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The number of years lived with obesity and the risk of all-cause and cause-specific mortality

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Background The role of the duration of obesity as an independent risk factor for mortality has not been investigated. The aim of this study was to analyse the association between the duration of obesity and the risk of mortality.

Methods A total of 5036 participants (aged 28–62 years) of the Framingham Cohort Study were followed up every 2 years from 1948 for up to 48 years. The association between obesity duration and all-cause and cause-specific mortality was analysed using time-dependent Cox models adjusted for body mass index. The role of biological intermediates and chronic diseases was also explored.

Results The adjusted hazard ratio (HR) for mortality increased as the number of years lived with obesity increased. For those who were obese for 1–4.9, 5–14.9, 15–24.9 and $\geqslant$25 years of the study follow-up period, adjusted HRs for all-cause mortality were 1.51 [95% confidence interval (CI) 1.27–1.79], 1.94 (95% CI 1.71–2.20), 2.25 (95% CI 1.89–2.67) and 2.52 (95% CI 2.08–3.06), respectively, compared with those who were never obese. A dose–response relation between years of duration of obesity was also clear for all-cause, cardiovascular, cancer and other-cause mortality. For every additional 2 years of obesity, the HRs for all-cause, cardiovascular disease, cancer and other-cause mortality were 1.06 (95% CI 1.05–1.07), 1.07 (95% CI 1.05–1.08), 1.03 (95% CI 1.01–1.05) and 1.07 (95% CI 1.05–1.11), respectively.

Conclusions The number of years lived with obesity is directly associated with the risk of mortality. This needs to be taken into account when estimating its burden on mortality.

Keywords Obesity, duration of obesity, body mass index, mortality, all-cause mortality, cause-specific mortality

Background

Obesity has been associated with an increased risk of mortality, both all-cause and cause-specific mortality, in middle-aged adults and the elderly.[1–5] Results of a meta-analysis pooling person-level data from 26 observational studies that included middle-aged adults from several ethnic groups indicated that the risk of mortality for those with obesity [body mass index (BMI)] $\geqslant 30\,kg/m^2$ was 22% higher than for the normal weight group (BMI 18.5–24.9).[2] In the elderly, a recent meta-analysis study pooling 27 population-based cohort studies including only people aged $\geqslant 65$ years reported that the risk of mortality was 10% higher compared with those with normal weight.[3] A recent study pooling 57 prospective studies with a total of 900 000 adults also reported a strong association with several specific causes of mortality.[6]

The quantification of this association, however, has primarily been accomplished by considering the severity of body weight. No study has examined the impact of the duration of obesity on the risk of mortality. It seems unlikely that the risk of mortality would be the same for people who have been obese for 1 year and those obese for 20 years. We hypothesize that in addition to the intensity of obesity, the duration of obesity is also a risk factor for mortality. Studies estimating the risk of mortality, by only considering the intensity of obesity, might underestimate the adverse effect of obesity. With an earlier age of onset of obesity, and, consequently, a longer duration of obesity, increasingly common in the community, estimates of this relationship are essential for accurate determination of the health burden associated with obesity, including the consequences for health system planning and estimating future life expectancy.[7]

There are a number of pathways through which an increasing duration of obesity might increase mortality risk, independent of the level of BMI achieved. Longer exposure to obesity might be expected to lead to a longer exposure to endogenous production of reactive oxygen species and oxidative DNA damage, alterations in carcinogen-metabolizing enzymes, alteration in endogenous hormone metabolism[8] and partial exhaustion of beta cells, with the resultant insulinopenia causing depressed glucose oxidation and impaired glucose tolerance.[9–11] Consequently, any association between duration of obesity and mortality might be expected to be partially explained by intermediate variables in the causal pathway to mortality such as blood pressure, serum cholesterol and serum glucose, with a longer duration of obesity potentially linked to an increased risk of chronic diseases[12] such as diabetes,[10,13,14] cardiovascular disease (CVD)[15] and cancer.

The objective of this study was to examine whether the number of years lived with obesity is associated with the risk of mortality (all-cause mortality and mortality due to CVDs, cancer and other causes) and whether the association is independent of the severity of BMI. The second objective was to examine to what extent any association is mediated by biological intermediate variables[4,16] (i.e. blood pressure, serum cholesterol and blood glucose) and by incident chronic disease (diabetes, CVD and cancer) during the study follow-up. We investigated these objectives using a long-term prospective longitudinal study where BMI, mortality data and other covariates were measured regularly in 24 biennial examinations, spanning 48 years[17] using dynamic survival models[18] of the extended Cox model[19] to capture the time-varying relationship.

Research design and methods

Data source

We used data from the original cohort study of the Framingham Heart Study (FHS).[20] This cohort study followed up 5209 participants (aged 28–62 years at the time of enrolment) for ~48 years from 1948 with examinations at 2-yearly intervals. The current study included only participants who were free from pre-existing diseases of diabetes, cardiovascular diseases and cancer at baseline ($n = 5036$).

Measurement of variables

In the FHS, body weight, height, demographics, health behaviours, physiological covariate variables and the occurrence of certain chronic diseases were measured regularly, as has been described in detail previously.[17] A participant was considered obese if their BMI was $>30\,kg/m^2$. A number of demographic and health behaviour variables were included in the analysis, including age, educational level, country of birth, marital status, smoking status, number of cigarettes smoked per day (for those who smoked), alcohol consumption and physical activity. Methods of measurement of these variables have been described in detail elsewhere.[14,21,22]

Chronic diseases that were regularly measured and included in the analysis are CVD, diabetes and cancer. A panel of three physicians reviewed each cardiovascular event according to pre-established criteria. The FHS defines CVD as a composite of Coronary Heart Disease (coronary death, myocardial infarction, coronary insufficiency and angina), cerebrovascular events (including ischaemic stroke, haemorrhagic stoke and transient ischaemic attack), peripheral artery disease (intermittent claudication) and heart failure.[21] Details regarding the methods of disease measurement and laboratory analysis have been described elsewhere.[22] Each examination included CVD assessment, 12-lead electrocardiogram and blood testing. A participant was defined as having type-2 diabetes if the participant had taken insulin and/or an oral hypoglycaemic agent or if the participant's fasting plasma glucose was >200 mg/dl. For cancer, the initial

record was later microscopically confirmed or clinically diagnosed.

Measurement of the duration of obesity

For each participant, the cumulative duration of obesity at each examination was calculated. Duration of obesity was only calculated for those individuals with at least two consecutive occurrences of obesity (which implies at least 2 years of being continuously obese), to account for potential misclassification of body weight, either due to measurement error or due to fluctuations between the borderline of the 'overweight' BMI category and the 'obese' category. For those individuals without two consecutive obesity occurrences, duration was considered to be zero at all examinations. For those individuals with two consecutive obesity occurrences, the beginning of their obesity interval was defined as 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 (Table 1). Using this definition, individuals could have multiple periods of obesity duration during follow-up. The cumulative duration of obesity at each examination was calculated as the sum of these periods of obesity prior to that examination.[14]

Age of onset of obesity was calculated as age at the first onset of obesity. For those who were obese at the baseline, the age of onset was estimated from age at the baseline minus the average of age of onset of obesity from those who are not obese at baseline.

Time to event (mortality)

The outcomes of interest were all-cause, CVD, cancer and other-cause mortality. All deaths were adjudicated by a panel of three investigators using previously described criteria.[22] Information on cause of death was obtained from death certificates or hospital admission or medical records or information from family members. CVD was identified as the cause of death if any of the following conditions were responsible for the death: coronary heart disease, intermittent claudication, congestive heart failure, stroke or transient ischaemic attack. Time to event (survival time) was calculated in days from examination 1 (baseline) to survival date, which was either date of death, loss to follow-up or end of follow-up at examination 24.

Table 1 Illustration of the method used to identify the start and endpoints of obesity duration and the consequent calculation of the cumulative duration of obesity in seven hypothetical subjects

Participants	Start time(s) of obesity	End times(s) of obesity		Examinations (exam 1–exam 24)																							
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
A	Examination 1	Examination 24	SOB	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
			CYO	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
B	Examination 9	Examination 24	SOB	2	2	2	2	2	2	2	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
			CYO	0	0	0	0	0	0	0	0	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
C	Examination 4	Examination 14	SOB	2	2	2	3	3	3	3	3	3	3	3	3	3	3										
			CYO	0	0	0	0	2	4	6	8	10	12	14	16	18	20										
D	Examination 1	Examination 18	SOB	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	2	2				
			CYO	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	34	34				
E	Examination 12	Examination 23	SOB	2	2	2	2	2	3	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	2
			CYO	0	0	0	0	0	0	0	0	0	0	0	0	2	4	6	8	10	12	14	16	18	20	22	22
F	Examination 4	Examination 6	SOB	2	2	2	3	3	3	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	Examination 9	Examination 24	CYO	0	0	0	0	2	4	4	4	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
G	Examination 15	Examination 16	SOB	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	2	2	2	2	2	2		
			CYO	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	2	2	2	2	2		

Note: SOB = the severity of obesity; 3 = indicates the subject was obese; 2 = overweight; 1 = normal weight; CYO = cumulative years of obesity duration by examinations; Highlighted values indicate the subject with obesity and values of COY.

Subjects A, B and F were still alive at the end of study. Subject C had died or was censored before examination 15; subjects D and G had died or were censored before examinations 21 and 23, respectively.

The obesity interval for participant C begins at the 4th examination and ends at the 14th, their last examination, a total of 20 years. For participant E, the starting point was at examination 12, not at 6 since this participant was not obese at examination 7. In the case of participant F, the subject has two starting and ending times for the duration of obesity according to our definition. The first starting point was at examination 4 and the second starting point at examination 9. The total duration of obesity across the entire period of follow-up was the sum of these periods of obesity. In the analysis, the duration of obesity was considered to be a time-varying variable with values at a given examination given by the cumulative sum of the duration of obesity to that examination. For example, for individual C in Table 1, their obesity cumulative duration at examination 5 was 2 years, at examination 10 was 12 years and at examination 14 was 20 years.

Missing values and imputation

In the FHS, most variables were measured at each of the 24 examinations. However, some variables are missing. There are two different circumstances under which variables may be missing. The first is for those covariates that were not collected at every examination. For example, blood glucose was not measured at 3 examinations (5, 7 and 11), current smoking status was not recorded at 4 examinations (2, 3, 6 and 17), cholesterol was not measured at 7 examinations (11, 12, 17–20 and 22), alcohol consumption was measured only in 8 examinations (2, 4, 7, 19 and 20–23) and physical activity was measured only at 4 examinations (4, 11, 12 and 19). These missing covariates are not missing at random and in our analysis the missing value was imputed by using the value from the nearest examination. In this situation, an analysis based on multiple imputations, as suggested by Spratt *et al*.,[23] can be biased. Instead, we rely on the observation that lifestyle behaviour does not usually change greatly over short time periods, so that the nearest measured value is likely to be a good guide to the missing value.

In the second situation, imputing the values for BMI, the missing values occur at random. Most of the participants (12%) only have one missing value of BMI. Five to six percent of participants have 2–3 missing values of BMI and ~3% have >4 missing values of BMI. In this case, missing values for BMI were imputed with a conditional mean estimated by a multiple predictive linear regression model using age at prior examination, sex and several transformations of the previous BMI data (BMI, log BMI, BMI squared and BMI as a categorical variable).

Data analysis

To model the duration of obesity and other time-dependent variables that change as a function of follow-up time from the baseline to the end of the study, a dynamic survival model[18] or time-dependent Cox regression model[19,24] was used. Most variables included in the model were time varying, except for age (at baseline), sex and ethnicity.

The duration of obesity was analysed both as a continuous and as a categorical variable. The duration of obesity was grouped into short, medium and long periods representing durations of 1–4.9, 5–14.9, 15–24.9 and $\geqslant$25 years of the study follow-up period. Hazard ratios (HRs) are presented, both as crude HRs and as multivariate-adjusted HRs, for the total population and separately by sex and smoking status. Four models of analysis were used to examine the effect of the covariates on the relationship between the duration of obesity and mortality. Model 1 adjusted for age at baseline; Model 2 adjusted for the demographical variables of sex, marital status, educational level and country of birth; Model 3 additionally adjusted for smoking status, alcohol consumption and current BMI and was considered the primary model; and Model 4 analysed the potential pathways of the effect of duration of obesity by additionally adjusting for the potential intermediate factors of blood pressure, serum cholesterol and blood glucose as well as incident CVD, diabetes or cancer during the study follow-up. It should be noted that not all these chronic diseases were adjusted for in all analysis. For example, CVD was not adjusted for when the analysis was focused on the outcome of CVD-cause mortality. Log-rank tests[25] for trend of survival function across categories of duration of obesity were performed. The analyses were performed using the Stata statistical software package version 10.0 (StataCorp, College Station, TX, USA).[26]

Sensitivity analyses

A sensitivity analysis was performed to examine whether the association between the duration of obesity and the risk of mortality 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 ($n = 2534$). The effect of defining duration using two consecutive occurrences of obesity was tested by analysing a simple count of examinations with obesity as a measure of duration. The effect of the duration of obesity prior to baseline was tested by excluding those who were obese at baseline and by estimating the duration of obesity prior to baseline for those obese at baseline using the average age of onset for those who were obese during the study follow-up but not obese at the baseline. A sensitivity analysis was also conducted to examine the effect of the choice of duration categories by also dividing the duration of obesity into five categories. Those who were never obese (zero duration) were allocated to the reference category and those with obesity were allocated to four equal ordered sub-categories of obesity duration.

Results

Of the 5036 eligible study participants, 75% were not obese in any of the 24 examinations. For those participants who had at least two examinations with recorded obesity during study follow-up ($n = 1244$), the average age of onset of obesity was ~50 years and the average total number of years lived with obesity was ~13 years (range 2–46 years). During 166 130 person-years of follow-up, 3797 (75%) participants died. Of these deaths, 39% were caused by CVD, 25% by cancer and 36% by other non-CVD and non-cancer causes (Table 2).

The incidence of mortality according to age at baseline, sex, smoking status and the duration of obesity is shown in Table 3. The incidence of mortality, both all-cause and cause-specific mortality, for those who were never obese (zero obesity duration) and for

Table 2 Study participant characteristics[a]

Variables and characteristic	*n* (%)	Mean (range)
Eligible sample	5036	
Population characteristics		
Age at baseline (years)		44 (28–62)
Sex: females	2799 (56)	
Country of birth: born in USA	4082 (81)	
Marital status at baseline		
Single	452 (9)	
Married	4269 (85)	
Widowed, divorced or separated	315 (6)	
Educational level at baseline		
Eighth grade or less	1374 (27)	
High school	2306 (46)	
College	752 (15)	
Postgraduate/school	604 (12)	
Health behaviour		
Smoking status at baseline: yes	2893 (58)	
Ever smoking during study follow-up	3178 (63)	
Smoking at baseline: number cigarettes per day		9.3 (1–60)
Physical activities score at exam 4		32 (25–83)
Alcohol drinking at exam 2; fluid ounces/month		14 (0–360)
Blood pressure		
Systolic blood pressure at baseline (mmHg)		132 (85–270)
Diastolic blood pressure at baseline (mmHg)		84 (52–150)
Hypertension at baseline: yes	843 (17)	
Biochemical characteristics		
Serum cholesterol at baseline (mg/100 ml)		226 (96–586)
Blood glucose at baseline (mg/100 ml)		80 (40–197)
Body weight characteristics		
BMI at baseline (kg/m^2)		25.5 (16.2–46.3)
Underweight (<18.5 kg/m^2)	65 (1)	
Normal weight (18.5–24.9 kg/m^2)	2405 (48)	
Overweight (25–29.9 kg/m^2)	1989 (40)	
Obese ($\geqslant 30$ kg/m^2)	567 (11)	
Total obesity duration (years)		3.8 (0–46)
0 year	3792 (75)	
1–4.9 years	253 (5)	
5–14.9 years	432 (9)	
15–24.9 years	302 (6)	
$\geqslant 25$ years	257 (5)	
Events – all-cause mortality from sample	3797 (75)	
CVD mortality	1481 (39)	
Cancer mortality	941 (25)	
Other mortality	1375 (36)	

[a]Participants were free from existing diabetes, cardiovascular diseases and cancer at study baseline.

Table 3 Incidence of mortality (events/1000 person-year) according to age at baseline, sex, smoking status and the number of years lived with obesity[a]

	Number of years lived with obesity														
	0 year			1–4.9 years			5–14.9 years			15–24.9 years			⩾25 years		
Causes of mortality	Events	PYFU[b]	Incidence	Events	PYFU[b]	Incidence	Events	PYFU[b]	Incidence	Events	PYFU[b]	Incidence	Events	PYFU[b]	Incidence
All-cause mortality	2904	136 756	21.24	179	7946	22.53	300	11 525	26.03	230	6071	37.89	208	3833	54.26
Sex															
Males	1462	57 262	25.53	89	3271	27.21	132	4307	30.65	89	2200	40.45	72	1287	55.93
Females	1,442	79 494	18.14	90	4675	19.25	168	7219	23.27	141	3871	36.43	136	2546	53.42
Smoking status															
Non-smokers	962	49 171	19.57	63	3462	18.20	137	5461	25.09	95	2883	32.95	109	1977	55.13
Smokers	1,942	87 585	22.17	116	4484	25.87	163	6064	26.88	135	3188	42.35	99	1856	53.34
CVD-cause mortality	1079	136 756	7.89	74	7946	9.31	139	11 525	12.06	109	6071	17.95	80	3833	20.87
Sex															
Males	624	57 262	10.90	39	3271	11.92	60	4307	13.93	45	2200	20.45	31	1287	24.08
Females	455	79 494	5.72	35	4675	7.49	79	7219	10.94	64	3871	16.53	49	2546	19.25
Smoking status															
Non-smokers	365	49 171	7.42	21	3462	6.07	67	5461	12.27	42	2883	14.57	45	1977	22.76
Smokers	714	87 585	8.15	53	4484	11.82	72	6064	11.87	67	3188	21.02	35	1856	18.86
Cancer-cause mortality	747	136 756	5.46	36	7946	4.53	66	11 525	5.73	51	6071	8.40	41	3833	10.70
Sex															
Males	387	57 262	6.76	20	3271	6.12	34	4307	7.89	15	2200	6.82	16	1287	12.43
Females	360	79 494	4.53	16	4675	3.42	32	7219	4.43	36	3871	9.30	25	2546	9.82
Smoking status															
Non-smokers	215	49 171	4.37	9	3462	2.60	20	5461	3.66	22	2883	7.63	13	1977	6.58
Smokers	532	87 585	6.07	27	4484	6.02	46	6064	7.59	29	3188	9.10	28	1856	15.08
Other-causes mortality	1059	136 756	7.74	68	7946	8.56	93	11 525	8.07	69	6071	11.37	86	3833	22.44
Sex															
Males	440	57 262	7.68	30	3271	9.17	38	4307	8.82	29	2200	13.18	25	1287	19.42
Females	619	79 494	7.79	38	4675	8.13	55	7219	7.62	40	3871	10.33	61	2546	23.96
Smoking status															
Non-smokers	377	49 171	7.67	33	3462	9.53	49	5461	8.97	31	2883	10.75	50	1977	25.29
Smokers	682	87 585	7.79	35	4484	7.81	44	6064	7.26	38	3188	11.92	36	1856	19.39

[a]The same person can be represented in multiple duration categories as the results refer to the full follow-up period.
[b]PYFU = person-years of follow-up.

Table 4 Time-varying Cox regression analysis of the association between categories of the duration of obesity and all-cause, CVD, cancer and other-cause mortality[a]

Causes of mortality	Obesity duration categories	*n*(events):PYFU	Models			
			Model 1	Model 2	Model 3[b]	Model 4
All-cause	0 years	4525 (2904):136 756	1	1	1	1
	1–4.9 years	1244 (179):7946	1.06 (0.91–1.23)	1.05 (0.91–1.22)	1.51 (1.27–1.79)	1.28 (1.07–1.54)
	5–14.9 years	999 (300):11 525	1.16 (1.05–1.29)	1.22 (1.10–1.35)	1.94 (1.71–2.20)	1.72 (1.50–1.98)
	15–24.9 years	609 (230):6071	1.29 (1.13–1.48)	1.33 (1.17–1.51)	2.25 (1.89–2.67)	1.88 (1.58–2.24)
	⩾25 years	314 (208):3833	1.25 (1.08-1.45)	1.31 (1.13–1.51)	2.52 (2.08–3.06)	2.12 (1.75–2.57)
CVD-cause	0 years	4525 (1079):136 756	1	1	1	1
	1–4.9 years	1244 (74):7946	1.23 (0.97–1.57)	1.25 (0.98–1.59)	1.68 (1.29–2.18)	1.35 (1.04–1.74)
	5–14.9 years	999 (139):11 525	1.40 (1.18–1.66)	1.51 (1.27–1.79)	2.18 (1.78–2.68)	1.70 (1.39–2.08)
	15–24.9 years	609 (109):6071	1.65 (1.36–2.00)	1.75 (1.45–2.12)	2.53 (1.99–3.23)	1.84 (1.45–2.32)
	⩾25 years	314 (80):3833	1.52 (1.20–1.92)	1.66 (1.32–2.10)	2.76 (2.08–3.68)	1.72 (1.30–2.27)
Cancer-cause	0 years	4525 (747):136 756	1	1	1	1
	1–4.9 years	1244 (36):7946	0.84 (0.60–1.18)	0.82 (0.59–1.15)	1.13 (0.79–1.61)	0.86 (0.59–1.26)
	5–14.9 years	999 (66):11 525	0.98 (0.76–1.26)	0.99 (0.77–1.27)	1.41 (1.06–1.88)	1.37 (1.04–1.80)
	15–24.9 years	609 (51):6071	1.10 (0.83–1.47)	1.10 (0.83–1.47)	1.69 (1.20–2.39)	1.50 (1.06–2.12)
	⩾25 years	314 (41):3833	1.00 (0.72–1.37)	1.00 (0.72–1.39)	1.50 (1.00–2.24)	1.53 (1.03–2.26)
Other-causes	0 years	4525 (1059):136 756	1	1	1	1
	1–4.9 years	1244 (68):7946	1.04 (0.82–1.32)	1.05 (0.83–1.32)	1.64 (1.26–2.13)	1.64 (1.26–2.14)
	5–14.9 years	999 (93):11 525	1.06 (0.88–1.29)	1.11 (0.92–1.35)	2.06 (1.65–2.58)	2.03 (1.62–2.53)
	15–24.9 years	609 (69):6071	1.09 (0.85–1.40)	1.11 (0.87–1.42)	2.28 (1.67–3.13)	2.23 (1.63–3.05)
	⩾25 years	314 (86):3833	1.21 (0.97–1.53)	1.25 (0.99–1.57)	3.15 (2.33–4.26)	2.95 (2.18–4.01)

[a]The same person can be represented in multiple duration categories as the results refer to the full follow-up period.
[b]Primary model.
PYFU = person-years of follow-up.
Model 1 adjusted for age at baseline.
Model 2 adjusted for age at baseline, sex, marital status, educational level and country of birth.
Model 3 adjusted for sex, age at baseline, marital status, educational level, country of birth, time-varying smoking, alcohol consumption and BMI.
Model 4 adjusted for sex, age at baseline, marital status, educational level, country of birth, time-varying smoking, alcohol consumption, physical activity, BMI, blood pressure, serum cholesterol, time-dependent chronic diseases during study follow-up (type-2 diabetes, CVD and cancer for all-cause and other-cause mortality; type-2 diabetes and cancer for CVD-cause mortality; type-2 diabetes and CVD for cancer-cause mortality).

those who were obese for <5 years was relatively similar, but the incidence increased significantly with increasing duration of obesity, except for cancer-cause mortality which only increased marginally.

Table 4 provides HRs for the association between duration of obesity and mortality, based on the different models adjusted for covariates. HRs for all-cause mortality and CVD, cancer and other-cause mortality increased slightly after adjusting for age at baseline (Model 1) and adjusting for socio-demographic covariates (Model 2). However, HRs increased substantially after adjusting for BMI, smoking and alcohol (Model 3). The effect was mainly due to the additional adjustment for BMI. In general, for those who were obese for between 15 and 25 years of the study follow-up period, the risk of mortality was more than double compared with those who were never obese. The risk of all-cause, CVD-cause and other-causes (non-CVD and non-cancer mortality) was 3-fold higher for those who were obese for >25 years. Adjusted for time-varying physiological covariates and diseases during follow-up (Model 4), the HRs dropped slightly. Log-rank tests for linear association of the duration of obesity with the risk of all-cause mortality, CVD-cause, cancer-cause and other-cause mortality were strongly positive with *P*-values <0.001.

Table 5 shows the HRs of mortality for each additional 2 years lived with obesity. As in the previous analysis, HRs changed only slightly after adjusting for the socio-demographic variables of sex, education and ethnicity. After adjusting for the health-related behaviour variables of smoking, alcohol consumption and current BMI (Model 3), the HRs increased to 1.06 [95% confidence interval (CI) 1.05–1.07] for all-cause mortality, 1.07 (95% CI 1.05–1.08) for CVD-cause mortality both at *P*-value 0.0001, 1.03 (95% CI 1.01–1.05) for cancer-cause mortality at *P*-value 0.005 and 1.07 (95% CI 1.05–1.09) at *P*-value 0.0001 for

Table 5 Time-varying Cox regression analysis of the association between the number of years lived with obesity and the risk of all-cause, CVD, cancer and other-cause mortality[a]

		Hazard ratios (95% CI)			
	***n* (death): PYFU**	Model 1	Model 2	Model 3[b]	Model 4
All-causes mortality					
All sample	5036 (3821):166 130	1.02 (1.01–1.03)	1.02 (1.01–1.03)	1.06 (1.05–1.07)	1.05 (1.04–1.06)
Sex					
Males	2237 (1844):68 326	1.02 (1.01–1.03)	1.02 (1.01–1.03)	1.06 (1.05–1.08)	1.06 (1.04–1.08)
Females	2799 (1977):97 804	1.02 (1.01–1.03)	1.02 (1.01-1.03)	1.06 (1.04–1.07)	1.05 (1.04–1.07)
Smoking status					
Non-smokers	1858 (1366):62 953	1.03 (1.02–1.04)	1.03 (1.02–1.04)	1.06 (1.05–1.07)	1.05 (1.04–1.07)
Smokers	3178 (2455):103 177	1.02 (1.01–1.03)	1.02 (1.01–1.03)	1.06 (1.05–1.08)	1.05 (1.03–1.06)
CVD-cause mortality					
All sample	5036 (1481):166 130	1.04 (1.03–1.05)	1.04 (1.03–1.05)	1.07 (1.05–1.08)	1.04 (1.03–1.06)
Sex					
Males	2237 (799):68 326	1.04 (1.02–1.05)	1.04 (1.02–1.05)	1.07 (1.04–1.09)	1.05 (1.03–1.08)
Females	2799 (682):97 804	1.05 (1.03-1.06)	1.04 (1.03–1.06)	1.07 (1.04–1.09)	1.06 (1.04–1.08)
Smoking status					
Non-smokers	1858 (540):62 953	1.04 (1.03–1.06)	1.05 (1.03–1.06)	1.07 (1.04–1.09)	1.06 (1.04–1.08)
Smokers	3178 (941):103 177	1.04 (1.02–1.06)	1.04 (1.03–1.06)	1.07 (1.05–1.09)	1.06 (1.04–1.08)
Cancer-cause mortality					
All sample	5036 (941):166 130	1.00 (0.99–1.02)	1.00 (0.99–1.02)	1.03 (1.01–1.05)	1.03 (1.01–1.05)
Sex					
Males	2237 (472):68 326	1.00 (0.97–1.02)	0.99 (0.97–1.02)	1.04 (1.00–1.07)	1.04 (1.01–1.08)
Females	2799 (469):97 804	1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.03 (1.00–1.06)	1.02 (0.99–1.05)
Smoking status					
Non-smokers	1858 (279):62 953	1.00 (0.98–1.03)	1.01 (0.98–1.03)	1.03 (0.99–1.06)	1.02 (0.99–1.06)
Smokers	3178 (662):103 177	1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.04 (1.02–1.07)	1.04 (1.01–1.07)
All-cause mortality					
All sample	5036 (1375):166 130	1.01 (1.00–1.02)	1.01 (1.00–1.02)	1.07 (1.05–1.09)	1.07 (1.05–1.08)
Sex					
Males	2237 (562):68 326	1.02 (1.00–1.04)	1.02 (1.00–1.04)	1.08 (1.06–1.11)	1.07 (1.05–1.10)
Females	2799 (813):97 804	1.01 (0.99–1.02)	1.01 (0.99–1.02)	1.06 (1.04–1.09)	1.07 (1.04–1.09)
Smoking status					
Non-smokers	1858 (540):62 953	1.03 (1.01–1.04)	1.03 (1.01–1.04)	1.07 (1.05–1.09)	1.07 (1.05–1.09)
Smokers	3178 (835):103 177	1.00 (0.99–1.02)	1.00 (0.98–1.02)	1.07 (1.05–1.10)	1.07 (1.04–1.09)

[a]HRs refer to the increased mortality risk associated with each additional 2 years of obesity duration.
[b]Primary model.
Model 1 adjusted for age at baseline.
Model 2 adjusted for age at baseline, sex, marital status, educational level and country of birth.
Model 3 adjusted for sex, age at baseline, marital status, educational level, country of birth, time-varying smoking, alcohol consumption and BMI.
Model 4 adjusted for sex, age at baseline, marital status, educational level, country of birth, time-varying smoking, alcohol consumption, physical activity, BMI, blood pressure, serum cholesterol, time-dependent chronic diseases during study follow-up (type-2 diabetes, CVD and cancer for all-cause and other-cause mortality; type-2 diabetes and cancer for CVD-cause mortality; type-2 diabetes and CVD for cancer-cause mortality).
PYFU = person-years of follow-up.

other-cause mortality per additional 2 years of obesity duration. Adjusting for the biological intermediate variables of blood pressure, cholesterol, blood sugar level, physical activity and the chronic diseases, type-2 diabetes, CVD and cancer, the HR dropped from 1.06 to 1.05 for all-cause mortality and from 1.07 to 1.04 for CVD mortality. For cancer-cause mortality and other-cause mortality, the HRs remained unchanged per 2-year increase in the duration of obesity. In addition, no interaction was found between smoking status and sex for all-cause mortality, CVD, cancer and other-cause mortality, with *P*-values of 0.123, 0.079, 0.216 and 0.518, respectively. In a further model, age of onset was added to Model 3. This led to little change in the association between duration of obesity and mortality; an increase in the HR for mortality associated with duration of obesity to 1.10 (95% CI 1.08–1.12) for all-cause mortality, 1.13 (95% CI 1.09–1.16) for CVD mortality and 1.08 (95% CI 1.04–1.11) for cancer mortality.

The sensitivity analysis showed that the associations between the duration of obesity and risk of all-cause mortality and cause-specific mortality were not significantly different between a complete case analysis and the analysis using imputed missing values. The analysis of only the participants who had no missing values of BMI (2534 participants) during follow-up found an adjusted HR (Model 3) of 1.06 (95% CI 1.05–1.08), 1.06 (95% CI 1.03–1.08), 1.04 (95% CI 1.02–1.07) and 1.08 (95% CI 1.06–1.10), all with $P < 0.0001$, per 2-year obesity duration for all-cause mortality, CVD-cause mortality, cancer-cause mortality and other-cause mortality, respectively. A sensitivity analysis of the effect of the duration of obesity definition also demonstrated a similar finding for duration defined as the total number of examinations with obesity (data not shown). Imputing duration of obesity prior to baseline for those who were obese at the baseline did not affect the results (data not shown). Exclusion of those who were obese at baseline also produced similar results, with an HR for all-cause mortality of 1.06 (95% CI 1.04–1.08) per 2-year increase in duration of obesity; and HRs for all-cause mortality for those with obesity for 1–4.9, 5–14.9, 15–24.9 and $\geqslant$25 years compared with those who had zero duration of obesity of 1.56 (95% CI 1.28–1.89), 1.66 (95% CI 1.41–1.96), 2.08 (95% CI 1.67–2.59) and 2.11 (95% CI 1.48–2.98), respectively. A sensitivity analysis comparing the dose–response relationship between the defined categories of the duration of obesity with five categories showed a similar result (data not shown).

Discussion

This study has found that an increasing duration of obesity is significantly associated with an increased risk of mortality. The association remained significant after adjusting for current BMI, age, smoking status, CVD, cancer, diabetes and other confounding variables. The association was particularly strong for mortality from CVD and other causes (non-CVD and non-cancer). After adjustment for demographical variables and current BMI, even for short periods of obesity, the risk of mortality appeared to be increased compared with those who were never obese (zero duration). For those who had a medium number of years lived with obesity (5–14.9 years), the risk of mortality more than doubled and the risk almost tripled for those with the longest duration of obesity ($\geqslant$15 years) observed within the study. A dose–response relationship was clear for all endpoints: all-cause, CVD, cancer and other-cause mortality, but was less pronounced for cancer mortality compared with the other three outcomes. For every additional 2 years lived with obesity, the risk of mortality increased by ~6–7%. For mortality from cancer, the risk increased by ~3%.

Although the relationship between obesity and mortality risk has been clearly described,[1–4] there has been no prior analysis of the relationship between increasing duration of obesity and mortality. There have been a few descriptions of the relationship between an increasing duration of obesity and risk of diabetes, CVD, decreased quality of life and increased functional limitations,[13–15] suggesting a range of potential mechanisms for the mortality risk described here. However, we found that although adjustment for the potential intermediate factors such as incident CVD and diabetes, and biomedical risk factors, decreased the risk of mortality associated with increasing obesity duration, a strong relationship remained. This suggests that the relationship between the duration of obesity and mortality is not fully mediated by chronic diseases. The relationship was also not explained by age of onset of obesity, with the HR increasing after adjustment for age of onset.

In this study, we observed a strengthening of the association between the duration of obesity and the risks of mortality after adjustment for current BMI. We hypothesize that this might relate to the nature of the relationship between current BMI and mortality itself. Both at older ages and overall, current BMI itself was associated with a reduced risk of mortality. The adjusted HRs for current BMI (per unit kg/m^2) were 0.98 (95% CI 0.96–0.98), 0.96 (95% CI 0.95–0.98) and 0.98 (95% CI 0.96–0.99), all at *P*-value 0.0001 for overall mortality, CVD and cancer mortality, respectively. This is in contrast to the outcome for type-2 diabetes. A previous study revealed that the association between the duration of obesity and the risk of type-2 diabetes decreased after adjustment for current BMI.[14]

Our study is novel in that it assesses the duration of obesity, taking into account body weight changes over a lifetime that were measured at relatively short intervals, every 2 years, up to 48 years. Most covariates

were analysed as time-varying variables to capture changes in the values over time and we adjusted for a large number of potential confounding variables, including smoking status, which often confound the association between obesity and mortality.[4] The effect of current body weight, intermediate physiological variables and chronic diseases were also explored.

The key strength of this study, its long follow-up, is also its limitation. The original Framingham cohort study began in 1948 and the prevalence rates of obesity and type-2 diabetes were relatively low at that time. The prevalence of obesity in the 1950s was below 10%.[27] It could be argued that the results of this study might not reflect the current population, where the prevalence of obesity is markedly >50 years ago. In 2008, the prevalence of obesity among adults in USA was ~30%.[28] Yet, the contemporary obesity epidemic is also characterized by a much earlier onset of obesity, which should result in even longer exposure time when today's obese generation of children reach the age of our studied cohort. In our study, the average age of onset of obesity was ~50 years and the average number of years lived with obesity was ~13 years; however, today the average age of onset of obesity is likely to be >10 years earlier than in previous decades.[7] Whereas a number of reports have suggested that the relationship between obesity and mortality has decreased recently,[29] younger generations might experience a shortened overall life expectancy compared with the previous generation due to the overriding impact of obesity.[30] Another limitation of the data is that 21.3% of participants were missing a measure of BMI on at least one examination. However, we did not see varying results whether we included only participants with complete information for BMI or whether we imputed BMI.

Another potential limitation of this study was that the duration of obesity prior to baseline was unknown. Therefore, we did not know the exact duration of obesity for those who were obese at baseline. However, using Cox analysis, our model has the implicit assumption that each extra unit increase in the duration of obesity is associated with an equal increase in mortality risk regardless of how long a participant has been obese. The results of sensitivity analyses with and without those obese at baseline supported this assumption, as the results did not differ greatly.

Our study demonstrates that for every additional 10 years lived with obesity, the risks of all-cause mortality, CVD and cancer mortality more than doubled, implying that the risk of mortality associated with current obesity in adults might be significantly higher than in previous decades. This study confirmed that prior analyses examining the association between obesity and the risk of mortality by only considering the severity of obesity and ignoring the duration of obesity might have underestimated the adverse effects of current obesity. Therefore, it is suggested that in future studies the duration of obesity needs to be taken into account in estimating the future life expectancy and burden of disease for the general population.

Future research using contemporary, regularly measured body weight in a long-term cohort study is therefore necessary. We also recommend future analysis of an overall measure combining both the degree and duration of overweight and obesity, for example, estimating the risk of mortality for every additional 'obese-year' or 'BMI-year', analogous to the 'pack-years' concept used for smoking.[31]

Conclusion

This analysis shows that the duration of obesity is a strong predictor of mortality, independent of the actual level of BMI. As the onset of obesity occurs earlier and the number years lived with obesity increases, the risk of mortality associated with adult obesity in contemporary populations is expected to increase compared with previous decades. Obesity prevention strategies, therefore, need an additional focus on delaying the onset of obesity. In addition, it is necessary to take the duration of obesity into consideration when estimating the future health burden associated with current obesity trends.

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Conflict of interest: None declared.

KEY MESSAGES

- The duration of obesity is a strong predictor of mortality, independent of the actual level of BMI.
- Obesity prevention strategies therefore need an additional focus on delaying the onset of obesity.
- In estimating the future health burden associated with current obesity trends, it is necessary to take the duration of obesity into consideration.

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Commentary: Obesity-years—a new metric to measure health effects of obesity

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Obesity is one of the greatest threats to global health in a generation. Its rapidly rising prevalence and association with chronic disease suggests that it may undo longevity gains in Western countries that were made by reducing smoking rates.[1] In 2009, the prevalence of obesity in US adults was 34%,[2] which could rise to 50% in 2030 if current rates do not change.[3] In places such as India and China, which have large populations undergoing rapid urbanization and 'Westernization' of lifestyles, the number of people predicted to become obese is correspondingly large despite a lower overall prevalence.[4]

Obesity is the most important risk factor for type 2 diabetes, and is also major risk factor for cardiovascular disease (CVD; heart attack and stroke).[5] An accumulation of excess fat leads to metabolic dysfunction including insulin resistance, increased blood lipids and secretion of inflammatory factors.[5] Adipose tissue is also a potent source of hormones, which may elevate the risk of some cancers.[6] Consequently, individuals who are obese suffer from multiple comorbidities, and have a lower life expectancy—even after controlling for lifestyle differences associated with being obese.

Although obesity is associated with a substantially increased risk of chronic disease and mortality, the absolute risk per year is quite small. However, this risk compounds with time, making it more probable that the consequences of obesity will manifest over a longer duration of obesity. In a recent pooled analysis of 19 prospective cohort studies containing 1.46 million White adults, the relative risk of all-cause mortality comparing participants who were obese [body mass index (BMI) $\geqslant 30\,kg/m^2$] vs normal weight ($BMI < 25\,kg/m^2$) was the highest among those who were the youngest at baseline or with the greatest amount of follow-up.[7] This suggests that the relationship between obesity and mortality strengthens over time. However, the studies in this analysis relied on a single baseline measure of height and weight, and did not specifically assess the amount of time that participants were obese.

In this issue, Asnawi *et al*.[8] analysed data from 5036 participants enrolled in the Framingham Cohort Study. This included over 48 years of follow-up (1948–96), and 3797 deaths. BMI was determined every 2 years from repeated measures of height and weight. The authors used an algorithm to calculate the cumulative duration of obesity, which allowed for multiple periods of obesity and non-obesity. This assumes that obesity has a persistent biologic effect, which carries over to the next time period. A