Diabetes Risk Among Overweight and Obese Metabolically Healthy Young Adults

Gilad Twig,[1,2,3] Arnon Afek,[4,5] Estela Derazne,[3,4] Dorit Tzur,[3] Tali Cukierman-Yaffe,[4,6] Hertzel C. Gerstein,[7] and Amir Tirosh[2,8]

Diabetes Care 2014;37:2989–2995 | DOI: 10.2337/dc14-0869

OBJECTIVE

To determine diabetes incidence over time among obese young adults without metabolic risk factors.

RESEARCH DESIGN AND METHODS

Incident diabetes during a median follow-up of 6.1 years was assessed among 33,939 young men (mean age 30.9 ± 5.2 years) of the Metabolic, Lifestyle and Nutrition Assessment in Young Adults cohort who were stratified for BMI and the number of metabolic abnormalities (based on the Adult Treatment Panel-III). Metabolically healthy (MH) obesity was defined as BMI ≥30 kg/m^2 in the presence of normoglycemia, normal blood pressure, and normal levels of fasting triglyceride and HDL-cholesterol levels (n = 631).

RESULTS

A total of 734 new cases of diabetes were diagnosed during 210,282 person-years of follow-up. The incidence rate of diabetes among participants with no metabolic risk factors was 1.15, 2.10, and 4.34 cases per 1,000 person-years among lean, overweight, and obese participants, respectively. In a multivariable model adjusted for age, region of origin, family history of diabetes, physical activity, fasting plasma glucose, triglyceride level, HDL-cholesterol, systolic blood pressure, and white blood cell count, a higher diabetes risk was observed among MH-overweight (hazard ratio [HR] 1.89 [95% CI 1.25–2.86]; $P < 0.001$) and MH-obese (HR 3.88 [95% CI 1.94–7.77]; $P < 0.001$) compared with MH-normal weight subjects. There was no interaction between BMI and the number of metabolic abnormalities at enrollment in predicting diabetes risk.

CONCLUSIONS

Healthy metabolic profile and the absence of diabetes risk factors do not protect young adults from incident diabetes associated with overweight and obesity.

Heterogeneity in the metabolic risk status of individuals with normal weight (NW), overweight, or obesity raised the hypothesis that metabolically healthy (MH)-obese individuals have no additional metabolic risk (1–3). However, there is conflicting evidence regarding the metabolic course of this subpopulation. Adjusted diabetes risk, for example, was reported to be unchanged (1,3), 4-fold higher (4), or 13-fold higher in MH-obese compared with MH-NW individuals (5).

While the definition of healthy obesity suffers from inconsistency (6,7), the prevailing defining criteria of MH in most studies assessing diabetes risk include individuals with a BMI ≥30 kg/m^2 with one (1,4) or even two (3,5,7) metabolic

[1]Department of Medicine B, Sheba Medical Center, Tel Hashomer, Israel
[2]Dr. Pinchas Bornstein Talpiot Medical Leadership Program, Sheba Medical Center, Tel Hashomer, Israel
[3]Israel Defense Forces Medical Corps, Israel
[4]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[5]Israel Ministry of Health, Jerusalem, Israel
[6]Department of Endocrinology, Sheba Medical Center, Tel Hashomer, Israel
[7]Division of Endocrinology and Metabolism and Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada
[8]Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Corresponding author: Gilad Twig, gilad.twig@gmail.com.

Received 7 April 2014 and accepted 21 July 2014.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-0869/-/DC1.

abnormalities. Therefore, using the phrase "metabolically healthy" to label individuals who have one or more of the metabolic syndrome risk factors may contribute to confusion in the literature.

All of the men in the Israel Defense Forces (IDF) aged ≥25 years have been metabolically characterized and followed in a large ongoing study of the Metabolic, Lifestyle and Nutrition Assessment in Young Adults (MELANY) cohort. Data from this study were analyzed to compare the risk of diabetes among overweight and obese individuals with none of the metabolic syndrome risk factors with similar individuals with varying numbers of risk factors.

RESEARCH DESIGN AND METHODS

Study Population

The MELANY cohort is an ongoing investigation of the IDF Medical Corps (8,9). Army personnel that remain in military service beyond their mandatory service period (2 to 3 years) and are older than 25 years of age are referred every ~5 years for a routine health examination and screening tests at the Staff Periodic Examination Center. At each visit, subjects complete a detailed questionnaire reviewing demographic, lifestyle, and medical factors. Following a 14-h fast, blood samples are drawn and analyzed immediately. Weight and height are measured, and a complete physical examination is performed by a physician. All medical information is recorded in the same central database, thereby allowing ongoing, uniform follow-up as described previously (10). All participants in MELANY, independent of their rank and position, have similar access to medical services, which are provided free of charge.

Included in this study were men with measured body height and weight who attended the Staff Periodic Examination Center at least once between 1 January 1995 and 8 March 2011. Data on participants who developed type 1 or 2 diabetes prior to their first visit and those with a follow-up of <1 year from enrollment to the diagnosis of diabetes were excluded from the analysis. The Institutional Review Board of the IDF Medical Corps approved this study with assurance of strict maintenance of participants' anonymity during data analyses. Our data set included 5,112 women, 40 of whom developed diabetes (0.78%). This small incidence rate precluded meaningful statistical analyses; thus, the current analysis was limited to male participants.

Definitions of Study Groups

BMI was used to define obesity (≥30 kg/m^2), overweight (30 > BMI ≥ 25 kg/m^2), and NW (<25 kg/m^2). Each weight group was further divided according to the number of metabolic abnormalities present at enrollment. These were defined according to the criteria of the Adult Treatment Panel-III (ATP-III) (11) as triglyceride level ≥150 mg/dL (1.7 mmol/L) or use of lipid-lowering drugs, glucose ≥100 mg/dL (≥5.6 mmol/L), systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or use of antihypertensive drugs, and HDL-cholesterol <40 mg/dL. MH was defined as the absence of any metabolic abnormalities of the ATP-III criteria, while metabolically abnormal (MA) included at least one abnormality from the above criteria.

Follow-up and Outcomes

Follow-up began at participants' first visit to the Staff Periodic Examination Center and ended at the time of diabetes diagnosis, death, retirement from military service, or 8 March 2011, whichever came first. Screening for diabetes was performed at each visit based on fasting plasma glucose (FPG) levels. Incident cases of diabetes were based on a physician diagnosis of diabetes in accordance with the American Diabetes Association criteria by documenting either two FPG levels ≥126 mg/dL or a glucose level ≥200 mg/dL 2 h after ingestion of 75 g of glucose.

Laboratory Methods

All laboratory studies were performed on fresh samples in an ISO-9002 quality-assured, core facility laboratory. Glucose levels were determined at an on-site laboratory with the use of fresh blood samples collected in test tubes containing sodium fluoride to inhibit in vitro glycolysis. Lipids were measured directly, with the exception of LDL-cholesterol, which was calculated. Biochemical markers were measured with an automated analyzer (BM/Hitachi 917; Boehringer Mannheim).

Statistical Analysis

We first calculated the hazard ratios (HRs) and 95% CIs of BMI at enrollment on diabetes risk using Cox proportional hazards analysis adjusted for age, family history of diabetes, region of origin, physical activity, FPG, triglyceride level, and white blood cell (WBC) count. Next, the cohort was divided into 12 groups based on BMI status (NW, overweight, or obese) and the number of cumulative metabolic abnormalities: MH (absence of any ATP-III criteria), MA-1 (one ATP-III criterion), MA-2 (two ATP-III criteria), and MA-3 (three or four ATP-III criteria). Cox proportional hazards models were used to estimate the HR and 95% CI for developing diabetes across the 12 categories. MH participants with NW served as the reference group, unless stated otherwise. Continuous variables were summarized using means and SD or medians with intraquartile ranges. Counts with percentages were used for categorical variables. Multivariable models were adjusted for age, family history of diabetes, region of origin, physical activity, and WBC count (12), with additional adjustment for the metabolic risk factors (FPG, triglyceride level, HDL-cholesterol, and systolic blood pressure) where appropriate. Additional analysis was conducted using repeated assessments of BMI during the follow-up period as time-dependent variables in a Cox regression model. We controlled for the additional metabolic parameters only at baseline, since these variables might be part of the causal chain. Log minus log plots for each variable were inspected to verify the assumption of proportionality of the hazards. Subjects with missing data (~5.0%) were excluded from multivariable analysis. Analyses were performed with IBM SPSS statistical software, version 21.0.

RESULTS

Tables 1–3 present the baseline characteristics of the cohort across BMI and metabolic abnormalities categories (Table 1, NW; Table 2, overweight; and Table 3, obese participants). MH-obese constituted 14.7% of the obese group (1.9% of the entire cohort) and were characterized by younger age, mildly higher degree of physical activity, and lower current and past rates of smoking compared with obese subjects with metabolic abnormalities (Table 3).

There were 734 new cases of diabetes during 210,282 person-years of follow-up. In a multivariable analysis adjusted for age, family history of diabetes, region of origin, physical activity, FPG, triglyceride level, and WBC count, each one-unit increase in BMI was associated with a 10.6% increase in diabetes risk

Table 1—Baseline characteristics of the NW participants

Baseline characteristics	Number of ATP-III risk factors				Total	*P* of trend
	0	1	2	≥3		
N (%)	9,183 (55)	5,327 (32)	1,720 (10)	438 (2.7)	16,668	
Age (years)	29.5 ± 4.8	30.2 ± 5.4	31.9 ± 6.0	34.3 ± 6.4	30.1 ± 5.3	0.027
Region of origin						0.081
Israel	8	8	9	7	8	
Former USSR	13	12	10	8	12	
Asia	24	25	29	30	25	
Africa	29	29	27	27	29	
West	26	26	25	28	26	
BMI (kg/m^2)	22.3 ± 1.7	22.7 ± 1.7	23.1 ± 1.4	23.5 ± 1.2	22.6 ± 1.6	<0.001
Height	176.8 ± 6.6	177.0 ± 6.8	176.6 ± 6.6	176.7 ± 6.9	176.7 ± 6.6	0.452
Fasting glucose level (mg/dL)	86.3 ± 7.0	89.2 ± 9.1	92.2 ± 10.0	99.0 ± 10.4	88.2 ± 8.6	0.026
Impaired fasting glucose	—	13.3	26.5	60.7	8.6	0.033
Systolic BP (mmHg)	111.7 ± 8.6	118.4 ± 13.0	121.3 ± 13.4	127.2 ± 12.9	115.3 ± 11.6	0.009
Diastolic BP (mmHg)	70.4 ± 7.7	74.4 ± 9.6	76.8 ± 9.6	81.9 ± 9.7	72.7 ± 9.0	0.009
Abnormal BP	—	34.1	47.2	77.9	17.8	0.012
HDL (mg/dL)	52.6 ± 9.2	45.5 ± 10.9	39.8 ± 8.9	36.7 ± 7.3	48.6 ± 10.8	0.014
Abnormal HDL	—	39.1	69.6	86.5	21.9	0.014
TGs (mg/dL), median (25th; 75th)	74 (57; 95)	92 (69; 124)	156 (104; 196)	193 (161; 24)	84 (63; 117)	0.022
Abnormal TGs	—	13.5	56.7	88.3	12.5	0.017
LDL (mg/dL)	107.0 ± 29.2	112.7 ± 31.4	119.9 ± 33.7	127.3 ± 35.9	110.7 ± 30.9	0.002
Physical activity						0.011
None	59	61	67	71	61	
<150 min/week	32	30	28	24	31	
≥150 min/week	9	9	5	5	8	
Family history of diabetes	9.8	11.5	14.3	16.4	11.0	0.004
Smoking status						0.015
Never	65	62	54	47	63	
Ex-smoker	11	11	11	14	11	
Current	24	27	35	38	26	
WBC count (10^3 cells/mm^3)	6.2 ± 1.4	6.5 ± 1.5	6.9 ± 1.6	7.0 ± 1.5	6.4 ± 1.5	0.022

Categorical variables are presented by (%). For continuous variables, the mean ± SD is given unless otherwise indicated. Abnormal values of BP, HDL, and TG are based on the ATP-III criteria as detailed in the RESEARCH DESIGN AND METHODS section. BP, blood pressure; HDL, HDL-cholesterol; LDL, LDL-cholesterol; TG, triglyceride.

(95% CI 1.08–1.12; $P < 0.001$) across the entire BMI range. The incident rate of diabetes among MH participants was lower in those of NW compared with obese participants (1.15 vs. 4.34 cases per 1,000 person-years; $P < 0.001$). With increasing number of risk factors, diabetes incidence increased substantially less among NW participants than among obese participants, reaching an incidence rate of 3.17 and 19.17 cases per 1,000 person-years when at least three metabolic abnormalities were recorded among NW and obese young men, respectively (Fig. 1*A*). Fig. 1*C–E* depicts the cumulative incidence of diabetes over time in a multivariable model adjusted for age, region of origin, family history of diabetes, physical activity, and WBC count, with the corresponding HR values (± 95% CI) (Fig. 1*B* and Supplementary Table 1). It is evident that among MH individuals, those who were overweight (HR 1.60 [1.11–2.31]; $P = 0.012$) and obese (HR 2.74 [1.53–4.89]; $P < 0.001$) were at increased risk for diabetes compared with NW individuals. Addition of one metabolic abnormality (MA-1) increased the risk for incident diabetes by 67% (95% CI 1.18–2.36; $P = 0.003$) and 51% (95% CI 0.91–2.88; $P = 0.102$) among NW and obese participants, respectively. The increased diabetes risk of obese in either metabolic status persisted when BMI was treated as a time-dependent variable (Supplementary Table 2).

To better differentiate between the effect of obesity and its associated metabolic abnormalities on diabetes risk, we conducted an additional multivariate model adjusted for the metabolic risk factors entered as continuous variables. Fig. 2 demonstrates the cumulative diabetes incidence adjusted for age, region of origin, family history of diabetes, physical activity, WBC count, FPG, triglyceride level, HDL level, and systolic blood pressure among MH and MA-3 participants (Fig. 2*A* and *B*, respectively). Diabetes risk increased by more than threefold in the obese group compared with NW, within both clusters of metabolic abnormalities. A test of interaction between BMI and number of risk factors at enrollment was not significant (P of interaction = 0.78).

CONCLUSIONS

This analysis of 33,939 young men with 210,282 person-years of follow-up demonstrates that among young men, an abnormal BMI is associated with increased risk for diabetes, independent of the cluster of metabolic abnormalities (Fig. 1). In fact, compared with

Table 2—Baseline characteristics of the overweight participants

	Number of ATP-III risk factors					
Baseline characteristics	0	1	2	≥3	Total	*P* of trend
N (%)	4,207 (32)	4,545 (35)	2,947 (23)	1,297 (10)	12,996	
Age (years)	30.9 ± 5.5	31.9 ± 5.9	33.1 ± 6.1	34.8 ± 6.2	32.2 ± 6.2	0.008
Region of origin						0.114
Israel	8	9	10	9	9	
Former USSR	13	13	9	9	12	
Asia	22	22	24	25	23	
Africa	32	32	33	31	32	
West	25	24	24	26	25	
BMI (kg/m^2)	26.8 ± 1.3	27.1 ± 1.3	27.3 ± 1.3	27.5 ± 1.4	27.1 ± 1.4	0.006
Height	176.7 ± 6.6	177.0 ± 6.8	176.8 ± 6.6	176.9 ± 6.6	176.9 ± 6.6	0.600
Fasting glucose level (mg/dL)	87.6 ± 6.6	90.0 ± 8.5	92.2 ± 9.5	97.9 ± 10.5	90.5 ± 8.9	0.030
Impaired fasting glucose	—	11.3	22.0	52.2	14.1	0.037
Systolic BP (mmHg)	113.2 ± 8.0	119.5 ± 12.5	121.2 ± 12.9	128.6 ± 12.6	118.8 ± 12.3	0.024
Diastolic BP (mmHg)	72.0 ± 7.4	76.0 ± 9.3	77.9 ± 9.7	83.2 ± 9.6	75.9 ± 9.5	0.013
Abnormal BP	—	32.9	42.3	79.2	29.0	0.021
HDL (mg/dL)	50.4 ± 8.0	45.0 ± 9.7	39.2 ± 8.5	35.8 ± 6.0	44.5 ± 9.9	0.006
Abnormal HDL	—	34.1	66.7	89.1	36.0	0.004
TGs (mg/dL), median (25th; 75th)	89 (68; 113)	111 (83; 144)	173 (133; 221)	207 (170; 267)	118 (83; 168)	0.015
Abnormal TGs	—	21.8	69.1	93.8	71.0	0.011
LDL (mg/dL)	120 ± 31.9	123.9 ± 34.6	127.7 ± 35.9	130.5 ± 38.1	123.9 ± 34.1	0.002
Physical activity						0.041
None	59	66	69	71	65	
<150 min/week	31	26	24	23	27	
≥150 min/week	10	8	7	6	8	
Family history of diabetes	13.9	15.3	17.8	20.4	15.9	0.008
Smoking status						0.017
Never	61	57	53	45	56	
Ex-smoker	15	16	15	19	16	
Current	24	27	32	36	28	
WBC count (10^{3}cells/mm^3)	6.6 ± 1.4	6.8 ± 1.5	7.1 ± 1.5	7.2 ± 1.5	6.8 ± 1.5	0.016

Categorical variables are presented by (%). For continuous variables, the mean ± SD is given unless otherwise indicated. Abnormal values of BP, HDL, and TG are based on the ATP-III criteria as detailed in the RESEARCH DESIGN AND METHODS section. BP, blood pressure; HDL, HDL-cholesterol; LDL, LDL-cholesterol; TG, triglyceride.

MH-NW young adults, those who were overweight or obese, with no ATP-III metabolic abnormalities had nearly two- and fourfold higher risks for incident diabetes, respectively.

A subpopulation of apparently healthy or benign obese was thought to deviate from the natural course of obesity-related cardiovascular and metabolic risk (13,14). Indeed, both cross-sectional and prospective data have suggested that these individuals may be protected from diabetes. For example, comparable levels of fasting glucose (7,15,16) and diabetes prevalence (7,17) were reported in obese and NW individuals without metabolic risk factors for diabetes. Moreover, both the Framingham study (3) and an Australian cohort study (1) reported that MH-obese and NW individuals had similar diabetes incidence during up to 11 years of follow-up. In contrast, other studies reported up to 13-fold increase in diabetes risk among MH-obese (allowed to include up to one metabolic abnormality from ATP-III criteria) as compared with MH-NW individuals (4,5).

The definition of MH across studies is inconsistent and confusing, as its permits the inclusion of individuals with one (1,4) or even two metabolic abnormalities (3,5,7). Our stratification of diabetes risk factors argues against using such definitions of metabolic "healthiness," given an increase of 35–67% in diabetes risk observed in MA-1 compared with MH (Fig. 1 and Supplementary Table 1). Another potential explanation for the apparently conflicting reports in the literature may arise from lack of careful adjustment to the various risk factors (such as fasting glucose, HDL-cholesterol, triglycerides, and blood pressure) as continuous variables within risk factor groups. This is especially important in young adults, in whom diabetes risk attributed to increased levels of FPG, triglycerides, or WBCs could be demonstrated already within what is currently considered to be the normal range for these parameters (9,12,18). The definition of MH used in our study, along with an additional adjustment for other known risk factors (Fig. 2), allow us to adequately assess the independent role of increased BMI in mediating diabetes risk among young adults. Of note, we also stratified our analysis to WBC count, a marker of systemic inflammation that was recently shown to serve as an independent risk factor for diabetes in this population (12,19). Our results are in line with the notion that inflammatory burden, as reflected by WBC count, may not be a

Table 3—Baseline characteristics of the obese participants

Baseline characteristics	Number of ATP-III risk factors				Total	*P* of trend
	0	1	2	≥3		
N (%)	631 (15)	1,275 (30)	1,402 (33)	967 (23)	4,275	
Age (years)	31.4 ± 5.7	32.2 ± 5.9	32.8 ± 6.1	34.4 ± 6.2	32.8 ± 6.1	0.024
Region of origin						0.221
Israel	6	10	8	9	8	
Former USSR	13	9	13	12	12	
Asia	22	21	22	22	22	
Africa	35	33	33	29	33	
West	24	27	24	28	25	
BMI (kg/m^2)	32.0 ± 2.2	32.8 ± 2.6	32.9 ± 2.8	33.5 ± 3.2	32.9 ± 2.8	0.037
Height	176.9 ± 6.6	176.2 ± 6.8	176.7 ± 6.7	177.0 ± 6.8	176.6 ± 6.8	0.71
Fasting glucose level (mg/dL)	88.0 ± 6.7	90.3 ± 7.9	92.1 ± 9.0	98.4 ± 10.9	92.4 ± 9.5	0.045
Impaired fasting glucose	—	8.6	19.5	51.8	20.7	0.053
Systolic BP (mmHg)	114.4 ± 7.6	122.1 ± 13.6	124.8 ± 13.7	132.9 ± 13.9	124.3 ± 14.2	0.016
Diastolic BP (mmHg)	73.4 ± 7.2	77.7 ± 9.9	80.1 ± 9.9	85.3 ± 9.9	79.6 ± 10.3	0.009
Abnormal BP	—	39.8	52.7	86.1	48.6	0.016
HDL (mg/dL)	49.2 ± 7.8	45.4 ± 9.6	39.8 ± 8.5	35.4 ± 6.2	41.8 ± 9.6	0.002
Abnormal HDL	—	27.3	61.1	89.3	48.4	0.001
TGs (mg/dL), median (25th; 75th)	99 (78; 122)	120 (93; 149)	174 (133; 225)	217 (176; 289)	150 (108; 210)	0.013
Abnormal TGs	—	24.4	66.6	93.0	50.2	0.006
LDL (mg/dL)	123.5 ± 38.1	125.9 ± 32.9	128.2 ± 33.89	128.5 ± 35.6	126.8 ± 33.7	0.04
Physical activity						0.036
None	72	75	77	79	76	
<150 min/week	22	18	18	16	18	
≥150 min/week	6	7	4	5	6	
Family history of diabetes	17.4	19.3	19.5	21.8	19.7	0.04
Smoking status						0.01
Never	58	55	51	44	52	
Ex-smoker	16	17	17	19	17	
Current	26	28	32	36	31	
WBC count (10^{3}cells/mm^3)	7.0 ± 1.5	7.2 ± 1.5	7.4 ± 1.5	7.6 ± 1.6	7.3 ± 1.5	0.01

Categorical variables are presented by (%). For continuous variables, the mean ± SD is given unless otherwise indicated. Abnormal values of BP, HDL, and TG are based on the ATP-III criteria as detailed in the RESEARCH DESIGN AND METHODS section. BP, blood pressure; HDL, HDL-cholesterol; LDL, LDL-cholesterol; TG, triglyceride.

required mediator for diabetes onset among obese young adults (20). The independent role of obesity in mediating diabetes incidence even among individuals with normoglycemia, no evidence of dyslipidemia, and with normal blood pressure is intriguing. While obesity seems to mediate the incidence of diabetes, independent of the above-mentioned classic risk factors, it may still be mediated by significant insulin resistance and/or β-cell dysfunction that have not yet resulted in dysglycemia or dyslipidemia. In addition, it has also been demonstrated that diabetes risk associated with a positive family history of the disease may be mediated, at least in part, by obesity (21,22). Given the relatively young age of our cohort, it is likely that first degree relatives of participants reporting a negative family history for diabetes might still develop diabetes in the future. For these participants, overweight and obesity may carry an additional risk that is otherwise associated with a positive family history of diabetes.

The age of study participants may be another source of ambiguity when assessing diabetes risk among MH obese. The participants in our study were mostly in their late 20s or early 30s, as compared with other studies that included mostly participants in their 5th or 6th decades of life (1,3,4,6). It is therefore possible that MH obesity in middle-aged men confers a lower diabetes risk as a result of survival bias, as this group consists of men who were likely overweight or obese for many years and nevertheless have not developed diabetes or other metabolic abnormalities. Metabolically healthy obesity in young adults, in contrast, may consist of a more heterogeneous population that includes both obese subjects who are likely to develop various metabolic abnormalities in the near future as well as those who will maintain their metabolic health for several decades. In support of this concept, a recent study from the Young Finns cohort describing 34 cases of type 2 diabetes among young adults demonstrated that overweight at youth is a risk factor for diabetes, even in the absence of any metabolic abnormalities (23).

This study has several limitations. First, the MELANY cohort may be considered representative of a unique group of healthy young men. Nevertheless, the characteristics of the population are strikingly similar to other cohorts that included young men from various developed countries (24–26). The relatively homogeneous environment to which participants in our study were exposed might reduce the effect of

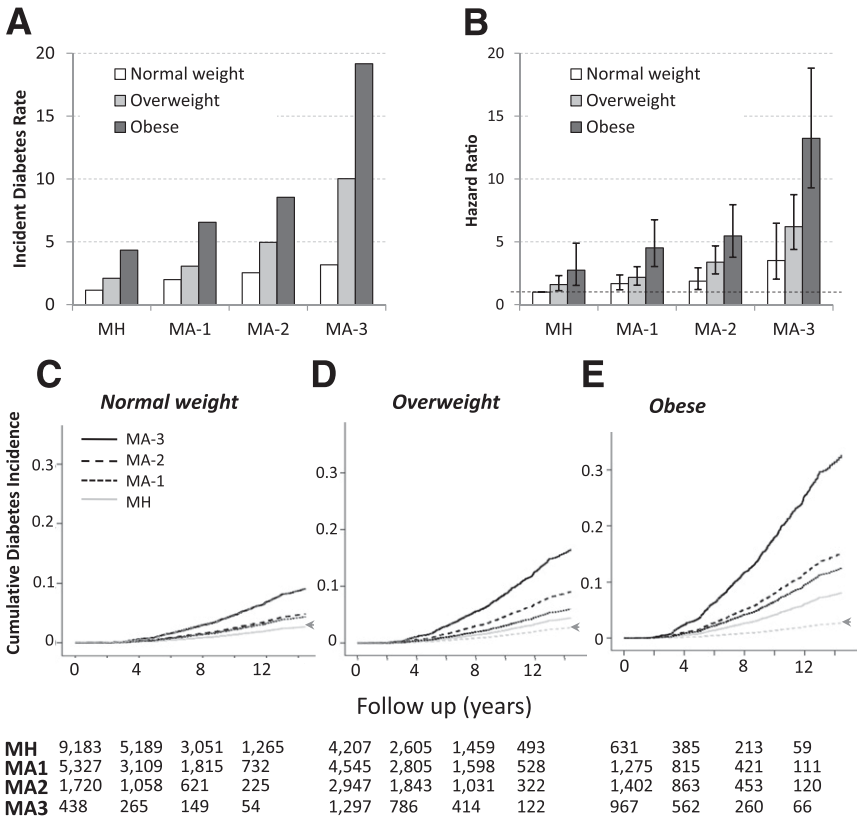

Figure 1—Incidence and risk of diabetes according to number of risk factors stratified by BMI. Diabetes rates (case per 1,000 person-years) (*A*) and HRs (± 95% CI) (*B*) of multivariable model adjusted for age, region of origin, family history of diabetes, physical activity, and WBC count. Data are available in Supplementary Table 1. *C*–*E*: Cox proportional survival curves by BMI categories. The values under each chart indicate the number of participants at risk at 0 (enrollment), 4, 8, and 12 years of follow-up. Diabetes incidence of MH-NW participants is shown for comparison (*D* and *E*, gray dashed line).

unknown confounders. In addition, our analysis pertains to people from a wide range of backgrounds and origins, reflecting that the development of diabetes is not origin specific. Second, although they did not compromise the outcome definition, measurements of waist circumference or specific fat compartments (27,28), circulating insulin and C-peptide, were not obtained in this study, limiting our ability to more directly assess adiposity and insulin resistance. Finally, the analysis was conducted only in men, thereby limiting the generalization of the results to women. The strengths of the study include the standardized and direct (rather than reported) measurements of height and weight (29), its large size and follow-up duration, which provided us with sufficient power to assess diabetes incident rates in this relatively young population.

To conclude, we found that overweight and obesity confers an increased risk for diabetes at any BMI status, including young obese adults with no other recognizable diabetes risk factors. This finding emphasizes the importance of tight follow-up of overweight and obese young adults for diabetes incidence, independent of the presence of other risk factors.

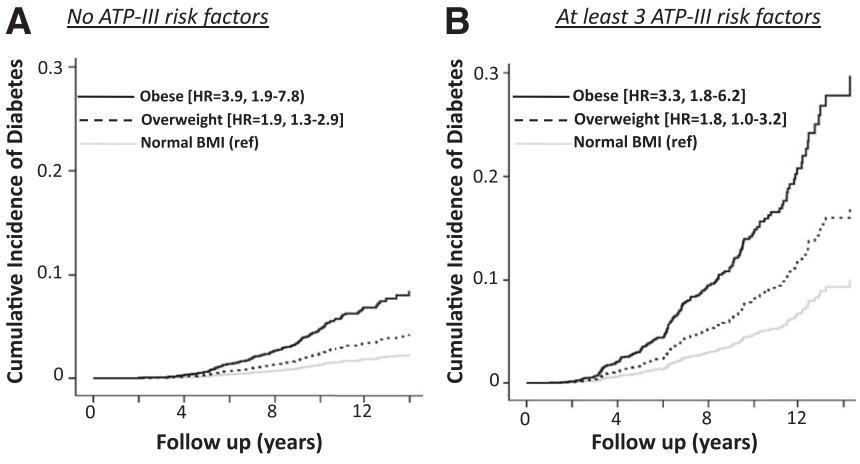

Figure 2—Diabetes incidence in men stratified by categories of BMI. Cox proportional survival functions for cumulative diabetes risk were calculated across BMI subgroups for participants with no metabolic risk (*A*) and those with at least three ATP-III criteria (*B*). The multivariable model was adjusted for age, region of origin, family history of diabetes, physical activity, WBC count, FPG, triglyceride level, HDL level, and systolic blood pressure. Within each panel, NW participants served as the reference. HRs (95% CI) are indicated next to each curve.

Funding. G.T. and A.T. were partially supported by a grant from the Dr. Pinchas Borenstein Talpiot Medical Leadership Program, Chaim Sheba Medical Center, Tel Hashomer, Israel.
Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. G.T. and A.T. were responsible for study concept and design, acquisition and interpretation of data, statistical analysis, and drafting of the manuscript. A.A., T.C.-Y., and H.C.G. were responsible for critical revision of the manuscript. E.D. was responsible for study concept and design, statistical analysis, and critical revision of the manuscript. D.T. was responsible for data acquisition. G.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Appleton SL, Seaborn CJ, Visvanathan R, et al.; North West Adelaide Health Study Team. Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study. Diabetes Care 2013;36:2388–2394
2. Blüher M. Are there still healthy obese patients? Curr Opin Endocrinol Diabetes Obes 2012;19:341–346
3. Meigs JB, Wilson PW, Fox CS, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. J Clin Endocrinol Metab 2006;91:2906–2912
4. Aung K, Lorenzo C, Hinojosa MA, Haffner SM. Risk of developing diabetes and cardiovascular disease in metabolically unhealthy normal-weight and metabolically healthy obese individuals. J Clin Endocrinol Metab 2014;99:462–468
5. Arnlöv J, Sundström J, Ingelsson E, Lind L. Impact of BMI and the metabolic syndrome on the risk of diabetes in middle-aged men. Diabetes Care 2011;34:61–65

6. Calori G, Lattuada G, Piemonti L, et al. Prevalence, metabolic features, and prognosis of metabolically healthy obese Italian individuals: the Cremona Study. Diabetes Care 2011;34:210–215
7. Ogorodnikova AD, Kim M, McGinn AP, Muntner P, Khan U, Wildman RP. Incident cardiovascular disease events in metabolically benign obese individuals. Obesity (Silver Spring) 2012;20:651–659
8. Tirosh A, Shai I, Afek A, et al. Adolescent BMI trajectory and risk of diabetes versus coronary disease. N Engl J Med 2011;364:1315–1325
9. Tirosh A, Shai I, Tekes-Manova D, et al.; Israeli Diabetes Research Group. Normal fasting plasma glucose levels and type 2 diabetes in young men. N Engl J Med 2005;353:1454–1462
10. Tirosh A, Afek A, Rudich A, et al. Progression of normotensive adolescents to hypertensive adults: a study of 26,980 teenagers. Hypertension 2010;56:203–209
11. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497
12. Twig G, Afek A, Shamiss A, et al. White blood cells count and incidence of type 2 diabetes in young men. Diabetes Care 2013;36:276–282
13. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions?: A systematic review and meta-analysis. Ann Intern Med 2013;159:758–769
14. Klöting N, Fasshauer M, Dietrich A, et al. Insulin-sensitive obesity. Am J Physiol Endocrinol Metab 2010;299:E506–E515
15. Arnlöv J, Ingelsson E, Sundström J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. Circulation 2010;121:230–236
16. Hosseinpanah F, Barzin M, Sheikholeslami F, Azizi F. Effect of different obesity phenotypes on cardiovascular events in Tehran Lipid and Glucose Study (TLGS). Am J Cardiol 2011;107:412–416
17. Hamer M, Stamatakis E. Metabolically healthy obesity and risk of all-cause and cardiovascular disease mortality. J Clin Endocrinol Metab 2012;97:2482–2488
18. Tirosh A, Shai I, Bitzur R, et al. Changes in triglyceride levels over time and risk of type 2 diabetes in young men. Diabetes Care 2008;31:2032–2037
19. Vozarova B, Weyer C, Lindsay RS, Pratley RE, Bogardus C, Tataranni PA. High white blood cell count is associated with a worsening of insulin sensitivity and predicts the development of type 2 diabetes. Diabetes 2002;51:455–461
20. Pecht T, Gutman-Tirosh A, Bashan N, Rudich A. Peripheral blood leucocyte subclasses as potential biomarkers of adipose tissue inflammation and obesity subphenotypes in humans. Obes Rev 2014;15:322–337
21. Samocha-Bonet D, Campbell LV, Viardot A, et al. A family history of type 2 diabetes increases risk factors associated with overfeeding. Diabetologia 2010;53:1700–1708
22. Jenkins AB, Batterham M, Samocha-Bonet D, Tonks K, Greenfield JR, Campbell LV. Segregation of a latent high adiposity phenotype in families with a history of type 2 diabetes mellitus implicates rare obesity-susceptibility genetic variants with large effects in diabetes-related obesity. PLoS ONE 2013;8:e70435
23. Koskinen J, Magnussen CG, Sabin MA, et al. Youth overweight and metabolic disturbances in predicting carotid intima-media thickness, type 2 diabetes, and metabolic syndrome in adulthood: the cardiovascular risk in Young Finns study. Diabetes Care 2014;37:1870–1877
24. Vassy JL, Hivert MF, Porneala B, et al. Polygenic type 2 diabetes prediction at the limit of common variant detection. Diabetes 2014;63:2172–2182
25. Würtz P, Soininen P, Kangas AJ, et al. Branched-chain and aromatic amino acids are predictors of insulin resistance in young adults. Diabetes Care 2013;36:648–655
26. Nguyen QM, Srinivasan SR, Xu JH, et al. Elevated liver function enzymes are related to the development of prediabetes and type 2 diabetes in younger adults: the Bogalusa Heart Study. Diabetes Care 2011;34:2603–2607
27. McLaughlin T, Lamendola C, Liu A, Abbasi F. Preferential fat deposition in subcutaneous versus visceral depots is associated with insulin sensitivity. J Clin Endocrinol Metab 2011;96:E1756–E1760
28. Heianza Y, Arase Y, Tsuji H, et al. Metabolically healthy obesity, presence or absence of fatty liver, and risk of type 2 diabetes in Japanese individuals: Toranomon Hospital Health Management Center Study 20 (TOPICS 20). J Clin Endocrinol Metab 2014:jc20134427.
29. Keith SW, Fontaine KR, Pajewski NM, Mehta T, Allison DB. Use of self-reported height and weight biases the body mass index-mortality association. Int J Obes (Lond) 2011;35:401–408