BMI at Age 17 Years and Diabetes Mortality in Midlife: A Nationwide Cohort of 2.3 Million Adolescents

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OBJECTIVE

The sequelae of increasing childhood obesity are of major concern. We assessed the association of BMI in late adolescence with diabetes mortality in midlife.

RESEARCH DESIGN AND METHODS

The BMI values of 2,294,139 Israeli adolescents (age 17.4 ± 0.3 years), measured between 1967 and 2010, were grouped by U.S. Centers for Disease Control and Prevention age/sex percentiles and by ordinary BMI values. The outcome, obtained by linkage with official national records, was death attributed to diabetes mellitus (DM) as the underlying cause. Cox proportional hazards models were applied.

RESULTS

During 42,297,007 person-years of follow-up (median, 18.4 years; range <1–44 years) there were 481 deaths from DM (mean age at death, 50.6 ± 6.6 years). There was a graded increase in DM mortality evident from the 25th to the 49th BMI percentile group onward and from a BMI of 20.0–22.4 kg/m^2 onward. Overweight (85th to 94th percentiles) and obesity (the 95th percentile or higher), compared with the 5th to 24th percentiles, were associated with hazard ratios (HRs) of 8.0 (95% CI 5.7–11.3) and 17.2 (11.9–24.8) for DM mortality, respectively, after adjusting for sex, age, birth year, height, and sociodemographic variables. The HR for the 50th through 74th percentiles was 1.6 (95% CI 1.1–2.3). Findings persisted in a series of sensitivity analyses. The estimated population-attributable fraction for DM mortality, 31.2% (95% CI 26.6–36.1%) for the 1967–1977 prevalence of overweight and obesity at age 17, rose to a projected 52.1% (95% CI 46.4–57.4%) for the 2012–2014 prevalence.

CONCLUSIONS

Adolescent BMI, including values within the currently accepted "normal" range, strongly predicts DM mortality up to the seventh decade. The increasing prevalence of childhood and adolescent overweight and obesity points to a substantially increased future adult DM burden.

The increasing global prevalence of diabetes mellitus (DM) (1) has been accompanied by a substantial increase in the burden of mortality. It is estimated that between 1990 and 2010, the total number of deaths attributable to coronary heart disease increased by 25%, whereas DM mortality nearly doubled (2), with predictions for a further increase (3).

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The most important modifiable risk factor for diabetes morbidity and mortality is excessive weight (4,5). While there is increasingly compelling evidence for the contribution of obesity during childhood and adolescence to future cardiometabolic morbidity (6–9) and mortality (10–13), less is known about the contribution of BMI in the so-called normal range to diabetes mortality. This question is of importance, particularly given the global increase in BMI (13,14) and recent evidence from this cohort showing that adolescent BMI already at the 50th percentile (and $\geq$20 kg/m^2) is associated with substantially increased risk for future cardiovascular mortality, excess noncardiovascular mortality, and total mortality (15,16). In light of the increase in childhood and adolescent obesity and the growing contribution of DM to total mortality (2), determining the fraction of DM mortality attributable to excessive weight in adolescence is a public health interest.

The goals of this study were to determine the association across the full range of adolescent BMI with the risk for DM mortality in midlife and to estimate the population burden of DM mortality attributable to adolescent BMI and its secular increase.

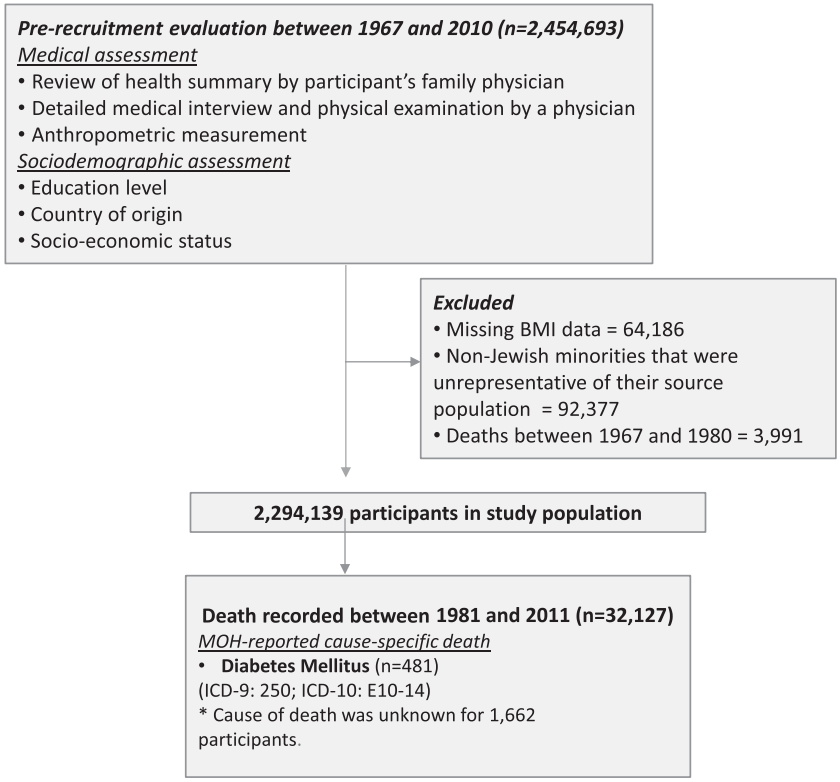

Figure 1—Schematic illustration of the study design and outcomes. Note that there were 3,991 deaths among the 512,699 participants who were assessed between 1967 and 1980 and for which underlying cause of death per the ICD was not available. Nearly 80% of these deaths (n = 3,188) were classified as military trauma. MOH, Israel Ministry of Health.

RESEARCH DESIGN AND METHODS

Study Population

At the age of 17, service-eligible Israeli citizens are called up for a medical examination to assess their suitability for military service. Figure 1 portrays the examination process and study design. The study sample included all Israeli adolescents (n = 2,454,693) who were evaluated at ages 16–19 years between 1 January 1967 and 31 December 2010. Excluded from this cohort were 64,186 examinees with missing BMI data and 92,377 examinees from non-Jewish minorities who were nonrepresentative of their source population (all Israeli Arabs and Druze women are exempt from military service), leaving 2,294,139 for analysis. Orthodox and ultraorthodox Jewish women are not obligated to serve, may not be examined, and are underrepresented in this cohort, whereas the sample of Jewish men can be regarded as nationally representative. The institutional review board of the Israel Defense Forces Medical Corps approved this study.

Study Outcome and Documentation of the Cause of Death

The primary outcome was death attributed to DM (see Fig. 1 for International Classification of Diseases [ICD] codes). Using the participants' national identification numbers, we linked the underlying cause of death, officially coded from death notifications by the Israel Central Bureau of Statistics according to the ICD-9 (1981–1997) and ICD-10 (1998–2011) classifications, to the database. Because cause of death was available to us only from 1981 onward, the follow-up of the main analysis commenced in 1981 and ceased on the date of death from any cause or 30 June 2011, whichever came first.

Data Collection and Study Variables

Trained medical personnel measured height using a stadiometer and weight using a beam balance at baseline. Examinees wore only underwear. BMI was calculated (weight in kilograms divided by height in meters squared). Military physicians who reviewed the participants' medical records and provided diagnostic codes where applicable conducted the medical examination. Data regarding education, residential socioeconomic status (SES), and country of origin are routinely recorded.

Age at examination, year of birth, and height were treated as continuous variables. Education was divided into four groups: $\leq$9, 10, 11, or 12 years of formal schooling. Residential SES, based on locality of residence at the time of examination, was coded on a 1 to 10 scale (17) and was grouped into high (8–10), medium (5–7) and low (1–4) categories. Country of origin (classified by the examinee's father's country of birth [or the grandfather's if the father was born in Israel]) and country of birth were classified as previously reported (16). BMI was classified according to the sex-specific U.S. Centers for Disease Control and Prevention (CDC) percentiles for age (by month) (18), as shown in Table 1, and in kilograms per meters squared by World Health Organization groupings. Table 1 displays the following subgroups: BMI $<$ 5th (underweight), 5th $\leq$ BMI $<$ 25th, 25th $\leq$ BMI $<$ 50th, 50th $\leq$ BMI $<$ 75th, 75th $\leq$ BMI $<$ 85th, 85th $\leq$ BMI $<$ 95th (overweight), and BMI $\geq$ 95th (obese).

Table 1—Characteristics of the study cohort of 2,294,139 adolescents by U.S. CDC BMI percentile category at baseline

	BMI percentiles							
	<5th	5th–24th	25th–49th	50th–74th	75th–84th	85th–94th	≥95th	Total cohort
Age, years (mean ± SD)	17.4 ± 0.5	17.4 ± 0.5	17.3 ± 0.4	17.3 ± 0.4	17.3 ± 0.4	17.3 ± 0.4	17.3 ± 0.4	17.3 ± 0.4
Participants, *n* (% men)	150,288 (73)	471,384 (64)	599,823 (59)	576,249 (56)	215,705 (54)	194,689 (56)	86,001 (69)	2,294,139 (60)
BMI range (kg/m^2)								
Men	12.0–19.1	17.2–21.2	18.9–23.0	20.6–25.4	22.8–27.0	24.3–30.5	27.7–47.9	—
Women	12.0–17.8	16.9–19.8	18.8–21.7	20.6–24.4	23.0–26.4	24.8–31.6	29.3–47.6	—
Height, cm (mean ± SD)								
Men	173.1 ± 7.1	173.3 ± 6.8	173.4 ± 6.7	173.6 ± 6.8	173.8 ± 6.8	174.0 ± 6.9	174.1 ± 7.3	173.5 ± 6.9
Women	163.2 ± 6.5	162.5 ± 6.1	162.1 ± 6.0	161.8 ± 6.0	161.8 ± 6.1	161.8 ± 6.2	162.3 ± 6.4	162.1 ± 6.1
Completed high school education (%)	75	78	80	82	83	82	81	80
Low socioeconomic status (%)	26	25	24	24	24	25	27	24
Country of origin (%)								
Israel	5	6	6	6	6	6	7	6
Former U.S.S.R.	12	12	12	13	14	14	16	13
Asia	32	28	25	23	22	22	21	25
Africa	22	24	25	25	25	25	26	24
Europe	25	28	31	32	33	32	30	31
Ethiopia	4	2	1	<1	<1	<1	<1	1

Statistical Analysis

Person-year mortality rates were calculated. We computed Kaplan-Meier survival curves for the BMI percentile study groups, commencing in 1967. We used Cox proportional hazard models to estimate the unadjusted hazard ratios (HRs) and 95% CIs for the association of BMI and DM mortality, then we adjusted for birth year, age at examination, and sex (model 1). Covariates considered as possible confounders were added singly to model 1. All variables selected as potential confounders and included in the multivariable models showed significant associations ($P \leq 0.005$) with DM mortality (Supplementary Table 1) and with BMI (except for height). The assumption of the proportionality of the hazards was confirmed for all variables. We further analyzed the BMI-DM mortality association using BMI classified in kilograms per meters squared, given that more than 98% of growth is completed by age 17 (19). Cox regression spline models (SmoothHR and survival packages, R software version 3.2.2) were fit to estimate the BMI value associated with minimum DM mortality risk. We accounted for competing risks (PROC PHREG, SAS software version 9.4). Multiple imputation algorithms were applied for missing data on origin, education, and SES (1.4% of the cohort) (SAS Miner version 13.1).

We calculated the population-attributable risk percentage or fraction (PAF) of DM mortality for being overweight or obese (≥85th percentile), assuming a causal relation between adolescent obesity and DM mortality in adulthood: PAF = Pe × (HR-1)/[Pe × (HR − 1) + 1], where HR is the adjusted HR of the relationship between being overweight or obese (≥85th percentile) and DM-related death, and Pe is the prevalence of adolescent overweight or obesity (≥85th CDC percentile) in the cohort. PAF was calculated for the 1967–1977 period of examination (which produced 86.7% of the DM-related deaths) using the average Pe for that period. We applied the average Pe for the 2012–2014 period of examination to the HRs derived for the 1967–1977 examinees to obtain a projection of the PAF of future DM mortality that would reflect the increased adolescent obesity.

We performed a series of sensitivity analyses (see details in RESULTS). Between 1967 and 1980, 3,991 deaths were recorded. Data on the underlying cause of death for this period were not available to us, except for deaths that were classified as military-related trauma, to which 79.9% of deaths (*n* = 3,188) were attributed. In addition, the underlying cause was missing for 1,662 deaths (5.2%) between 1981 and 2011. Of these deaths, 60% occurred before the age of 40 years (*n* = 990), whereas only 6.7% (*n* = 32) of all DM-related deaths occurred before this age. We used SPSS version 21.0 to analyze the data, unless stated otherwise.

RESULTS

Table 1 displays the baseline characteristics of the study cohort. The majority of participants (86%) were examined at age 17 years (mean age was similar for both sexes, 17.3 ± 0.4 years). Most participants (85%) were born in Israel. There is considerable diversity in their countries of origin. Of the cohort, 75% completed a high school education, with the lowest prevalence evident among the underweight group. Lower residential SES was more prevalent among both the underweight and obese groups. Examinees of North African and former U.S.S.R. origins tended to be more overweight and obese, whereas those of Asian origin (mostly from Iraq, Iran, Syria, and Yemen) tended to have lower BMIs.

Table 2 presents the follow-up characteristics across the BMI percentile groups. The median follow-up (18.4 years [interquartile range 9.9–29.3]) was lower for those with a higher BMI, a consequence of the onset of increasing overweight and obesity in our cohort in the 1980s (16). During 42,297,007 person-years of follow-up there were 481 deaths attributed to DM from among all 32,127 deaths that were recorded in the cohort between 1981 and 2011. The proportion of all deaths attributed to DM

Table 2—Duration of follow-up, numbers of DM-related deaths, age at death, unadjusted incidence per 100,000 person-years, and unadjusted and adjusted Cox proportional hazards models by BMI percentile categories (*A*) and by BMI value (kg/m^2) (*B*) in 16- to 19-year-old examinees

A: BMI categories by U.S. CDC percentiles

	BMI percentiles							
	<5th	5th–24th	25th–49th	50th–74th	75th–84th	85th–94th	≥95th	Total
Participants, *n*	150,288	471,384	599,823	576,249	215,705	194,689	86,001	2,294,139
Median follow-up, years (IQR)	18.4 (10.4–28.5)	19.2 (10.7–29.8)	19.5 (10.6–30.5)	18.9 (10.0–29.9)	17.7 (9.1–28.3)	15.8 (8.0–25.5)	12.0 (6.0–20.5)	18.4 (9.9–29.3)
Cumulative follow-up, person-years	2,778,208	8,697,197	11,494,064	10,782,121	3,848,492	3,229,522	1,197,402	42,297,007
Deaths from DM, *n* (% men)	18 (89)	47 (100)	87 (93)	84 (83)	67 (87)	104 (88)	74 (93)	481 (90)
Age at death from DM, years (mean ± SD)	48.9 ± 8.6	50.6 ± 7.0	51.0 ± 6.7	51.4 ± 6.5	51.0 ± 6.2	49.7 ± 6.0	49.7 ± 6.6	50.5 ± 6.6
Crude incidence rate, events/10^5 person-years	0.647	0.524	0.756	0.779	1.740	3.220	6.180	1.137
HR								
Unadjusted	1.31	1 (reference)	1.41	1.48	3.51	7.11	17.53	
95% CI	0.76–2.26		0.99–2.01	1.04–2.12	2.42–5.10	5.04–10.04	12.16–25.26	
P	0.33		0.059	0.031	6.1×10^{-11}	1.0×10^{-27}	1.0×10^{-48}	
Model 1	1.32	1 (reference)	1.41	1.52	3.71	7.38	16.98	
95% CI	0.77–2.27		0.99–2.01	1.06–2.17	2.55–5.38	5.23–10.42	11.77–24.48	
P	0.32		0.055	0.021	5.9×10^{-12}	6.3×10^{-30}	5.2×10^{-52}	
Model 2	1.29	1 (reference)	1.46	1.64	4.09	8.02	17.17	
95% CI	0.75–2.23		1.02–2.08	1.14–2.34	2.81–5.95	5.66–11.34	11.87–24.83	
P	0.35		0.038	0.007	1.8×10^{-13}	6.8×10^{-32}	1.6×10^{-51}	

B: BMI categories by value (kg/m^2)

	BMI range (kg/m^2)						
	<17.5	17.5–19.9	20.0–22.4	22.5–24.9	25.0–27.4	27.5–29.9	≥30.0
Participants, *n* (% men)	121,263 (59)	658,122 (59)	796,094 (61)	415,906 (58)	168,714 (58)	70,709 (58)	63,331 (60)
Median follow-up (IQR)	17.4 (9.6–27.2)	19.0 (10.5–29.5)	19.4 (10.6–30.4)	18.4 (9.7–29.3)	16.6 (8.5–26.5)	14.6 (7.5–23.9)	11.7 (6.0–19.8)
Cumulative person-years, *n*	2,156,264	12,419,305	15,208,764	7,648,531	2,885,353	1,119,482	859,307
Cases, *n* (% men)	11 (82)	66 (97)	117 (90)	101 (88)	88 (91)	43 (81)	55 (91)
HR							
Unadjusted	1.06	1 (reference)	1.40	2.50	6.33	8.88	18.83
95% CI	0.56–2.01		1.03–1.89	1.84–3.42	4.60–8.71	6.05–13.05	13.16–26.94
P	0.86		0.029	6.7×10^{-7}	8.9×10^{-30}	7.7×10^{-29}	4.5×10^{-58}
Model 1	1.19	1 (reference)	1.31	2.38	6.08	8.88	20.04
95% CI	0.63–2.25		0.97–1.77	1.74–3.24	4.42–8.37	6.05–13.05	14.11–28.67
P	0.60		0.083	4.8×10^{-8}	1.7×10^{-28}	7.9×10^{-29}	1.6×10^{-60}
Model 2	1.16	1 (reference)	1.37	2.68	6.94	9.81	20.38
95% CI	0.61–2.20		1.01–1.85	1.97–3.66	5.03–9.57	6.67–14.44	14.20–29.23
P	0.65		0.041	5.1×10^{-10}	3.1×10^{-32}	5.3×10^{-31}	2.9×10^{-60}

Cox models were adjusted for age at examination, birth year, and sex (model 1) and also for socioeconomic status, country of origin, education level, and height (model 2). IQR, interquartile range.

(1.50%), as well as the leading causes of death in our cohort, were similar to those of comparable age-stratified groups in the general Israeli population (Supplementary Table 2). The vast majority of DM-related deaths in the cohort (93.1%; *n* = 448) occurred after 1997 and predominantly among participants who were initially examined between 1967 and 1977 (86.7%; *n* = 417).

DM mortality rates increased steeply with age (Supplementary Table 3). The mean age at death from DM (50.5 ± 6.6 years) reflects the relatively young ages of the cohort at termination of the follow-up. Male sex, lower SES, lower education, North African and former U.S.S.R. origin, and shorter stature were associated with higher risk (Supplementary Table 1). There was a graded increase in the unadjusted person–time rate of DM mortality evident in the midnormal (25th–49th) BMI percentile onward, with a 12-fold higher mortality among the obese (≥95th BMI percentile) than the 5th–24th percentile group (0.618 vs. $0.052/10^5$ person-years). Unadjusted Cox proportional hazards modeling (Table 2) closely followed the Kaplan-Meier survival curves (Supplementary Fig. 1) and reflected the same graded pattern: the higher HRs associated with increasing BMI became evident in the 25th–49th percentiles. The association persisted in minimally adjusted analyses (that included age, birth year, and sex; model 1) and upon further multivariable adjustment (also adjusted for years of education, SES, country of origin, and height; model 2). In the full multivariable analysis, overweight and obesity (vs. the 5th–24th percentiles) were associated with HRs for DM mortality of 8.0 (95% CI 5.7–11.3; $P = 6.8 \times 10^{-32}$) and 17.2 (95% CI 11.9–24.8; $P = 1.6 \times 10^{-51}$), respectively. Mortality among underweight participants was elevated, but not significantly so, versus the 5th–24th BMI percentiles (Table 2). The findings persisted in a series of sensitivity analyses including restriction of the analysis to adolescents with unimpaired health status (Supplementary Table 4), sex-specific analysis (Supplementary Table 5), restriction to participants examined between 1967 and 1977 (Supplementary Table 6), beginning the follow-up in 1967 instead of 1981 (and ignoring the small number of DM-related deaths expected among deaths with missing cause) (Supplementary Table 7), and accounting for competing risks (deaths other than from diabetes; Supplementary Table 8). The association was attenuated when the entire conventional normal range (5th–84th BMI percentiles) was used as the reference, with HRs of 4.9 (95% CI 3.9–6.1) and 10.3 (95% CI 7.9–13.4) for overweight and obesity, respectively, or 6.2 (95% CI 5.1–7.5) for overweight and obesity grouped together (Supplementary Table 9).

To assess whether the association between adolescent BMI and the study outcome differs by the age at death, we analyzed separately DM-related deaths occurring up to and after the age of 50 years (Supplementary Table 10). The generally graded shape and strength of the association between BMI and DM-related death were similar between the two age groups: for DM-related deaths occurring after age 50, significantly increased risk was evident from the 25th BMI percentile onward, whereas for DM deaths occurring at or before age 50 years, increased risk was evident above the 50th BMI percentile (Supplementary Table 10). A sensitivity analysis restricted to those who attained at least the age of 35 years during follow-up was consistent with the main analysis (Supplementary Table 11).

The association between BMI and DM mortality was accentuated when we excluded participants with a diagnosis of diabetes at enrollment (2,417 participants [most likely type 1 DM], among whom 10 deaths were attributed to DM]; Supplementary Table 12), when we excluded all deaths that were assigned to type 1 diabetes (*n* = 38; Supplementary Table 13), or when we separately analyzed deaths that were assigned to type 2 diabetes (168 deaths, as coded by the ICD-10 and that occurred from 1998 onward; Supplementary Table 14). Deaths assigned to diabetes of unspecified cause (*n* = 265) showed substantial, though modestly weaker, associations.

Upon grouping the cohort by absolute BMI values (Table 2b), participants with a BMI 20.0–22.4 kg/m^2 displayed an increased multivariable-adjusted risk for DM mortality (HR 1.4 [95% CI 1.0–1.9]; $P = 0.041$) compared with the 17.5–19.9 kg/m^2 reference group. Adolescents with a BMI ≥30 kg/m^2 had an adjusted HR of 20.4 (95% CI 14.2–29.2; $P = 2.9 \times 10^{-60}$) for DM mortality. Figure 2*B* depicts the DM mortality function during the study period. The findings were undiminished when the analysis was limited to those with unimpaired health status during adolescence (Supplementary Table 4*B*). A multivariable spline model indicated a minimum risk for DM mortality close to 18 kg/m^2, with significantly increased risk seen above adolescent BMI values of 21.6 kg/m^2 (Supplementary Fig. 2).

The prevalence of overweight and obesity in our cohort has increased consistently over the past four decades, from 8.7% in the 1967–1977 period to 20.8% between 2012 and 2014, with an increase of 0.45 kg/m^2 per decade for the entire cohort between 1980 and

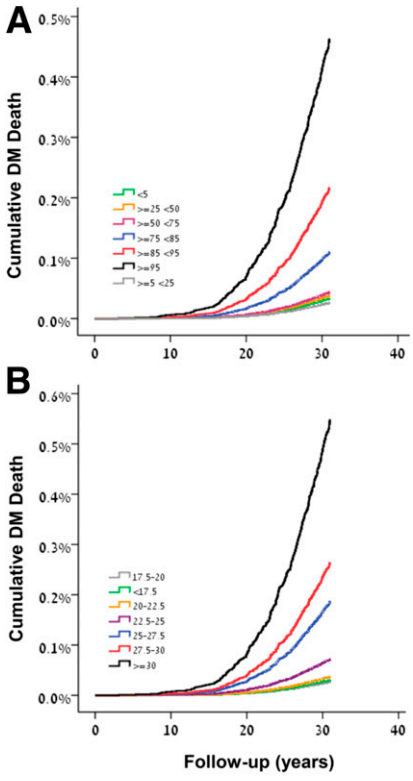

Figure 2—The relationship between BMI measured during adolescence and diabetes mortality during a follow-up of between 1 and 44 years. Multivariable Cox survival functions (colored lines) by BMI category are shown for deaths attributed to DM (*n* = 481 deaths), with BMI categorized by U.S. CDC groupings (*A*) or by absolute BMI values (kilograms per meter square) (*B*). The model was adjusted for sex, age at examination, birth year, education, residential socioeconomic status, country of origin, and height.

2010, similar to the reported worldwide trend (14,20). The PAF for DM mortality attributable to overweight and obesity (computed for those examined from 1967–1977 and for the 8.7% prevalence of overweight and obesity) was 31.2% (95% CI 26.6–36.1%), and the projected PAF for the 20.8% prevalence of overweight and obesity in 2012–2014 was 52.1% (95% CI 46.4–57.4%).

CONCLUSIONS

In this nationwide, population-based study we report the association between BMI in late adolescence and DM mortality in midlife based on a follow-up of over 42 million person-years, during which 481 DM-related deaths occurred. The key findings are extremely high HRs for BMI in the overweight (HR = 8.0) and obese (HR = 17.2) categories (with lower 95% CI bounds of 5.7 and 11.9, respectively), and that BMI values that are currently considered in the midnormal range were associated with increased DM mortality, exhibiting a graded increase from the 25th–49th percentiles onward, with 4.1-fold higher hazard in adolescents in the upper normal range (75th–84th BMI percentiles), and an HR of 2.7 for the 22.5–25.0 kg/m^2 BMI category. Findings from spline models suggest that absolute adolescent BMI values in the region of 18 and 20 kg/m^2 are associated with the minimum risk for DM and all-cause mortality. Global mortality attributed to diabetes has increased by 76% during the past two decades and was ranked globally as the ninth cause of death (2), with a forecast of a further increase in most parts of the world within the next decade (3). Notwithstanding its importance, mortality attributable to diabetes is underestimated and inconsistently reported (21–23). Among U.S. adults with a known history of diabetes, less than 40% of the decedents had diabetes listed anywhere on their death certificate (24). While we have no similar data for the Israeli population, the proportional DM mortality in our cohort is comparable to that reported elsewhere. For example, a recent Swedish study that followed 1.3 million male adolescents from age 18 over 3 decades reported 508 DM-related deaths among a total of 44,313 deaths (1.15%) (25), which is comparable with 1.50% in our cohort. Nevertheless, it is likely that diabetes was the underlying determinant of many deaths that were assigned to other causes, such as coronary heart disease and ischemic stroke. In that respect, we recently assessed the association between BMI at adolescence and cardiovascular death, demonstrating that an increased hazard is expected above the 50th BMI percentile and above an absolute value of 20 kg/m^2 (9).

Overall, the strength of the association between BMI (at age 17) and all-cause mortality in the present cohort is similar to that of other cohorts. We reported HRs of 1.88 (1.69–2.09) and 2.05 (1.55–3.01) for overweight and obese male adolescents in this cohort, respectively, when the full "normal" range (5th–84th U.S. CDC BMI percentiles) was used as the reference (15). Among 6,502 male Danish recruits whose BMI was measured at age 17, obesity was associated with an HR of 2.1 (95% CI 1.3–3.5) for death before age 55 (26). Engeland et al. (27) reported HRs of 1.82 (95% CI 1.48–2.25) and 2.03 (95% CI 1.51–2.72) for all-cause mortality among obese male and female Norwegian adolescents, respectively, who were followed for approximately three decades (n = 227,000).

A previous study that was based on a selective subsample of 37,000 participants from our cohort assessed the association between adolescent BMI (classified in deciles) and the incidence of type 2 diabetes with a follow-up from age 17 until age 45 (9). When applying the decile groupings used in that study, we found among men age-adjusted HRs of 1.7 (95% CI 1.0–2.9) for DM-related death vs. 1.7 (95% CI 1.3–2.2) for DM incidence for a BMI between 22.35 and 23.39 kg/m^2 (decile 8), 2.8 (95% CI 1.7–4.8) vs. 2.3 (95% CI 1.7–3.0) for a BMI between 23.40 and 25.06 kg/m^2 (decile 9), and 8.0 (95% CI 4.9–13.0) vs. 4.2 (95% CI 3.2–5.4) for a BMI between 25.06 and 36.0 kg/m^2 (decile 10) when using a BMI of 15.0–18.11 kg/m^2 (decile 1) as the reference group. The associations were generally similar in magnitude, except for the top decile.

Our data suggest that the contribution of elevated adolescent BMI to the risk of DM mortality may be underestimated in the literature. When the full conventionally accepted normal percentile range of BMI was used as a reference, and when overweight and obesity were grouped together (Supplementary Table 9), the resulting HR of 6.2 was similar to that of a previous report of overweight and obese female Norwegian adolescents (HR = 5.7) (28). Thus classification of BMI according to the accepted "normal" range (5th–84th BMI percentiles) may underestimate the actual risk associated with obesity, as the high-normal BMI range (75th–84th percentiles) was associated with a more than fourfold increase in DM mortality.

Turning our attention to population measures, a pooled global analysis (13) estimated that the PAF for overweight and obese adults accounted for approximately 30% of worldwide DM-related deaths in 2010, similar to our findings for the prevalence of adolescent overweight/obesity preceding the childhood obesity epidemic, and considerably less than the projections for the prevalence in 2012–2014. The participants included in that analysis spanned a wide age range (15–84 years), which may lead to underestimation of the risk in the youngest age group (29), with an assumption of an optimal BMI distribution between 21 and 23 kg/m^2 (13,30). Additionally, misclassification as a result of the use of recalled weight and height rather than measured data is major source of bias (31,32) because it typically results in shifting the BMI distribution "to the left" and would act to dilute the strength of the association. Finally, our hazard estimates are for premature deaths from DM occurring before age 64, which may well differ from later deaths in the magnitude of the association.

The finding that BMI values associated with minimum risk for DM and all-cause mortality reside in the low-normal and underweight ranges is consistent with a recent report of this cohort that assessed cardiovascular mortality outcomes (15). We suggest two potential explanations for the associations of adolescent BMI with DM mortality in midlife. The first is that BMI in adolescence, particularly within the overweight and obese ranges, is associated with increased expression of deleterious risk factors for DM at a young age (6). Second, BMI "tracks" quite substantively into adulthood (9,33,34), such that those within the higher or lower BMI range as adolescents are more likely to have higher or lower values in adulthood. Therefore it is possible that adult BMI mediates and accentuates the effect of

adolescent BMI. In the absence of adult measures of BMI in our cohort, we were unable to assess whether adolescent BMI is risk factor for DM mortality, independent of adult BMI. However, a previous study, undertaken using a selective subset of this cohort, indicated that the association of adolescent obesity with incident diabetes in midlife was not independent of adult BMI in young adulthood (9). Nevertheless, whether adolescent BMI acts as a predictor of adulthood obesity, is an independent risk factor, or both, it is clearly a strong risk marker for DM and all-cause mortality, independent of sociodemographic and other health-related variables at age 17. With regard to the strong associations found in our study, we note that early onset type 2 diabetes among obese young adults seems to be a more aggressive disease from a vascular standpoint, leading to an increased risk of complications (35). Moreover, obesity per se is reported to increase the likelihood of progression of diabetes complications by numerous mechanisms, such as promoting endothelial dysfunction and oxidative stress, increasing proatherogenic lipid particles, and increasing coagulability (36).

There are several limitations to this study. First, we lacked data on the incidence of diabetes, precluding us from examining whether the mortality association with BMI expresses incidence, case fatality, or both. However, HRs for the incidence of DM in a small subsample of our cohort (9) were not very different in the "normal" range of BMI from DM mortality in a comparable reanalysis we undertook, whereas above BMIs of 25 kg/m^2, the association with DM mortality was accentuated. Second, most diabetes-related deaths in our cohort were coded as "unspecified" type, thereby precluding valid assessment of associations by diabetes type. Nevertheless, stratification of DM mortality by diabetes type (Supplementary Table 14), or exclusion of those with a diagnosis of diabetes in adolescence (Supplementary Table 12), or excluding those with any chronic illness (Supplementary Table 3) left the association either unchanged or even accentuated. Third, as stated above, lack of data regarding BMI in adulthood prevented us from examining the pathway by which adolescent obesity might affect DM mortality and assessing an independent association with adolescent BMI (9). Fourth, data regarding risk factors for diabetes, including smoking, physical activity, inflammation, glycemic control, and medications used during follow-up, were not routinely collected in this cohort. In particular, smoking may play a role both as a risk factor for diabetes (37) and as a determinant of increased fatality among patients with diabetes (38). Smoking was reported to be associated with overweight and obesity in overlapping subsamples of our cohort (n = 29,745 and 25,935) that were interviewed at ages 20–22 after completion of their military service (39,40), and this may have contributed to the high risk estimates in the obese group. Fifth, waist circumference, which reflects abdominal adiposity and has been shown to be associated with mortality even after accounting for BMI (41), was not measured in our cohort. Finally, the data presented here are from a young cohort, which reflects only a fraction of the overall diabetes mortality that will manifest as this cohort ages, as evidenced by the young mean age at death from DM. The strengths of the study include the nationwide representative sample of the Jewish population, its fully prospective design with standardized measurement of BMI at baseline, and the ability to evaluate associations across the full BMI range with adequate statistical power, given a very large sample size and a follow-up extending for over four decades.

In conclusion, BMI in late adolescence, including measures well within the currently accepted normal range, is strongly associated with diabetes mortality in midlife, exceeding that of cardiovascular mortality (15). The PAFs point to its substantial population impact and public health importance. The increasing prevalence of overweight and obesity, and of adolescents in the mid- and high-normal range, are likely to account for a large and increasing proportion of DM incidence, its related microvascular and macrovascular complications, and DM mortality.

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