Each model adjusted for sex, age, marital status, education, smoking, alcohol consumption, and physical activity.

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Estimating the risk of cardiovascular disease using an obese-years metric

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ABSTRACT:

Objective: To examine the association between obese-years and the risk of cardiovascular disease (CVD).

Study design: Prospective cohort study

Setting: Boston, USA

Participants: 5036 participants of the Framingham Heart Study were examined.

Methods: Obese-years was calculated by multiplying for each participant the number of BMI units above 29 kg/m^2 by the number of years lived at that BMI during approximately 50 years of follow-up. The association between obese-years and CVD was analyzed using time-dependent Cox regression adjusted for potential confounders and compared with other models using the Akaike Information Criterion (AIC). The lowest AIC indicated better fit.

Primary outcome: Cardiovascular disease.

The Results: The median cumulative obese-years was 24 (range, 2–556 obese-years). During 138,918 person-years of follow-up, 2753 (55%) participants were diagnosed with CVD. The incidence rates and adjusted hazards ratios (AHR) for CVD increased with an increase in the number of obese-years. AHR for the categories 1–24.9, 25–49.9, 50–74.9, and ≥75 obese-years were respectively 1.31 (95% CI: 1.15–1.48), 1.37 (95% CI: 1.14–1.65), 1.62 (95% CI: 1.32–1.99), and 1.80 (95% CI: 1.54–2.10) compared with those who were never obese (i.e. had zero obese-years). The effect of obese-years was stronger in males than females. For every 10 unit increase in obese-years, the AHR of CVD increased by 6% (95% CI 4% to 8%) for males and 3% (95% CI 2% to 4%) for females. The AIC was lowest for the model containing obese-years compared with models containing either the level of BMI or the duration of obesity alone.

Conclusions: This study demonstrates that obese-years metric conceptually captures the cumulative damage of obesity on body systems, and is found to provide slightly more precise estimation of the risk of CVD than level or the duration of obesity alone.

Key Words: *Obesity, BMI, the duration of obesity, obese-years, risk factor, cardiovascular disease*

Strengths of this study

- The obese-years metric combines the number of years lived with obesity and the level of BMI to examine the total effect of obesity.
- The Framingham Heart Study is a long term prospective cohort study with approximately 50 years of follow-up, and biennial measurements of body weight, covariates and health outcomes.
- By using time-dependent Cox proportional hazards regression, the analysis takes into account changes in covariates during study follow-up and adjusts for a large number of potential confounding variables.

Limitations of this study

- The obese-years metric was developed based on the measurement of BMI. It is unclear whether using anthropometric measures other than BMI would produce different results.
- Data used for this study was from a relatively old cohort study, which began in 1948.

Background

The association between obesity and cardiovascular disease (CVD) is well known[1 2]. However, these findings are generally based on analysing only the level of BMI in relation to CVD. More recently, studies have demonstrated the importance of taking into account the potential cumulative effect of the duration of obesity, rather than the simple assessment of obesity at a single point in time (e.g. at baseline). Duration of obesity has been shown to be a risk factor for CVD[3], type-2 diabetes[4] and mortality[5], independent of body mass index (BMI). Nevertheless, analyses based on either level of BMI alone or duration lived with obesity alone, may not reflect the total effect of obesity and may underestimate the risk of CVD attributable to obesity. We have recently demonstrated the additional benefit of combining the level of obesity with the number of years lived with obesity into a single measure, finding that an obese-years metric is a better predictor of the risk of type-2 diabetes than level of BMI or duration of obesity alone[7].

The use of the obese-years metric to estimate the risk of CVD has not been investigated yet. We hypothesized that the obese-years metric is likely a similar independent risk factor for CVD and would provide an improved estimation of the risk of future CVD. This study aimed to examine the association between obese-years and risk of CVD and to examine whether the obese-years metric is a better predictor for risk of CVD than current BMI or duration of obesity alone. We investigated these objectives using the Framingham Heart Study (FHS), a long term prospective cohort study where body weight, health outcomes and other covariates were measured biennially for almost 50 years[11].

METHODS

Data source

We used data from the Framingham Heart Study (FHS)[12]. In this prospective cohort study, 5,209 participants (aged 28–62 years at the time of enrolment) attended biennial examinations for approximately 50 years beginning from 1948. For the purpose of this study, only participants who were free from CVD (any type), cancer and type-2 diabetes at baseline were included in the analysis (n = 5,036).

Variables: measurement, missing and imputation

Most variables in the FHS were measured regularly at the two-yearly examinations, including body weight, height, demographic variables, health behaviors, and health outcomes (including cardiovascular disease)[11]. Some values are missing by design where variables were not collected at every examination. For example current smoking status was not recorded at four examinations (2, 3, 6 and 17), cholesterol was not measured at seven examinations (11, 12, 17-20 and 22), alcohol consumption was measured only at eight examinations (2, 4, 7, 19, 20–23), and physical activity was measured only at four examinations (4, 11, 12, and 19). In this circumstance, the most contemporary measured value of the variable was used in place of missing values at the examination times when the variable was not measured. Another missing data circumstance was when missing values occurred intermittently during study follow-up; for example body weight and hence BMI. In this case missing values for BMI were imputed with a conditional mean estimated by a multiple linear regression model using age at prior exam, sex and several transformations of the previously measured BMI (BMI, log BMI, BMI squared and BMI as a categorical variable). Methods of measurement of these variables have been described in detail elsewhere[4 7].

The level of obesity, duration and obese-years measurement

A participant was considered obese at a given examination if their BMI was greater than or equal to 30 kg/m^2. The level of obesity was defined as follows: (1) if BMI < 30 kg/m^2, the level was zero; and (2) if BMI ≥ 30 kg/m^2, the level was BMI minus 29 kg/m^2. For example, if BMI was 35 kg/m^2, the level was 6 (35 – 29) obese units.

The duration of obesity followed a similar definition to that described previously[4]. The duration of obesity was calculated for those individuals with at least two consecutive examinations with occurrence of obesity (which is interpreted as indicating at least two years of being continuously obese). The requirement for two consecutive examinations with obesity was to avoid the potential misclassification of body weight, either due to measurement error or fluctuations between the borderline of the 'overweight' category or the 'obese' category. For those individuals without two consecutive obesity occurrences, duration was considered to be zero at all exams. For those individuals with two consecutive obesity occurrences, the beginning of their obesity duration interval was defined as the date of the first of these two examinations and from that time, the individual was considered to be continuously obese until either the first of two consecutive non-obese examinations, or death, or the end of follow-up at examination 24. Individuals could have multiple periods of obesity duration during follow-up.

The level of obesity and the duration of obesity were combined as a single variable called obese-years. Obese-years was calculated at each examination as the defined level of obesity (in "obese units") multiplied by the defined duration of obesity (in years). Then the cumulative total of obese-years for each examination was calculated as a sum of all obese-year "exposures" up to and including that examination.

Table 1 illustrates the calculation of obese-years for a single individual. This participant first had a measurement of obesity at examination 2 and was assigned obesity duration of zero at this examination. At examination 3, this participant was assumed to have lived with obesity for 2 years (the interval between examination 2 and examination 3) with a degree of obesity of 1 kg/m2. This approach assumes that an individual's BMI is carried forward from a given examination (i.e., examination 2) and does not change until a different BMI value at a subsequent examination (i.e., examination 3). The number of obese-years at examination 3 was therefore 2 obese-years (1 BMI unit X 2 years in the preceding interval). From examination 3 to examination 4 (a 3 year interval), the participant was still obese with a degree of obesity of 3 kg/m^2 (BMI 32 kg/m^2). At examination 4, the number of obese-years was 9 (3BMI unit X 3 years) and the cumulative obese-years at this examination was 11 obese-years (2 plus 9).

This method implies that individuals accumulating 50 obese-years, for example, could have reached this quantity either by having been obese with BMI of 30 kg/m^2 for approximately 50 years or by having been obese with BMI of 34 kg/m^2 for approximately 10 years or, indeed, many other combinations.

Measurement of the outcome and time to event

The main outcome of interest in this study was CVD incidence (the first event of any type of CVD; defined as a composite of coronary heart disease (CHD), cerebrovascular accident (CVA), peripheral artery disease, and congestive heart failure (CHF)[13]. Additional outcomes were individual types of CVD: hard CVD, CHD, CVA, and CHF. Hard CVD was defined as a composite of hard CHD (coronary death, myocardial infarction), stroke (fatal and nonfatal), peripheral artery disease and heart failure. In the FHS, the criteria for each cardiovascular outcome during follow-up were standardized[14] and a panel of Framingham investigators made an adjudication regarding diagnosis. CHD includes the diagnoses of (1) angina pectoris, evidenced by a typical history of chest pain on a physician-administered questionnaire; (2) myocardial infarction, determined by specified electrocardiographic changes, diagnostic elevation of serum enzymes with prolonged ischemic chest pain, or on autopsy; (3) coronary insufficiency, defined as prolonged ischemic chest pain accompanied by transient ischemic abnormalities on ECG; and (4) sudden (in less than 1 hour) or non-sudden coronary death. CHF was indicated when at least two major or one major and two minor diagnostic conditions existed concurrently upon examination.

Time to event was measured as the time from cohort entry until the date a participant was diagnosed as having CVD. Individuals who died or reached the end of the follow-up (examination 24) before developing CVD were censored at date of death or examination 24, respectively.

Data analysis

To model the relationship between the various measures of obesity and risk of CVD in a dynamic survival model way[6] an extended Cox regression model involving time-dependent (time-varying) variables[15-18] was used. The demographic and health behavior variables included in the analysis were age, sex and country of birth at baseline, and the time-varying values of education level, marital status, smoking status, alcohol consumption (ounces/month), and physical activity. The regression coefficients from these models were exponentiated and interpreted as hazard ratios noting that care is required with this interpretation[17] since the model does not technically define proportional hazards in the presence of time-varying variables.

The obese-years metric was analysed both as a continuous and as a categorical variable using the same categories as using in the previous study[7] for comparison purposes. For analyses of continuous obese-years, hazard ratios are presented per 10 obese-years. For analyses of categorical obese-years, participants who were never obese during study follow-up (zero obese-years) were assigned as a comparator (reference category) and the level of obese-years was grouped into short, medium long and extensive periods representing 1-24.9, 25-49.9, 50-74.9 and >=75 obese-years. Hazard ratios are presented, both as crude hazard ratios and as multivariate-adjusted hazard ratios for both continuous and categorical versions of obese-years. Three models were used to examine the hazard ratios with the addition of different confounding variables. Model 1 was adjusted for age. Model 2 was adjusted for age, sex, marital status, educational level and country of birth. Model 3 included adjustment for all variables in model 2 plus the health behavior variables of smoking status, alcohol consumption and physical activity. The analyses were stratified by sex and a test for interaction between sex/smoking status and obese-years was performed.

To compare the relative predictive values of obesity level, obesity duration and the obese-years metric, each of these three variables were divided into an equal number of categories. One group was created for those who were never obese (BMI less than 30 kg/m^2) as a reference. For those with obesity, ten deciles were used to create categories. The goodness of fit of the models incorporating each of the three variables was compared using Akaike's information criterion (AIC), computed as –2(log-likelihood) + 2 (number of estimated parameters); with a lower AIC indicating a better fit[19]. All analyses were performed using the Stata statistical software package version 11.0 (StataCorp, College Station, TX, USA)[20].

Sensitivity analyses

A sensitivity analysis was performed to examine whether the associations were influenced by the imputation method for missing BMI. The analysis was repeated by including only participants with no missing values of BMI at any examinations. The effect of the duration of obesity prior to baseline was tested by excluding those who were obese at baseline (n = 576).

RESULTS

Characteristics of the Participants

Of the 5,036 eligible study participants, 1230 (24%) participants were obese for at least 2 consecutive examinations during the study follow-up. For those who were ever obese during the study, the median cumulative duration of obesity was approximately 12 years (range, 2–46 years), and the median cumulative obese-years was 24 (range, 2–556 obese-years). 2753 (55%) participants were diagnosed with cardiovascular disease over approximately 138,918 person-years of follow-up (Table 2).

Incidence and Hazards Ratios for **Cardiovascular Disease**

The incidence rates and adjusted hazards ratios for CVD increased with an increase in the number of obese-years (Table 3 and Table 4). In Model 3 for males and females combined, the adjusted hazard ratios for the categories 1–24.9, 25–49.9, 50–74.9, and ≥75 obese-years were respectively 1.31 (95% CI: 1.15-1.48), 1.37 (95% CI: 1.14-1.65), 1.62 (95% CI: 1.32-1.99), and 1.80 (95% CI: 1.54-2.10) compared with those who were never obese (i.e. had zero obese-years). For obese-years as a continuousvariable , with every 10 unit increase in obese-years the adjusted hazard ratio for CVD was estimated to increase by

4% (95% CI 3% - 5%) (Table 5). There were no significant interactions between obese-year categories with sex or smoking status. There was evidence of an interaction between obese-years as a continuous variable and sex (*P* value = 0.01). The effect of obese-years was stronger in males than in females.

Comparing Obesity Metrics and Akaike's Information Criterion (AIC),

Table 6 demonstrates the risk of CVD for each of the three different constructs for obesity: level of obesity (based on BMI), duration of obesity, and the obese-years metric. Each construct was analysed in a separate model as an additive effect and the strength of association was compared using the Akaike Information Criterion (AIC). In all outcomes, the AIC was lowest in the model using the obese-years metric compared with the other models for the total population and by sex.

Sensitivity analysis

The sensitivity analyses showed that the association between obese-years and risk of CVD was similar in a complete case analysis and the analysis using imputed missing values for BMI. Exclusion of participantswho were obese at baseline showed only a slightly lower adjusted hazard ratio: 1.03 (95% CI: 1.01-1.05)

DISCUSSION

This study found that measuring the total effect of obesity by combining the level and the duration of obesity into a single metric of obese-years is a stronger predictor for the risk of CVD compared to using duration of obesity or level of obesity alone. A clear dose-response relationship between obese-years and risk of CVD was observed. A stronger effect was found in males than in females

Although the hazard ratios were very similar between the three different constructs, and it is not possible to perform a statistical comparison of discrimination between the models due to the fact that they are non-nested, the AIC does indicate that combining the level and duration of obesity into a single construct of obese-years provides greater discriminative power than a model with level of obesity or obesity duration alone. However the disparity in AIC between the competing models was not as great as was observed with diabetes as the outcome of interest[7] and so it is unclear the extent to which this finding has important implications for future studies of the total health impact associated with obesity and whether future studies should take into account both the impact of obesity level and changes in the duration of obesity.

There are different ways to operationalize the impact of excess weight over time. A recent systematic review identified at least four models: an additive model, a duration-of-obesity model, an additive-weight-change model, and an interactive model [21]. In addition to these models, findings using the obese-year model suggest that analyzing the combined effect of the duration and the level of obesity as a predictor of CVD is worthwhile. Such approaches add information over and above simply the level of excess weight or length of time with obesity. As has been argued previously[7] other potential addition to this analysis is examining the excess body weight as higher than 25 kg/m^2.

The findings in this study were derived from analysis of a long term prospective cohort study with biennial measurements of body weight, covariates and health outcomes which enabled us to analyze change in level of obesity and duration of obesity over a long period. The analysis takes into account changes in covariates, such as smoking status, alcohol consumption and physical activity and adjusts for a large number of potential confounding variables. However, some potential confounders, such as diet, were not collected consistently in the Framingham Heart Study and therefore have not been adjusted for in our analysis.

As has been described elsewhere[7], the limitation of this analysis might relate to the population being a relatively old cohort study, the Framingham Heart Study that began in 1948, and the prevalence rates of obesity were relatively low at that time (in the 1950s was below 10%)[22]. It could be argued that the results of this study might not reflect contemporary populations, where the prevalence of obesity is markedly higher than 50 years ago. In 2008 , the prevalence of obesity among adults in the United States was more than 30%[23 24]. Moreover, the contemporary obesity epidemic is also characterized by a much earlier onset of obesity, which could result in even longer exposure by the time today's obese generation of children reach the age of our studied cohort. In our study, the average age at onset of obesity was approximately 50 years, and the average number of years lived with obesity was approximately 13 years but in today's society, the average age at onset of obesity is likely to be more than 10 years earlier than in previous decades[25]. Nevertheless, our results indicate that the obese-years metric is still valid and may provide more precision in predicting the risk of CVD than level of BMI or duration of obesity alone.

The obese-years metric in this study was based on the measurement of BMI. It is unclear whether using anthropometric measures other than BMI would produce different results. Although a recent meta-analysis study has showed that BMI, waist circumference (WC), and the waist/hip ratio (WHR) each estimate a similar risk, particularly for type-2 diabetes[26]; it is still worthwhile explore the relationship between obese-years and risk of CVD using WC or WHR.

As discussed in our previous study[7], the obese-years metric was developed based on the assumption that level and duration of obesity have a similar impact, an assumption that has been used for the concept of pack-years in smoking studies. In some smoking studies, it was highlighted that for certain health outcomes, the effect of the duration was more important than intensity[27], while in others, duration was not significant after adjustment for intensity[28]. As we have previously discussed, the notion that obese-years is only "switched on" when BMI reaches 30 kg/m^2 is crude[7], however it is an important construct to consider whether the combination of level and duration is relevant for a particular outcome. In addition, although obese-years does find a parallel in pack-years for smoking, which is a construct that ignores any effects of passive smoking, the nature of cumulative exposure in obesity is not as straightforward as in smoking.

These findings demonstrate that it is important to consider not only the level of obesity but also the duration of obesity and their combination when examining the association between obesity and the risk of chronic disease. This effect is likely to be because the obese-years metric takes into account the cumulative damage of obesity to body systems, and consequently is likely to be applicable to other chronic diseases. However, further investigations are recommended to be undertaken, of other possible level/duration constructs of obesity such as considering the effect of BMI above 25 kg/m^2, and of relationships between obese-years and other chronic diseases and mortality.

We acknowledge that a major challenge in examining the obese-years metric is to have information on both the degree of obesity and the duration of obesity. Few cohort studies measure obesity and health outcomes regularly as in the FHS. However, we believe there would be value in more detailed assessment of height and weight on multiple repeated occasions in future cohort studies and to identify other more readily available proxies of duration, such as peak weight or age of onset of obesity and to test to what extent those variables are equivalent to the obese-year metric.

It is important that these results inform future epidemiological analyses, suggesting that the risk of obesity on some health outcomes is being underestimated if duration is not being taken into account. This has consequent implications for underestimation of obesity-related burden of disease modelling and cost-effectiveness analyses. In addition, the results inform public health policy, demonstrating further rationale for preventing weight gain and delaying the onset of obesity.

CONCLUSION

This study demonstrates that the risk of CVD associated with obesity is derived both from the level of obesity attained and also the length of time lived with obesity. The obese-years metric conceptually captures the cumulative damage of obesity on body systems, and is found to provide slightly more precise estimation of the risk of CVD than level or the duration of obesity alone.

CONFLICT OF INTEREST:

None declared.

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CONTRIBUTORS

Author AA developed the analytical techniques of study, performed data analysis, interpretation, drafting of the article and prepared the final version for publication; FAA performed data analysis and interpretation of data; JS, ST, and JB helped review the data analysis and reviewed the article; RW contributed to the study design and reviewing of the article; and AP supervised the implementation of the study, designed the study's analytic strategy, and reviewing of the article

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Table 1: Illustration of the Calculation of an Obese-Years Metric for a Single Hypothetical Individual

ID	Examination	Interval Between Examinations, years[a]	Body Mass Index[b]	Degree of Obesity	Duration of Obesity, years	Obese-Years[a]	Cumulative Obese-Years
6	1 (baseline)	-	28	0	-	0	0
6	2	2	30	1	0	0	0
6	3	2	32	3	2	2	2
6	4	3	34	5	3	9	11
6	5	1	32	3	1	5	16
6	6	2	30	1	2	6	22
6	7	1.5	28	0	1.5	1.5	23.5
6	8	2.5	28	0	0	0	23.5
6	9	2	30	1	0	0	23.5
6	10	1.5	32	3	1.5	1.5	25
6	11	3	34	5	3	9	34
6	12	2	32	3	2	10	44
6	13	2	30	1	2	6	50

[a] All intervals refer to the interval between the current examination and the prior examination
[b] Body mass index; weight (kg)/height (m)^2.

Table 2: Characteristics of the study population[a]

	Number			Percentage			Median			Range			P value[e]
Participant Characteristics	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**	
Eligible sample	5,036	2,237	2,799	100	44	46							
Participants ever obese during study follow-up	1,247	494	750	24.7	40	60							0.000
Age at baseline (years)							43	43	43	28–62	29-62	28-62	0.483
Born in the United States	4,082	1,826	2,256	81	44.7	55.3							0.355
Marital status													0.000
Single	452	117	335	9	5	12							
Married	4,269	2,075	2,194	85	93	78							
Widowed, divorced, or separated	315	45	270	6	2	10							
Educational level													0.000
Eighth grade or less	1,374	616	758	27	28	27							
High school	2,306	1,022	1,284	46	46	46							
College	752	392	360	15	18	13							
Graduate school	604	207	397	12	9	14							
Health behavior													
Current smoker at baseline	2,583	1,435	1,154	52	55	45							0.000
Ever-smoker during study follow-up period	3,178	1,837	1,341	63	58	42							0.000
Physical activity score at examination 4							32	33	31	25–83	25-83	25-55	0.000
Alcohol drinking at examination 2, yes, ounces/month[b]	3,183	1,648	1,535	63	52	48	8	15	4	1–360	1-360	1-240	0.000
Body weight characteristics													
Body mass index at baseline (kg/m^2)[c]							25.1	25.6	24.6	16.2–46.3	16.8-38.1	16.2–46.3	0.000
Underweight (<18.5)	65	14	51	1	1	2							0.000
Normal weight (18.5–24.9)	2,405	945	1,460	48	42	52							
Overweight (25–29.9)	1,989	1,057	932	40	47	33							
Obese (≥30)	567	217	350	11	10	13							
Cumulative obesity duration (years) [d]							12	10	12	2–46	2–46	2–46	0.001
Cumulative obese-years [d]							24	15	31	2–556	2-251	2-556	0.000
Cumulative obese-years category [d]													0.000
1–24.9	579	269	319	52	62	45							
25–49.9	192	77	115	17	18	17							
50–74.9	119	31	87	11	7	13							

	Number			Percentage			Median			Range			P value[e]
Participant Characteristics	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**	**Total**	**Males**	**Females**	
≥75	233	54	179	21	13	26							
Cardiovascular disease (any type of CVD)	2753	1,375	1,378	55	50	50							0.000
Hard CVD	1890	952	938	38	51	49							0.000
Coronary heart disease	1872	1036	836	37	55	45							0.000
Heart attack	1538	920	618	31	60	40							0.000
Myocardial infarction	1105	666	439	22	60	40							0.000
Coronary insufficiency	259	146	113	5	56	44							0.000
Angina pectoris	945	498	447	19	53	47							0.000
Cerebrovascular accident	950	411	539	19	43	57							0.426
Congestive heart failure	876	397	479	17	45	55							0.556

[a] Participants were free from existing diabetes, cardiovascular disease, and cancer at baseline.
[b] One ounce ≈ 28.35 g. [c] Body mass index: weight (kg)/height (m)^2.
[d] For those who were obese during study follow-up.
[e] This P value is for the comparison of males vs females.

Table 3: Incidence of Cardiovascular Disease (Events/1,000 Person-Years) According to Categories of Cumulative Obese-Years

	Obese-Years	Events	PYFU	Incident Rate
Total population				
	0 year	2,177	116,681	18.66 (17.89-19.46)
	1-25 years	276	10,846	25.45 (22.62-28.63)
	25-50 years	124	4,509	27.50 (23.06-32.80)
	50-75 years	78	2,365	32.98 (26.42-41.18)
	>=75years	186	4,517	41.17 (35.66-47.54)
Males				
	0 year	1,138	46,950	24.24 (22.87-25.69)
	1-25 years	134	4,669	28.70 (24.23-34.00)
	25-50 years	56	1,710	32.75 (25.21-42.56)
	50-75 years	36	720	50.02 (36.08-69.34)
	>=75years	49	951	51.51 (38.93-68.16)
Females				
	0 year	1,039	69,731	14.90 (14.02-15.83)
	1-25 years	142	6,177	22.99 (19.50-27.10)
	25-50 years	68	2,799	24.30 (19.16-30.81)
	50-75 years	42	1,645	25.53 (18.87-34.54)
	>=75years	137	3,566	38.42 (32.49-45.42)

PYFU = Persons years of follow-up

Table 4: Risk of Cardiovascular Disease According to Categories of Obese-Years

	Hazard Ratio (95% Confidence Interval)		
	Total population*	Males	Females
Model 1			
0 obese-years	1	1	1
1-25 obese-years	1.28 (1.13-1.45)	1.18 (0.99-1.41)	1.37 (1.15-1.64)
25-50 obese-years	1.31 (1.09-1.57)	1.28 (0.97-1.67)	1.40 (1.09-1.79)
50-75 obese-years	1.50 (1.21-1.85)	1.78 (1.35-2.36)	1.46 (1.08-1.96)
>=75 obese-years	1.59 (1.36-1.85)	1.72 (1.33-2.22)	1.78 (1.48-2.15)
Dose-response *P* value	0.0001	0.0001	0.0001
Model 2			
0 obese-years	1	1	1
1-25 obese-years	1.26 (1.11-1.43)	1.18 (0.99-1.41)	1.33 (1.11-1.60)
25-50 obese-years	1.32 (1.10-1.59)	1.29 (0.99-1.70)	1.35 (1.05-1.74)
50-75 obese-years	1.55 (1.27-1.91)	1.80 (1.36-2.38)	1.40 (1.04-1.88)
>=75 obese-years	1.74 (1.50-2.03)	1.71 (1.32-2.21)	1.71 (1.42-2.07)
Dose-response *P* value	0.0001	0.0001	0.0001
Model 3			
0 obese-years	1	1	1
1-25 obese-years	1.31 (1.15-1.48)	1.22 (1.02-1.45)	1.37 (1.14-1.65)
25-50 obese-years	1.37 (1.14-1.65)	1.39 (1.05-1.83)	1.36 (1.05-1.76)
50-75 obese-years	1.62 (1.32-1.99)	1.89 (1.42-2.51)	1.44 (1.08-1.94)
>=75 obese-years	1.80 (1.54-2.10)	1.81 (1.39-2.36)	1.74 (1.44-2.10)
Dose-response *P* value	0.0001	0.0001	0.0001

Model 1 adjusted for age.
Model 2 adjusted for age, marital status, education, country of birth.
Model 3 adjusted for age, marital status, education, country of birth, smoking status, alcohol consumption, physical activity
* Analyses for total population were adjusted for sex.

Table 5: The Hazard Ratio of Cardiovascular Disease per 10 Obese-Years

CVD	Hazard Ratio per additional 10 Obese-Years (95% Confidence Interval)		
	Total population*	Males	Females
Cardiovascular diseases (all types CVD)			
Model 1	1.03 (95% CI 1.02-1.04)	1.05 (95% CI 1.03-1.07)	1.03 (95% CI 1.02-1.04)
Model 2	1.03 (95% CI 1.02-1.04)	1.05 (95% CI 1.03-1.07)	1.03 (95% CI 1.02-1.04)
Model 3	1.04 (95% CI 1.03-1.05)	1.06 (95% CI 1.04-1.08)	1.03 (95% CI 1.02-1.04)
Hard Cardiovascular diseases (Hard CVD)			
Model 1	1.03 (95% CI 1.02-1.04)	1.06 (95% CI 1.04-1.08)	1.03 (95% CI 1.02-1.05)
Model 2	1.04 (95% CI 1.03-1.05)	1.06 (95% CI 1.04-1.08)	1.03 (95% CI 1.02-1.04)
Model 3	1.04 (95% CI 1.03-1.05)	1.06 (95% CI 1.04-1.08)	1.03 (95% CI 1.02-1.04)
Coronary heart disease (CHD)			
Model 1	1.02 (95% CI 1.01-1.03)	1.03 (95% CI 1.01-1.06)	1.03 (95% CI 1.02-1.04)
Model 2	1.03 (95% CI 1.02-1.04)	1.03 (95% CI 1.01-1.06)	1.03 (95% CI 1.02-1.04)
Model 3	1.03 (95% CI 1.02-1.04)	1.04 (95% CI 1.02-1.06)	1.03 (95% CI 1.02-1.04)
Cerebrovascular accident (CVA)			
Model 1	1.03 (95% CI 1.02-1.04)	1.06 (95% CI 1.04-1.09)	1.03 (95% CI 1.01-1.04)
Model 2	1.03 (95% CI 1.02-1.04)	1.06 (95% CI 1.04-1.09)	1.02 (95% CI 1.01-1.04)
Model 3	1.03 (95% CI 1.02-1.04)	1.06 (95% CI 1.04-1.09)	1.02 (95% CI 1.01-1.04)
Congestive health failure (CHF)			
Model 1	1.05 (95% CI 1.03-1.06)	1.06 (95% CI 1.04-1.09)	1.05 (95% CI 1.03-1.06)
Model 2	1.05 (95% CI 1.04-1.06)	1.06 (95% CI 1.04-1.09)	1.04 (95% CI 1.03-1.06)
Model 3	1.05 (95% CI 1.04-1.06)	1.06 (95% CI 1.04-1.09)	1.04 (95% CI 1.03-1.06)

Model 1 adjusted for age.
Model 2 adjusted for age, marital status, education, country of birth.
Model 3 adjusted for age, marital status, education, country of birth, smoking status, alcohol consumption, physical activity
* For total population also adjusted for sex

Table 6: Comparison of the Obese-Years Metric, Body Mass Index and Obesity Duration as Predictors of the Risk for Cardiovascular Disease

Constructs	Akaike Information Criterion (AIC)		
	Total population	Males	Females
Cardiovascular diseases (all types CVD)			
Construct 1: Level of BMI	43390	19227	20307
Construct 2: Duration of obesity	43379	19221	20306
Construct 3: Obese-Years	43368	19209	20294
Hard Cardiovascular diseases (Hard CVD)			
Construct 1: Level of BMI	34069	15102	15976
Construct 2: Duration of obesity	34065	15099	15968
Construct 3: Obese-Years	34050	15096	15955
Coronary heart disease (CHD)			
Construct 1: Level of BMI	29038	14355	12156
Construct 2: Duration of obesity	29039	14354	12162
Construct 3: Obese-Years	29028	14351	12152
Cerebrovascular accident (CVA)			
Construct 1: Level of BMI	13575	5211	7147
Construct 2: Duration of obesity	13577	5208	7141
Construct 3: Obese-Years	13573	5208	7136
Congestive health failure (CHF)			
Construct 1: Level of BMI	13141	5275	6667
Construct 2: Duration of obesity	13122	5263	6663
Construct 3: Obese-Years	13104	5255	6649

Each construct was split into 11 categories; 1 represents "not obese" and 2-11 represent deciles of obesity exposure (level, duration and obese-years)
Each model adjusted for sex, age, marital status, education, smoking, alcohol consumption, and physical activity.

Title:

Estimating the risk of cardiovascular disease using an obese-years metric

Running title:

Obese-years and cardiovascular disease

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ABSTRACT:

Objective: To examine the association between obese-years and the risk of cardiovascular disease (CVD).

Study design: Prospective cohort study

~~for approximately 50 years of follow-up.~~

Setting: Boston, USA

Participants: 5036 participants of the ~~original~~ Framingham Heart Study were examined.

Methods: ~~The variable of o~~Obese-years was calculated by multiplying for each participant the number of BMI units above ~~30~~29 kg/m^2 by the number of years lived at that BMI during approximately 50 years of follow-up. The association between obese-years and ~~the outcome~~ CVD was analyzed ~~by~~ using time-dependent Cox regression adjusted for potential confounders and compared with ~~the current~~other models using the Akaike Information Criterion (AIC). The lowest AIC indicated better fit.

Primary outcome: Cardiovascular disease~~s~~.

The Results: The ~~average~~median cumulative obese-years was ~~63~~ 24 (range, 2–556 obese-years). During 138,918 person-years of follow-up, 2753 (55%) participants were diagnosed with CVD~~cardiovascular disease~~. The incidence rates and adjusted hazards ratios (~~OR~~AHR) for CVD increased with an increase in the number of obese-years. ~~OR~~ AHR for the categories 1–24.9, 25–49.9, 50–74.9, and ≥75 obese-years ~~was~~ were respectively 1.31 (95% CI: 1.15–1.48), 1.37 (95% CI: 1.14–1.65), 1.62 (95% CI: 1.32–1.99), and 1.80 (95% CI: 1.54–2.10) compared with those who were never obese (i.e. had zero obese-years) ~~respectively~~. ~~A dose-response relationship (across the 5 categories) was significant (*P* trend= 0.001). Effect~~ The effect of obese-years was ~~higher~~ stronger in males than females. For every 10 unit increase in obese-years, the A~~O~~HR of CVD increased by 6% (95% CI 4% to 8%) for males and 3% (95% CI 2% to 4%) for females. The AIC was lowest ~~in~~ for the model containing obese-years compared with models containing either the level of BMI or the duration of obesity alone.

Conclusions: This study demonstrates that obese-years metric conceptually captures the cumulative damage of obesity on body systems, and is found to provide slightly more precise estimation of the risk of CVD than level or the duration of obesity alone.

~~*This study confirms that the obese-years construct is an independent risk factor for CVD. Obese-years metric is a better predictor the risk of CVD although it shows similar risk estimation to other two models.*~~

Key Words: *Obesity, BMI, the duration of obesity, obese-years, risk factor, cardiovascular disease*

Strengths ~~and limitations~~ of this study

- The obese-years metric combines the number of years lived with obesity and the level of BMI to examine the total effect of obesity. ~~Examining the total effect of obesity by combining the number years lived with obesity and the level of BMI into a single measurement of obese-years.~~
- The Framingham Heart Study is ~~A~~ a long term prospective cohort study with approximately 50 years ~~of follow-up~~ of follow-up~~followed-up with~~, and biennial measurements of body weight, covariates and health outcomes.
- By using time-dependent Cox proportional hazards regression, ~~T~~the analysis takes into account changes in covariates during study follow-up and ~~adjusted~~ adjusts for a large number of potential confounding variables.

Limitations of this study

- The obese-years ~~construct~~metric was developed based on the measurement of BMI. It is unclear whether using anthropometric measures other than BMI would produce different results.
- Data used for this study was from a relatively old cohort study, which began in 1948.

Background

The association between Oobesity has been associated with an increased risk of and cardiovascular disease (CVD) is well known[1 2]. However, these findings are generally based on analysing only the level of BMI in relation to CVD. More recently, studies have demonstrated the importance of taking into account the potential cumulative effect of the duration of obesity, rather than the simple assessment of obesity at a single point in time (e.g. at baseline). In addition, we have recently demonstrated that the dDuration of obesity has been shown to be ais also risk factor for CVD[3], type-2 diabetes[4] and mortality[5], independent of level of body mass index (BMI)[3]. Nevertheless, analyses based on either level of BMI alone or duration lived with obesity alone, However, the quantification of these association by only analysing the level of BMI [6] or the duration lived with obesity[4 5]. This approach may not reflect the total effect of obesity and may underestimated the risk of CVD associated withattributable to obesity.

We have recently demonstrated the additional benefit of constructs combining the level of obesity with the number of years lived with obesity into a single measure, finding that an obese-years constructmetric is a better predictor of the risk of type-2 diabetes than level of BMI or duration of obesity alone[7]. A similar approach that has been used in smoking studies, examining the adverse health effects associated with the combination of number of cigarettes or packs smoked per day (degree) and duration of smoking as a cigarette-years or pack-years [8-10].

The use of a similar construct for body weightthe obese-years constructmetric, to estimate the risk of CVD has not been investigated yet. We hypothesized that the obese-years constructmetric is likely a similar independent risk factor for CVD and would provide an improved estimation of the risk of future CVD. This study aimed to examine the association between obese-years and risk of CVD and to examine whether the obese-years constructmetric wais a better predictor for risk of CVD than current BMI or duration of obesity alone. We investigated these objectives using the original Framingham Heart Study (FHS), a long term prospective cohort study where body weight, health outcomes and other covariates were measured regularly biennially for almost 50 years[11].

METHODS

Data source

We used data from the original Framingham Heart Study (OFHS)[12]. In this prospective cohort study, 5,209 participants (aged 28–62 years at the time of enrolment) were examined regularly at 2-years intervalsattended biennial examinations for approximately 50 years beginning from 1948. For the purpose of this study, only participants who were free from CVD (any types), cancer and type-2 diabetes at baseline were included in the analysis (n = 5,036).

Variables: measurement, missing and imputation

Most of variables in the FHS was were measured regularly at every the two-yearsyearly intervalexaminations, including body weight, height, demographic variables, health behaviors, and health outcomes (including cardiovascular disease)[11]. However sSome values are missing by design where variables were not collected at every examination. For example the variables of current smoking status was not recorded at four examinations (2, 3, 6 and 17), cholesterol was not measured at seven examinations (11, 12, 17-20 and 22), alcohol consumption was measured only atin eight examinations (2, 4, 7, 19, 20–23), and physical activity was measured only at four examinations (4, 11, 12, and 19). For In this circumstance, the nearest most contemporary measured value of the covariatevariable was used in place of missing values at the examination times when the variable was not measured. Another missing data circumstance was when missing values occurred intermittently missing one or more values during study follow-up; for example body weight and hence BMI. In this case missing values for BMI were imputed with a conditional mean estimated by a multiple linear regression model using age at prior exam, sex and several transformations of the previously measured BMI (BMI, log BMI, BMI squared and BMI as a categorical variable). Methods of measurement of these variables have been described in detail elsewhere[4 7].

The level of obesity, duration and obese-years measurement

A participant was considered obese at a given examination if their BMI was greater than or equal to 30 kg/m^2. The level of obesity was defined as follows: (1) if BMI < 30 kg/m^2, the level was zero; and (2) if BMI ≥ 30 kg/m^2, the level was BMI minus 29 kg/m^2. For example, if BMI was 35 kg/m^2, the level was 6 (35 – 29) obese units.

The duration of obesity ~~was defined using~~followed a similar definition to that ~~as has been~~ described previously[4]. The duration of obesity was calculated for those individuals with at least two consecutive examinations with ~~the~~ occurrence~~s~~ of obesity (which ~~implies~~ is interpreted as indicating at least two years of being continuously obese). The requirement for two consecutive examinations with obesity was to avoid the potential misclassification of body weight, either due to measurement error or fluctuations between the borderline of the 'overweight' category or the 'obese' category. For those individuals without two consecutive obesity occurrences, duration was considered to be zero at all exams. For those individuals with two consecutive obesity occurrences, the beginning of their obesity duration interval was defined as the date of the first of these two examinations and from that time, the individual was considered to be continuously obese until either the first of two consecutive non-obese examinations, or death, or the end of follow-up at examination 24. ~~The duration increased incrementally at each exam according to the time (in years) between the current exam and the first obese examination.~~ Individuals could have multiple periods of obesity duration during follow-up.

~~The level of obesity and the duration of obesity then was combined into a single variable called obese-years. Obese-years lived were The variable was calculated at each examination as the defined level of obesity (in "obese units") multiplied by the defined duration of obesity (in years). The cumulative number of obese-years was calculated at each examination as a sum of all obese-year "exposures" up to and including that examination as has been illustrated in the previous paper[7]~~

The level of obesity and the duration of obesity were combined as a single variable called obese-years. Obese-years was calculated at each examination as the defined level of obesity (in “obese units”) multiplied by the defined duration of obesity (in years). Then the cumulative total of obese-years for each examination was calculated as a sum of all obese-year “exposures” up to and including that examination.

Table 1 illustrates the calculation of obese-years for a single individual. This participant first had a measurement of obesity at examination 2 and was assigned obesity duration of zero at this examination. At examination 3, this participant was assumed to have lived with obesity for 2 years (the interval between examination 2 and examination 3) with a degree of obesity of 1 kg/m2. This approach assumes that an individual’s BMI is carried forward from a given examination (i.e., examination 2) and does not change until a different BMI value at a subsequent examination (i.e., examination 3). The number of obese-years at examination 3 was therefore 2 obese-years (1 BMI unit X 2 years in the preceding interval). From examination 3 to examination 4 (a 3 year interval), the participant was still obese with a degree of obesity of 3 kg/m^2 (BMI 32 kg/m^2). At examination 4, the number of obese-years was 9 (3BMI unit

X 3 years) and the cumulative obese-years at this examination was 11 obese-years (2 plus 9).

This method implies that individuals accumulating 50 obese-years, for example, could have reached this quantity either by having been obese with BMI of 30 kg/m^2 for approximately 50 years or by having been obese with BMI of 34 kg/m^2 for approximately 10 years or, indeed, many other combinations.

Measurement of the outcome and time to event

The main outcome of interest in this study was CVD incidencet (the first event of any type of CVD; defined as a composite of coronary heart disease (CHD), cerebrovascular accident (CVA), peripheral artery disease, and congestive heart failure (CHF)[13]. Additional outcomes were individual types of CVD: hard CVD, CHD, CVA, and CHF. Hard CVD was defined as a composite of hard CHD (coronary death, myocardial infarction), stroke (fatal and nonfatal), peripheral artery disease and heart failure. In the OFHS, the criteria for each cardiovascular outcome during follow-up were standardized[14] and a panel of Framingham investigators made the decisionan adjudication regarding diagnosis. CHD includes the diagnoses of (1) angina pectoris, evidenced by a typical history of chest pain on a physician-administered questionnaire; (2) myocardial infarction, determined by specified electrocardiographic changes, diagnostic elevation of serum enzymes with prolonged ischemic chest pain, or on autopsy; (3) coronary insufficiency, defined as prolonged ischemic chest pain accompanied by transient ischemic abnormalities on the ECG; and (4) sudden (in less than 1 hour) or non-sudden coronary death. CHF was indicated when at least two major or one major and two minor diagnostic conditions existed concurrently upon examination.

Time to event was measured as the time from cohort entry until the date a participant was diagnosed as having cardiovascular diseaseCVD. Individuals who died or reached the end of the follow-up (examination 24) before developing CVD were censored at date of death or examination 24, respectively.

Data analysis

To model the relationship between the various measures of obesity and risk of CVD in a dynamic survival model way[6] an (extended time-dependent Cox regression model involving time-dependent (time-varying) variables[15-18] was used. The demographic and health behavior variables included in the analysis were age, sex and country of birth at baseline, and the time-varying values of , sex and country of birth at baseline, and the time-varying values of sex, education level, country of birth, marital status, smoking status, alcohol consumption (ounces/month), and physical activity. Most of these variables included in the model were time-varying, except for sex, age (at baseline) and country of birth. The regression coefficients from these models were exponentiated and interpreted as hazard ratios noting that care is required with this interpretation[17] since the model does not technically define proportional hazards in the presence of time-varying variables.

The obese-years constructmetric was analysed both as a continuous and as a categorical variable using a similar the same categories as using in the previous study[7] for comparison purposes. For continuous analyses of continuous obese-years, hazard ratios were are presented per 10 obese-years. For analyses of categorical obese-years, those participants who were never obese during study follow-up (zero obese-years) were was assigned as a comparator (reference category) and the level of Those who values of obese-years within the study follow-up period, then obese-years was grouped into short, medium and long and extensive periods representing 1-24.9, 25-49.9, 50-74.9 and >=75 obese-years. Hazard ratios were are presented, both as crude hazard ratios and as multivariate-adjusted hazard ratios for both continuous and categorical variable versions of obese-years. Three models of analysis were used to examine the change in hazard ratios associated with the addition of different confounding variables. Model 1 was adjusted for age. Model 2 was adjusted for age, sex, marital status, educational level and country of birth. Model 3 includesd adjustment for all variables in model 2 plus the health behavior variables of smoking status, alcohol consumption and physical activity and this model was considered the primary model of the study. The analyses were additionally stratified by sex and a test for interaction between sex/smoking status and obese-years was performed for all models.

To compare the relative predictive values of obesity level, obesity duration and the obese-years constructmetric, each of these three variables were divided into an equal number of categories. One group was created for those who were never obese (BMI less than 30 kg/m^2) as a reference. For those with obesity, ten deciles were used to create categories were created. The goodness of fit of the models incorporating each of the three variables was compared using Akaike's information criterion (AIC), computed as −2(log-likelihood) + 2 (number of estimated parameters); with a lower AIC indicating a better fit[19]. All analyses were performed using the Stata statistical software package version 11.0 (StataCorp, College Station, TX, USA)[20].

Sensitivity analyses

A sensitivity analysis was performed to examine whether the associations were might be influenced by the imputation method for missing BMI.; specifically, an The analysis was performed repeated that by includinged only participants with no missing values of BMI in at any examinations. The effect of the duration of obesity prior to baseline was tested by performing extra analyses that excludinged those who were obese at baseline (no = 576).

RESULTS

Characteristics of the Participants Respondents

Of the 5,036 eligible study participants, 1230 (24%) participants were obese for at least 2 consecutive examinations during the study follow-up. Mean For those who were ever obese during the study, the median cumulative duration of obesity was approximately 16 12 years (range, 2–46 years), and the mean median cumulative obese-years was 63 24 (range, 2–556 obese-years). 2753 (55%) participants were diagnosed with cardiovascular disease over approximately during 138,918 person-years of follow-up (Table 1 2).

Incidence and Hazards Ratios for of Cardiovascular Disease

The incidence rates and adjusted hazards ratios for CVD increased with an increase in the number of obese-years (Table ~~2~~ 3 and Table ~~3~~4). In ~~the primary model (~~Model 3~~)~~ for males and females combined~~the total population~~sample, the adjusted hazard ratios for the categories 1–24.9, 25–49.9, 50–74.9, and ≥75 obese-years ~~for total population was~~ were respectively 1.31 (95% CI: 1.15-1.48), 1.37 (95% CI: 1.14-1.65), 1.62 (95% CI: 1.32-1.99), and 1.80 (95% CI: 1.54-2.10) compared with those who were never~~-~~ obese (i.e. had zero obese-years) ~~respectively~~. ~~A dose-response relationship (across the 5 categories) was significant (*P* trend= 0.001).~~ For obese-years as a continuous~~es~~ variable ~~analysis~~, with every 10 unit increase in obese-years~~,~~ the adjusted hazard ratio~~s~~ for CVD was estimated to ~~in the total population~~ increase~~d~~ by 4% (95% CI 3% - 4~~5~~%) (Table 4~~5~~). There were no significant interactions between obese-year~~s~~ categories ~~and~~ with sex ~~and~~ or smoking status. ~~but t~~ There was evidence of an interaction between obese-years as a continuous variable and ~~each of~~ sex (*P* value = 0.01). ~~Effect~~ The effect of obese-years was ~~higher~~ stronger in males than in females.

Comparing ~~o~~Obesity ~~construct~~Metrics and Akaike's Information Criterion (AIC),

Table ~~5~~ 6 demonstrates the risk of CVD for each of the three different constructs for obesity: level of obesity (based on BMI), duration of obesity, and the obese-years ~~construct~~metric ~~as additive effects~~. Each construct was analysed in a separate model as an additive effect and the strength of association was compared using the Akaike Information Criterion (AIC). In all outcomes, the AIC was lowest in the model using the ~~construct of~~ obese-years metric compared with the other models ~~two constructs both in analysis by~~ for the total population and by sex.

Sensitivity analysis

The sensitivity analyses showed that the association between obese-years and risk of CVD was similar ~~between~~ in a complete case analysis and the analysis using imputed missing values for BMI. Exclusion of participants ~~who had no record of body mass index at baseline has no change in adjusted hazard ratio, but exclusion of those~~ who were obese at baseline showed only a slightly lower adjusted hazard ratio: 1.03 (95% CI: 1.01-1.05)

DISCUSSION

This study found that ~~the approach of~~ measuring the total effect of obesity by combining the level and the duration of obesity into a single metric of obese-years, is a stronger predictor for of the risk of CVD than compared to using the duration of obesity or the intensity level of obesity alone. A clear dose-response relationship between obese-years and the risk of CVD was observed. The A stronger effect was found in males than in females

Although the hazard ratios were very similar between the three different constructs, and it is not possible to perform a statistical comparison of discrimination between the models due to the fact that they are non-nested, the AIC does tell us indicate that combining the level of obesity and the duration of obesity into a single construct of obese-years provides us with more greater discriminative power than a model with level of obesity based on BMI or obesity duration alone. However the disparity in AIC between the competing models was not as great as was observed with diabetes as the outcome of interest[7] and so it is unclear the extent to which Tthis finding has important implications for future studies of the total health impact associated with obesity and whether future studies that should be taken into account both the impact of obesity level and changes in the duration of obesity.

There are different ways to operationalize the impact of excess weight over time. A recent systematic review identified at least four models: an additive models, a duration-of-obesity model, an additive-weight-change model, and an interactive model [21]. In addition to these models, findings using the obese-year model confirms suggest that analyzing the combined effect of the duration and the level of obesity as a predictor of the cardiovascular CVD is worthwhile. Such approaches add information over and above simply the level of excess weight or length of time with obesity. As has been argued previously [7] other potential additions to this analysis is examining the excess body weight as higher than 25 kg/m^2.

The findings in this study were is derived from analysis of a long term prospective cohort study with biennial measurements of body weight, covariates and health outcomes which enabled us to analyze change in level of obesity and the duration of obesity over a long term period. The analysis takes into account changes in covariates, such as smoking status, alcohol consumption and physical activity and adjusted adjusts for a large number of potential confounding variables. However, some potential confounders, such as diet, were not collected consistently in the original Framingham Heart Study and therefore have not been adjusted for in this studyour analysis.

As has been described elsewhere[7], the limitation of this analysis might related to the population of study us being a relatively old cohort study, – of the original Framingham Heart Study that began in 1948, and the prevalence rates of obesity and cardiovascular diseaseCVD were relatively low at that time (in the 1950s was below 10%)[22]. Therefore some people It could be argued that the results of this study might not reflect contemporary the current populations, where the prevalence of obesity is markedly higher than 50 years ago. In 2008 alone, the prevalence of obesity among adults in the United States was more than 30%[23 24]. Moreover, the contemporary obesity epidemic is also characterized by a much earlier onset of obesity, which should could result in even longer exposure by the time today's obese generation of children reach the age of our studied cohort. In our study, the average age at onset of obesity was approximately 50 years, and the average number of years lived with obesity was approximately 13 years but, in today's society, the average age at onset of obesity is likely to be more than 10 years earlier than in previous decades[25]. HoweverNevertheless, our results indicate that the obese-years constructmetric is still valid and may provide more precision in predicting the risk of CVD is a better tool than level of BMI or duration of obesity alone. If further analysis is conducted, the association between obese-years and CVD could be even stronger today since the exposure to obesity is now greater than it was.

The obese-years constructmetric in this study was based on the measurement of BMI. It is unclear whether using anthropometric measures other than BMI would produce different results. Although a recent meta-analysis study has showed that BMI, waist circumference (WC), and the waist/hip ratio (WHR) to each estimate a similar risk, particularly for type-2 diabetes[26]; it is still worthwhiley to explore the relationship between obese-years and risk of CVD using WC or WHR.

As discussed in our previous study[7], the obese-years metric was developed based on the assumption that level and duration of obesity -have a similar impact, an assumption that has been used for the concept of pack-years in smoking studies. In some smoking studies, it was highlighted that for certain health outcomes, the effect of the duration was more important than intensity[27], while in others, duration was not significant after adjustment for intensity[28]. As this is a new concept in obesity studies, it requires further exploration. As we have previously discussed, Tthe notion that obese-years is only "switched on" when BMI reaches 30 kg/m^2 is crude[7], however it is an important construct to consider whether the combination of intensitylevel and duration is relevant for a particular outcome. In addition, although it obese-years does find a parallel in pack-years for smoking, which is a construct that ignores any effects of passive smoking, the nature of cumulative of exposure in obesity e-years measurement is not as straightforward as in smoking.. As this is a new concept in obesity studies, it requires further exploration.

This These findings demonstrate one again that it is important to consider not only the level of obesity but also the duration of obesity and its their combination when examining the association between obesity and the risk of chronic disease. This effect is likely to be because it the obese-years constructmetric takes into account is taken of the cumulative damage of obesity onto body systems, and consequently is likely to be applicable to other chronic diseases. However, further investigations are recommended to be undertaken, of other possible intensitylevel/duration constructs of obesity such as considering the effect of BMI above 25 kg/m^2, and of relationships between obese-years and other chronic diseases and mortality.

We acknowledge that a major challenge in examining the obese-years metric is to have information on both the degree of obesity and the duration of obesity.

Few cohort studies measure obesity and health outcomes regularly as in the FHS. However, we believe there would be value in more detailed assessment of height and weight on multiple repeated occasions in future cohort studies and to identify other more readily available proxies of duration, such as peak weight or age of onset of obesity and to test to what extent those variables are equivalent to the obese-year metric.

It is important that these results inform future epidemiological analyses, suggesting that the risk of obesity on some health outcomes is being underestimated if duration is not being taken into account. This has consequent implications for underestimation of obesity-related burden of disease modelling and cost-effectiveness analyses. In addition, the results inform public health policy, demonstrating further rationale for preventing weight gain and delaying the onset of obesity.

CONCLUSION

This study suggestsed possible value in demonstrates the importance of measuring the total effect of obesity by combining both the level and the duration of obesity when estimating demonstrates that the risk of

~~cardiovascular disease~~CVD ~~-~~associated with obesity is derived both from the level of obesity attained and also the length of time lived with obesity. The obese-years ~~construct~~metric conceptually captures ~~might takes into account of~~ the cumulative damage of obesity on body systems, and is found to ~~therefore~~ provide~~s~~ slightly ~~better~~ more precise estimation of the risk of CVD than level or the duration of obesity alone. ~~This approach of examining total effect of obesity is suggested to use in measuring the burden of obesity related diseases in the community.~~

CONFLICT OF INTEREST:

None declared.

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CONTRIBUTORS

Author AA developed the analytical techniques of study, performed data analysis, interpretation, drafting of the article and prepared the final version for publication; FAA performed data analysis and interpretation of data; JS, ST, and JB helped review the data analysis and reviewed the article; RW contributed to the study design and reviewing of the article; and AP supervised the implementation of the study, designed the study's analytic strategy, and reviewing of the article.

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Table 1: Illustration of the Calculation of an Obese-Years Metric for a Single Hypothetical Individual

ID	Examination	Interval Between Examinations, years[a]	Body Mass Index[b]	Degree of Obesity	Duration of Obesity, years	Obese-Years[a]	Cumulative Obese-Years
6	1 (baseline)	-	28	0	-	0	0
6	2	2	30	1	0	0	0
6	3	2	32	3	2	2	2
6	4	3	34	5	3	9	11
6	5	1	32	3	1	5	16
6	6	2	30	1	2	6	22
6	7	1.5	28	0	1.5	1.5	23.5
6	8	2.5	28	0	0	0	23.5
6	9	2	30	1	0	0	23.5
6	10	1.5	32	3	1.5	1.5	25
6	11	3	34	5	3	9	34
6	12	2	32	3	2	10	44
6	13	2	30	1	2	6	50

[a] All intervals refer to the interval between the current examination and the prior examination
[b] Body mass index; weight (kg)/height $(m)^2$.

Table 2: Characteristics of the study population[a]

	Number			Percentage			Median			Range			P value[e]
Participant Characteristics	Total	Males	Females	Total	Males	Females	Total	Males	Females	Total	Males	Females	
Eligible sample	5,036	2,237	2,799	100	44	46							
Participants ever obese during study follow-up	1,247	494	750	24.7	40	60							0.000
Age at baseline (years)							43	43	43	28–62	29-62	28-62	0.483
Born in the United States	4,082	1,826	2,256	81	44.7	55.3							0.355
Marital status													0.000
Single	452	117	335	9	5	12							
Married	4,269	2,075	2,194	85	93	78							
Widowed, divorced, or separated	315	45	270	6	2	10							
Educational level													0.000
Eighth grade or less	1,374	616	758	27	28	27							
High school	2,306	1,022	1,284	46	46	46							
College	752	392	360	15	18	13							
Graduate school	604	207	397	12	9	14							
Health behavior													
Current smoker at baseline	2,583	1,435	1,154	52	55	45							0.000
Ever-smoker during study follow-up period	3,178	1,837	1,341	63	58	42							0.000
Physical activity score at examination 4							32	33	31	25–83	25-83	25-55	0.000
Alcohol drinking at examination 2, yes, ounces/month[b]	3,183	1,648	1,535	63	52	48	8	15	4	1–360	1-360	1-240	0.000
Body weight characteristics													
Body mass index at baseline (kg/m^2)[c]							25.1	25.6	24.6	16.2–46.3	16.8-38.1	16.2–46.3	0.000
Underweight (<18.5)	65	14	51	1	1	2							0.000
Normal weight (18.5–24.9)	2,405	945	1,460	48	42	52							
Overweight (25–29.9)	1,989	1,057	932	40	47	33							
Obese (≥30)	567	217	350	11	10	13							
Cumulative obesity duration (years) [d]							12	10	12	2–46	2–46	2–46	0.001
Cumulative obese-years [d]							24	15	31	2–556	2-251	2-556	0.000
Cumulative obese-years category [d]													0.000
1–24.9	579	269	319	52	62	45							
25–49.9	192	77	115	17	18	17							
50–74.9	119	31	87	11	7	13							

Participant Characteristics	Number Total	Number Males	Number Females	Percentage Total	Percentage Males	Percentage Females	Median Total	Median Males	Median Females	Range Total	Range Males	Range Females	P value[e]
≥75	233	54	179	21	13	26							
Cardiovascular disease (any types of CVD)	2753	1,375	1,378	55	50	50							0.000
Hard CVD	1890	952	938	38	51	49							0.000
Coronary heart disease	1872	1036	836	37	55	45							0.000
Heart attack	1538	920	618	31	60	40							0.000
Myocardial infarction	1105	666	439	22	60	40							0.000
Coronary insufficiency	259	146	113	5	56	44							0.000
Angina pectoris	945	498	447	19	53	47							0.000
Cerebrovascular accident	950	411	539	19	43	57							0.426
Congestive heart failure	876	397	479	17	45	55							0.556

[a] Participants were free from existing diabetes, cardiovascular disease, and cancer at baseline.
[b] One ounce ≈ 28.35 g. [c] Body mass index: weight (kg)/height $(m)^2$.
[d] For those who were obese during study follow-up.
[e] This P value is for the comparison of males vs females.

Table 3: Incidence of Cardiovascular Disease (Events/1,000 Person-Years) According to Categories of Cumulative Obese-Years

	Obese-Years	Events	PYFU	Incident Rate
Total population				
	0 year	2,177	116,681	18.66 (17.89-19.46)
	1-25 years	276	10,846	25.45 (22.62-28.63)
	25-50 years	124	4,509	27.50 (23.06-32.80)
	50-75 years	78	2,365	32.98 (26.42-41.18)
	>=75years	186	4,517	41.17 (35.66-47.54)
Males				
	0 year	1,138	46,950	24.24 (22.87-25.69)
	1-25 years	134	4,669	28.70 (24.23-34.00)
	25-50 years	56	1,710	32.75 (25.21-42.56)
	50-75 years	36	720	50.02 (36.08-69.34)
	>=75years	49	951	51.51 (38.93-68.16)
Females				
	0 year	1,039	69,731	14.90 (14.02-15.83)
	1-25 years	142	6,177	22.99 (19.50-27.10)
	25-50 years	68	2,799	24.30 (19.16-30.81)
	50-75 years	42	1,645	25.53 (18.87-34.54)
	>=75years	137	3,566	38.42 (32.49-45.42)

PYFU = Persons years of follow-up

Table 4: Risk of Cardiovascular DdDisease According to cCategories of Obese-Years Category

	Hazard Ratio (95% Confidence Interval)		
	Total population*	Males	Females
Model 1			
0 obese-years	1	1	1
1-25 obese-years	1.28 (1.13-1.45)	1.18 (0.99-1.41)	1.37 (1.15-1.64)
25-50 obese-years	1.31 (1.09-1.57)	1.28 (0.97-1.67)	1.40 (1.09-1.79)
50-75 obese-years	1.50 (1.21-1.85)	1.78 (1.35-2.36)	1.46 (1.08-1.96)
>=75 obese-years	1.59 (1.36-1.85)	1.72 (1.33-2.22)	1.78 (1.48-2.15)
Dose-response *P* value	0.0001	0.0001	0.0001
Model 2			
0 obese-years	1	1	1
1-25 obese-years	1.26 (1.11-1.43)	1.18 (0.99-1.41)	1.33 (1.11-1.60)
25-50 obese-years	1.32 (1.10-1.59)	1.29 (0.99-1.70)	1.35 (1.05-1.74)
50-75 obese-years	1.55 (1.27-1.91)	1.80 (1.36-2.38)	1.40 (1.04-1.88)
>=75 obese-years	1.74 (1.50-2.03)	1.71 (1.32-2.21)	1.71 (1.42-2.07)
Dose-response *P* value	0.0001	0.0001	0.0001
Model 3			
0 obese-years	1	1	1
1-25 obese-years	1.31 (1.15-1.48)	1.22 (1.02-1.45)	1.37 (1.14-1.65)
25-50 obese-years	1.37 (1.14-1.65)	1.39 (1.05-1.83)	1.36 (1.05-1.76)
50-75 obese-years	1.62 (1.32-1.99)	1.89 (1.42-2.51)	1.44 (1.08-1.94)
>=75 obese-years	1.80 (1.54-2.10)	1.81 (1.39-2.36)	1.74 (1.44-2.10)
Dose-response *P* value	0.0001	0.0001	0.0001

Model 1 adjusted for age.
Model 2 adjusted for age, marital status, education, country of birth.
Model 3 adjusted for age, marital status, education, country of birth, smoking status, alcohol consumption, physical activity
* Analyses for total population were adjusted for sex.

Table 5: The Hazard Ratio of Cardiovascular ~~d~~Disease per 10 Obese-Years

CVD	Hazard Ratio per additional 10 Obese-Years (95% Confidence Interval)		
	Total population*	Males	Females
Cardiovascular diseases (all types CVD)			
Model 1	1.03 (95% CI 1.02-1.04)	1.05 (95% CI 1.03-1.07)	1.03 (95% CI 1.02-1.04)
Model 2	1.03 (95% CI 1.02-1.04)	1.05 (95% CI 1.03-1.07)	1.03 (95% CI 1.02-1.04)
Model 3	1.04 (95% CI 1.03-1.05)	1.06 (95% CI 1.04-1.08)	1.03 (95% CI 1.02-1.04)
Hard Cardiovascular diseases (Hard CVD)			
Model 1	1.03 (95% CI 1.02-1.04)	1.06 (95% CI 1.04-1.08)	1.03 (95% CI 1.02-1.05)
Model 2	1.04 (95% CI 1.03-1.05)	1.06 (95% CI 1.04-1.08)	1.03 (95% CI 1.02-1.04)
Model 3	1.04 (95% CI 1.03-1.05)	1.06 (95% CI 1.04-1.08)	1.03 (95% CI 1.02-1.04)
Coronary heart disease (CHD)			
Model 1	1.02 (95% CI 1.01-1.03)	1.03 (95% CI 1.01-1.06)	1.03 (95% CI 1.02-1.04)
Model 2	1.03 (95% CI 1.02-1.04)	1.03 (95% CI 1.01-1.06)	1.03 (95% CI 1.02-1.04)
Model 3	1.03 (95% CI 1.02-1.04)	1.04 (95% CI 1.02-1.06)	1.03 (95% CI 1.02-1.04)
Cerebrovascular accident (CVA)			
Model 1	1.03 (95% CI 1.02-1.04)	1.06 (95% CI 1.04-1.09)	1.03 (95% CI 1.01-1.04)
Model 2	1.03 (95% CI 1.02-1.04)	1.06 (95% CI 1.04-1.09)	1.02 (95% CI 1.01-1.04)
Model 3	1.03 (95% CI 1.02-1.04)	1.06 (95% CI 1.04-1.09)	1.02 (95% CI 1.01-1.04)
Congestive health failure (CHF)			
Model 1	1.05 (95% CI 1.03-1.06)	1.06 (95% CI 1.04-1.09)	1.05 (95% CI 1.03-1.06)
Model 2	1.05 (95% CI 1.04-1.06)	1.06 (95% CI 1.04-1.09)	1.04 (95% CI 1.03-1.06)
Model 3	1.05 (95% CI 1.04-1.06)	1.06 (95% CI 1.04-1.09)	1.04 (95% CI 1.03-1.06)

Model 1 adjusted for age.
Model 2 adjusted for age, marital status, education, country of birth.
Model 3 adjusted for age, marital status, education, country of birth, smoking status, alcohol consumption, physical activity
* For total population also adjusted for sex

Table 6: Comparison of the Obese-Years ~~construct~~Metric, Body Mass Index and Obesity Duration as Predictors of the Risk ~~of~~for Cardiovascular Disease~~CVD~~

Constructs	Akaike Information Criterion (AIC)		
	Total population	Males	Females
Cardiovascular diseases (all types CVD)			
Construct 1: Level of BMI	43390	19227	20307
Construct 2: Duration of obesity	43379	19221	20306
Construct 3: Obese-Years	43368	19209	20294
Hard Cardiovascular diseases (Hard CVD)			
Construct 1: Level of BMI	34069	15102	15976
Construct 2: Duration of obesity	34065	15099	15968
Construct 3: Obese-Years	34050	15096	15955
Coronary heart disease (CHD)			
Construct 1: Level of BMI	29038	14355	12156
Construct 2: Duration of obesity	29039	14354	12162
Construct 3: Obese-Years	29028	14351	12152
Cerebrovascular accident (CVA)			
Construct 1: Level of BMI	13575	5211	7147
Construct 2: Duration of obesity	13577	5208	7141
Construct 3: Obese-Years	13573	5208	7136
Congestive health failure (CHF)			
Construct 1: Level of BMI	13141	5275	6667
Construct 2: Duration of obesity	13122	5263	6663
Construct 3: Obese-Years	13104	5255	6649

Each construct was split into 11 categories; 1 represents "not obese" and 2-11 represent deciles of obesity exposure (~~intensity~~level, duration and obese-years)
Each model adjusted for sex, age, marital status, education, smoking, alcohol consumption, and physical activity.