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Original Article

CUN-BAE adiposity index prediction of incident type 2 diabetes: the Seguimiento Universidad de Navarra prospective cohort

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ABSTRACT

Background: Obesity is currently a pandemic and a cardinal risk factor for incident diabetes, a parallel growing pandemic. Measures commonly used to define obesity, i.e., BMI and waist circumference, do not accurately reflect body fatness.

Methods: We examined the prognostic value of body fatness assessed with the 'Clínica Universidad de Navarra-Body Adiposity Estimator' (CUN-BAE, range: 18.4–65.0 %) in 18,594 participants of the "Seguimiento Universidad de Navarra" prospective longitudinal cohort (60.5% women) without diabetes at baseline. Participants were followed-up with biennial questionnaires and multivariable-adjusted Cox models were used to estimate incident diabetes.

Results: During 13.7 years of median follow-up, 209 participants developed diabetes. Progressively ascending quartiles of CUN-BAE were significantly associated with incident diabetes in multivariable-adjusted models, even after adjusting for BMI > 30 kg/m^2. For each 2-unit increment in the CUN-BAE index, diabetes risk relatively increased by 46% in men and women (95% CI: 33%–62%). When comparing ROC AUC for CUN-BAE and BMI the association was stronger for CUN-BAE ($p < 0.001$).

Conclusions: CUN-BAE index, an easy equation that can be used in any clinical setting, predicted better the risk of incident diabetes compared to BMI. Our results emphasize the importance of reducing and maintaining a low adiposity in order to prevent diabetes.

1. Introduction

At present, obesity has become a pandemic. About two thirds of adults in Western countries are obese (body mass index [BMI] >30 kg/m^2) or overweight (BMI > 25 kg/m^2), considering only BMI as a classifying parameter. Since 1975, the prevalence of obesity has tripled mainly due to the spread of unhealthy diets and adoption of sedentary lifestyles [1]. Compelling evidence confirms that being obese translates into decreased life expectancy and an overwhelmingly increased risk of numerous chronic non-communicable diseases, including type 2 diabetes (T2D), coronary heart disease, hypertension, stroke, fatty liver disease, dementia, different types of cancer, and obstructive sleep apnea [2].

In parallel with the obesity pandemic, the T2D pandemic continues to grow worldwide [3]. According to the International Diabetes Federation assessment in 215 countries, the global prevalence of diabetes in adults aged 20–79 years was estimated at 10.5% (536.6 million) in 2021, with prospects for increasing to 12.2% (783.2 million) in 2045. Global diabetes-related health expenses were estimated at 966 billion USD in 2021, projected to reach 1054 billion USD in 2045 [3]. The unprecedented increase in the prevalence of obesity in all age groups is a cardinal risk factor for the exponential growth in T2D. There is growing epidemiological and clinical evidence on the connections between these twin pandemics and extensive research is currently dedicated to explaining their deep relationship [4]. It is urgent to identify

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simple and efficient methods to improve the early accurate detection of these costly conditions.

Although BMI is the most widely used method to detect obesity, its ability to discriminate the amount of fatty or lean tissue is limited because it does not consider body composition [5]. A similar BMI value can be associated with a wide range of body fat (BF) percentage making clinical interpretation difficult. A recent large study showed that the relative increase in mortality risk ranged from 21% to 108% in participants with BMI $\geq 30\,kg/m^2$ vs. those with normal weight; BMI did not increase mortality independently, while other factors such as body composition and comorbidity are needed to fully characterize the association between BMI and mortality [6].

Obesity can be assessed by direct and indirect measures of fatness other than BMI. The methods to estimate BF include air displacement plethysmography, isotope dilution techniques, dual x-ray absorptiometry, skinfold method, bioelectrical impedance, magnetic resonance imaging, and computed tomography, among others [7]. These methods are expensive, complex, implicate radiation risk, and cannot be easily transported, which make them unfeasible in clinical practice. Hence, some BF estimation indices have been developed showing better correlation with BF than BMI [8]. Among them, the 'Clínica Universidad de Navarra-Body Adiposity Estimator' (CUN-BAE), has been widely used in clinical studies due to its accuracy, strong correlation with objective BF parameters [9], and significant associations with cardiometabolic diseases [8–16].

We aimed to prospectively investigate the association of BF as assessed by the CUN-BAE index with the risk of incident diabetes compared to BMI in the Mediterranean population of the SUN ("Seguimiento Universidad de Navarra") longitudinal project.

2. Methods

2.1. Study design and population

The SUN Project is a prospective, longitudinal, multipurpose, and constantly open cohort study of university graduates that started in 1999, obtaining updated information biennially on diet, lifestyle, and other health risk factors, as well as on medical disorders present at baseline and identified during follow-up. Details on the SUN Project design have been formerly reported in detail [17,18].

Data for the analyses in the present study were those obtained from the SUN project database up to the 31st May 2022, corresponding to 23 133 participants. We excluded from the analyses 421 participants with a prevalent diagnosis of T2D or those who reported receiving treatment for diabetes (insulin or oral antidiabetic drugs) at baseline; 232 participants whose follow-up time was less than two years and nine months considering the lag time for returning the questionnaire; 2103 participants with total energy intake out of predefined limits [19]; and 1783 participants who were lost to follow-up. The final effective sample for longitudinal analyses was 18 594 participants with an overall retention rate of 93.0 (Supplementary Fig. S1).

2.2. CUN-BAE

We calculated the CUN-BAE index with the equation proposed by Gomez-Ambrosi et al. [9]:

$BF\% = -44.988 + (0.503 \times age) + (10.689 \times sex) + (3.172 \times BMI) - (0.026 \times BMI^2) + (0.181 \times BMI \times sex) - (0.02 \times BMI \times age) - (0.005 \times BMI^2 \times sex) + (0.00021 \times BMI^2 \times age)$ where age is measured in years and sex is codified as men = 0 and women = 1. The observed range was from 18.4 to 65.0%. The mean (SD) was 36.3% (4.9%) in men and 42.4% (5.2%) in women.

2.3. Outcome

In the event that in any of the follow-up biennial questionnaires the participant reported a new diagnosis of T2D (probable incident case), an additional specific questionnaire was sent requesting further detailed information on the medical report of aspects relevant for T2D diagnosis (i.e., confirmation of the diagnosis, date of diagnosis, type of diabetes, highest plasma glucose objectively assessed, glycated hemoglobin, eventual oral glucose tolerance test, and details on glucose-lowering medications). An endocrinologist, blinded to the exposure, adjudicated the incident cases of T2D, according to the diagnostic criteria recommended by the American Diabetes Association [20]. During follow-up, 209 cases of T2D were confirmed.

2.4. Ethical principles

All participants received written and specific information about the data requested in the successive questionnaires, about the future feedback from the SUN project research team, and about the protection and safeguarding of their privacy on the information sent by them. They were also informed on their right to refuse to participate in the SUN longitudinal project and the possibility of removing their consent to participate at any time with no retaliation, as recommended by the Declaration of Helsinki on the ethical principles in medical research involving humans. The compilation and return of the first questionnaire sent at baseline in a completely voluntary modality was considered as the informed consent as approved by the Institutional Review Board of the University of Navarra (Project identification code 2001_30).

2.5. Other covariates

For multivariable statistical models we considered also other covariates, including sex (for analyses of the total population), marital status, body weight changes, years of university education, smoking habit (3 categories and pack-year), physical activity, daily hours spent watching television, family history of diabetes, total energy intake, adherence to Mediterranean diet [21], hypercholesterolemia, hypertriglyceridemia, hypertension, or cancer at baseline, sugar-sweetened beverages consumption, snacking between meals, adoption of special diets, dietary potassium intake, dietary magnesium intake, and year of entrance to the cohort. The CUN-BAE index calculation already included age, sex, and BMI. Physical activity assessment was conducted with a previously validated questionnaire by comparisons with objective measurements with a triaxial accelerometer (RT3 Triaxial Research Tracker) (Spearman correlation coefficient of 0.51; $p < 0.001$) [22], expressed in metabolic equivalent tasks (METs-h/week; time spent at each activity in hours/week multiplied by its usual energy expenditure) [23]. To calculate BMI, we used self-reported weight and height as formerly validated in a subsample of the SUN cohort [24].

2.6. Statistical analyses

Baseline characteristics of the sample, means and SDs for continuous variables and proportions for categorical variables across even quartiles of BF as captured by the CUN-BAE index, were computed separately for men and women. To calculate the follow-up time we considered the date in which each participant returned the baseline questionnaire to the date of incident diabetes diagnosis, the date of returning the last follow-up questionnaire or date of death, whichever came first. We performed Cox regression analyses to assess the association of progressively increased fat mass (as assessed by CUN-BAE) with incident diabetes. The incident cases of diabetes were computed along the baseline quartiles of CUN-BAE index (keeping the lowest quartiles –Q1 and Q2 together– as the reference category), and hazard ratios (HRs) and 95% CI were calculated via Cox proportional hazards models. We considered the lowest quartiles (Q1 and Q2) together to increase the number of participants as reference, which was low individually, and the statistical power. Evaluation of the proportional-hazards assumption was based on Schoenfeld residuals after fitting the model. Repeated measurements of CUN-BAE index were analyzed with updated information in the follow-up questionnaires in time-dependent Cox models.

We first estimated HRs without any adjustment (crude), followed by adjustments for multiple confounders, as follows: i) Model 1: HRs were adjusted for sex, marital status, body weight changes before baseline, years of university education, smoking (never, former or current smokers), pack-year of cumulative exposure to cigarette smoking, leisure-time physical activity (METS-h/week, television watching (h/d, continuous), family history of diabetes, total energy intake (kcal/d, continuous), categories of adherence to Mediterranean diet [0 to 9 points, according to reference [21], sugar-sweetened beverages (2 categories: no/yes), between-meal snacking, adoption of special diet, dietary potassium (quintiles), dietary magnesium (quintiles), hypercholesterolemia, hypertriglyceridemia, hypertension, cancer, and year of entrance to the cohort (4 categories). ii) Model 2: HRs were adjusted for factors in Model 1 plus BMI higher than 30 kg/m^2. The median of CUN-BAE index quartiles was used as a continuous variable to calculate linear trend significance. We also calculated the multivariable-adjusted HRs estimates for the association of the increase of 2 units of the CUN-BAE index in relation to the incidence of diabetes. In addition, analyses considering the risk of incident T2D for each increase of one standard deviation (z-BF) of BF assessed with CUN-BAE index as a continuous variable were performed for the total population and for men and women separately. Several sensitivity analyses were conducted estimating the fully-adjusted HRs for the comparison between the highest versus the lowest quartile of BF assessed with the CUN-BAE index and its association with incident diabetes after changing several assumptions: (i) adopting total energy intake percentiles 1 to 99 as allowed limits; (ii) including only participants younger than 50 years; (iii) excluding participants with prevalent cancer at baseline; (iv) excluding participants with prevalent hypertension at baseline; (v) excluding participants with prevalent hypertriglyceridemia at baseline; and (vi) excluding participants with prevalent hypercholesterolemia at baseline. We assessed interaction between sex and CUN-BAE index quartiles using likelihood ratio tests (3 degrees of freedom) in the fully-adjusted Cox models. We introduced a product-term with both sex and CUN-BAE index in quartiles (3 d.f.). Receiver-operating characteristic (ROC) analyses were performed to examine the discriminative power of CUN-BAE index and BMI to predict T2D; roccomp Stata command was used to compare the statistical significance between area under the curve (AUC) values of CUN-BAE index and BMI. We performed these analyses with Stata software package version 12 (Stata Corp). All p values were 2-tailed and significance was set at $p < 0.05$. Values in the text are means ± SDs unless otherwise indicated.

3. Results

3.1. Characteristics of participants

Among 239 770 person-years of follow-up (median follow-up: 13.7 years; IQR range: 8.6, 17.3 years) during the 1999–2022 period we identified 209 cases of incident T2D in the SUN cohort. Table 1 shows the baseline characteristics of participants, including demographic,

Table 1
Baseline characteristics of men and women according to quartiles (Q) of Body Fat (as captured by the CUN-BAE index) among participants in the SUN ("Seguimiento Universidad de Navarra") cohort, 1999-2022[1].

Men				
	Q1	Q2	Q3	Q4
Limits of estimated body fat (range)	18.4, 32.9	32.9, 36.4	36.4, 39.6	39.6, 58.4
N	1835	1834	1835	1834
Age, y	31.2 (8.1)	39.9 (9.9)	47.0 (11.4)	51.7 (12.3)
Married men, %	29.5	61.2	75.8	79.5
University education, y	5.2 (1.6)	5.5 (1.7)	5.5 (1.8)	5.4 (1.8)
BMI, kg/m^2	22.2 (1.4)	24.4 (1.1)	26.1 (1.2)	29.4 (2.6)
Smoking				
- Never, %	63.3	48.8	37.2	29.6
- Current, %	21.2	22.3	19.6	20.1
- Former smoker, %	15.5	28.9	43.2	50.3
Leisure-time physical activity, METs-h/wk	32.1 (31.4)	27.4 (26.3)	25.2 (24.1)	19.9 (20.8)
Television watching, h/d	1.5 (1.2)	1.5 (1.0)	1.6 (1.1)	1.7 (1.1)
Family history of diabetes, %	10.1	13.6	18.6	21.8
Hypertension at baseline, %	5.5	10.1	19.5	37.6
CVD at baseline, %	0.7	1.5	3.3	5.4
Hypertriglyceridemia at baseline, %	2.8	7.9	13.7	23.7
Hypercholesterolemia at baseline, %	9.1	19.3	29,1	36.3
Cancer at baseline, %	1.5	1.3	2.7	4.1
Total energy intake, kcal/d	2565 (660)	2444 (633)	2369 (668)	2298 (673)
Adherence to Mediterranean Diet[2]	3.8 (1.8)	4.3 (1.8)	4.6 (1.8)	4.6 (1.8)
Adoption of special diets, %	6.2	7.8	9.1	12.9
Between-meal snacking, %	30.8	23.1	24.4	30.0
Siesta, %	46.4	54.4	60.3	64.1
Weight gain before baseline (5 y), %	24.6	32.3	38.5	49.1
Dietary consumption				
Vegetables (g/d)	436 (294)	450 (279)	484 (339)	491 (315)
Fruit (g/d)	214 (196)	244 (214)	279 (259)	272 (267)
Legumes (g/d)	25 (19)	25 (20)	24 (19)	24 (19)
Cereals (g/d)	117 (80)	110 (76)	109 (82)	104 (85)
Whole bread (g/d)	9 (25)	9 (26)	11 (33)	12 (30)
Nuts (g/d)	8 (12)	8 (11)	8 (13)	8 (12)
Olive oil (g/d)	16 (14)	16 (13)	16 (14)	17 (15)
Eggs (g/d)	27 (19)	25 (19)	23 (17)	23 (18)
Fish and other seafood (g/d)	88 (53)	95 (55)	103 (62)	109 (64)
Whole-fat dairy products (g/d)	290 (240)	223 (196)	187 (189)	169 (193)
Low-fat dairy products (g/d)	147 (219)	169 (224)	190 (226)	197 (243)
Meat (g/d)	197 (83)	184 (78)	174 (81)	174 (77)
Coffee (cups/d)	3 (2)	4 (2)	4 (2)	4 (2)
Alcohol (g/d)	7.8 (8.8)	10.0 (12.2)	11.6 (13.8)	12.9 (16.2)

(continued on next page)

Table 1 ***(continued)***

Men				
	Q1	Q2	Q3	Q4
SSB (servings/d)[3]	0.3 (0.5)	0.3 (0.5)	0.2 (0.5)	0.2 (0.5)
Dietary intakes				
Carbohydrate (% of energy)	44 (7)	44 (7)	44 (8)	43 (8)
Protein (% of energy)	17 (3)	18 (3)	18 (3)	18 (4)
Total fat (% of energy)	37 (6)	36 (6)	35 (7)	35 (7)
MUFAs (% of energy)	15 (3)	15 (3)	15 (3)	15 (4)
SFAs (% of energy)	13 (3)	13 (3)	12 (3)	12 (3)
PUFAs (% of energy)	5 (2)	5 (1)	5 (1)	5 (1)
Vitamin C (mg/d)	245 (141)	249 (132)	259 (147)	255 (143)
Vitamin D (mcg/d)	6.2 (4.0)	6.3 (4.3)	6.5 (4.7)	6.5 (4.5)
K (mg/d)	4600 (1434)	4584 (1465)	4679 (1665)	4636 (1630)
Mg (mg/d)	415 (119)	411 (120)	415 (131)	408 (129)
Dietary fibre (g/d)	21 (9)	22 (10)	23 (11)	22 (10)
Women				
	Q1	Q2	Q3	Q4
Limits of Body fat (range)	27.9, 38.6	38.6, 41.9	41.9, 45.7	45.7, 65.0
N	2815	2813	2814	2814
Age, y	27.2 (5.2)	32.1 (7.4)	37.5 (9.3)	43.8 (11.2)
Married women, %	19.6	38.7	53.2	58.6
University education, y	4.7 (1.2)	4.9 (1.3)	4.9 (1.4)	4.9 (1.4)
BMI, kg/m^2	19.2 (1.0)	20.9 (0.9)	22.5 (1.1)	26.1 (2.9)
Smoking				
- Never, %	60.9	53.9	48.0	44.4
- Current, %	24.8	23.6	21.9	19.9
- Former smoker, %	14.3	22.5	30.2	35.7
Leisure-time physical activity, METs-h/wk	19.8 (20.9)	19.9 (20.2)	19.7 (20.1)	16.6 (17.1)
Television watching, h/d	1.6 (1.3)	1.6 (1.4)	1.6 (1.3)	1.7 (1.2)
Family history of diabetes, %	9.2	12.4	16.0	22.1
Hypertension at baseline, %	1.6	2.8	4.6	13.4
CVD at baseline, %	0.5	0.5	0.6	0.9
Hypertriglyceridemia at baseline, %	1.5	1.6	1.7	6.5
Hypercholesterolemia at baseline, %	7.6	9.4	12.9	20.9
Cancer at baseline, %	1.4	1.7	3.7	4.4
Total energy intake, kcal/d	2346 (565)	2307 (571)	2277 (564)	2232 (586)
Adherence to Mediterranean Diet[2]	3.9 (1.8)	4.1 (1.8)	4.3 (1.8)	4.5 (1.8)
Adoption of special diets, %	6.5	7.7	10.9	18.0
Between-meal snacking, %	38.4	35.0	34.1	41.0
Siesta, %	49.1	52.1	54.1	58.2
Weight gain before baseline (5 y), %	10.3	19.5	29.4	46.7
Dietary consumption				
Vegetables (g/d)	543 (342)	548 (330)	570 (336)	614 (383)
Fruit (g/d)	286 (253)	289 (245)	320 (246)	349 (288)
Legumes (g/d)	22 (16)	22 (17)	21 (17)	22 (19)
Cereals (g/d)	98 (65)	97 (62)	98 (68)	93 (67)
Whole bread (g/d)	14 (31)	15 (32)	16 (33)	16 (33)
Nuts (g/d)	7 (12)	7 (11)	7 (12)	7 (12)
Olive oil (g/d)	19 (15)	19 (15)	20 (15)	21 (16)
Eggs (g/d)	22 (15)	22 (14)	22 (13)	22 (14)
Fish and other seafood (g/d)	93 (56)	94 (61)	98 (60)	106 (65)
Whole dairy products (g/d)	205 (195)	189 (188)	174 (181)	143 (170)
Low-fat dairy products (g/d)	240 (252)	248 (249)	263 (255)	292 (251)
Meat (g/d)	173 (79)	169 (77)	171 (77)	171 (78)
Coffee (cups/d)	4 (2)	4 (2)	4 (2)	4 (2)
Alcohol (g/d)	3.5 (4.7)	4.1 (5.9)	4.3 (6.4)	4.2 (6.3)
SSB (servings/d)[3]	0.2 (0.4)	0.2 (0.3)	0.2 (0.3)	0.1 (0.3)
Dietary intakes				
Carbohydrate (% of energy)	44 (7)	44 (7)	44 (7)	43 (8)
Protein (% of energy)	18 (3)	18 (3)	19 (3)	19 (4)
Total fat (% of energy)	37 (7)	37 (6)	37 (7)	36 (7)
MUFAs (% of energy)	16 (4)	16 (4)	16 (4)	16 (4)
SFAs (% of energy)	13 (3)	13 (3)	12 (3)	12 (3)
PUFAs (% of energy)	5 (2)	5 (2)	5 (2)	5 (2)
Vitamin C (mg/d)	287 (159)	290 (152)	302 (153)	318 (173)
Vitamin D (mcg/d)	6.2 (4.3)	6.0 (4.2)	6.3 (4.8)	6.5 (4.7)
K (mg/d)	4798 (1570)	4772 (1554)	4883 (1539)	5052 (1717)
Mg (g/d)	415 (121)	413 (120)	419 (121)	427 (131)
Dietary fibre (g/d)	22 (10)	22 (9)	23 (10)	24 (10)

CVD: cardiovascular disease; MET: metabolic equivalent task; MUFA: monounsaturated fatty acid; SFA: saturated fatty acid; SSB: sugar sweetened beverages; PUFA: polyunsaturated.
fatty acid.

[1] Values are mean (SD) unless otherwise stated.

[2] Mediterranean Diet Score, 0–9 points, according to reference [21].

[3] One serving of sugar-sweetened beverages = 200 mL.

anthropometric, lifestyle parameters, food consumption and nutrient intake, according to quartiles of BF captured with CUN-BAE index. Among all participants, men and women, those within the highest vs. the lowest quartile of CUN-BAE index were more likely to be older, married, smokers, and had higher BMI, higher family history of diabetes, higher personal history of hypertension, CVD, hypercholesterolemia, hypertriglyceridemia and cancer, more likely to follow a special diet, to take a nap after meals (siesta), and to had a higher weight gain in the 5 years before baseline evaluation. Men in the highest quartile of CUN-BAE index were more likely to drink higher amounts of alcohol.

3.2. Body fat and incident diabetes

The main results for the analyses of incident T2D in the Cox models are shown in Table 2 and the cumulative incidence curves in Fig. 1. There was a strong and significant direct association of the CUN-BAE index quartiles at baseline with incident T2D during follow-up in all the models, showing a monotonic trend: from the crude model and after multivariable adjustments (Model 1) in both men and women we found significant linear trends for all these analyses. In order to evaluate if the association was independent of being or not obese, we repeated the analyses further adjusting for BMI $> 30\,kg/m^2$ (Model 2). In these latter analyses the results remained significant confirming that the risk of developing diabetes does not start with obesity but even before reaching a BMI $> 30\,kg/m^2$, and progressively continue in a linear fashion. The continuous risk of incident T2D for each 2-unit increase in CUN-BAE index was strong and significant in the fully-adjusted multivariate adjusted analyses increasing the risk of diabetes by 46% in both men and women (HR 1.46; 95% CI 1.33, 1.62).

Considering longitudinally repeated measures capturing also changes in BF assessed with CUN-BAE index in the biennial follow-up questionnaires, the results were consistent, suggesting a strong and significant association in the fully-adjusted multivariable models. For each 2-unit increase in CUN-BAE index in the fully-adjusted analyses with repeated measures, there was a 70% higher risk of developing T2D in both men and women (HR 1.70; 95% CI 1.47, 1.97) (Table 2).

For the analyses of the association of CUN-BAE and incident T2D considering the increase of one standard deviation (z-BF) of BF captured with CUN-BAE index as a continuous variable, we found a significant increased risk of incident T2D for crude analyses as well as for multivariable adjusted Model 1 and Model 2, considering CUN-BAE index at baseline, as well as considering longitudinal repeated measures of BF for all the participants and separately for men and women (Supplementary Tables S1 and S2). We repeated the analyzes considering z-BMI, which were also significant but with lower values respect to those we found for z-BF (Supplementary Table S3). Fig. 2 shows the ROC analysis curves of BMI and BF assessed with CUN-BAE index for the prediction of T2D in men and women. When comparing AUC between CUN-BAE index and BMI in both men and women the prediction was stronger for CUN-BAE vs. BMI ($p < 0.001$).

3.3. Interaction between CUN-BAE index and sex

We assessed the interaction of the potential modifying effect of sex by CUN-BAE index in quartiles (3 d.f.). We found a statistically significant interaction when considering quartiles of CUN-BAE index in the fully-adjusted models ($p < 0.001$). For z-BF the interaction with sex was also significant ($p = 0.019$).

3.4. Sensitivity analyses

Several sensitivity analyses were performed to confirm if the significant association of BF, as captured by quartiles of CUN-BAE index, and incident T2D in the multivariable fully-adjusted models were maintained in different conditions (Table 3). This association remained robustly significant for both men and women in the following conditions: (1) considering allowed limits for total energy intake from percentile 1–99; (2) including only participants younger than 50 years; (3) excluding participants with prevalent cancer; (4) excluding participants with prevalent hypertension; (5) excluding participants with prevalent hypertriglyceridemia; (6) excluding participants with prevalent hypercholesterolemia.

4. Discussion

The present analyses on data from a prospective, well-characterized, and large cohort of university graduates suggested that BF as appraised by means of the CUN-BAE index was strongly and positively associated with

Table 2
Association between Quartiles of Body Fat (BF), as captured by the CUN-BAE index, and incident diabetes among men and women in the SUN ("Seguimiento Universidad de Navarra") cohort, 1999-2022[1].

	BF Quartiles				
	Q1 & Q2	Q3	Q4	*P-trend*	HR for +2 units of BF increase
n	9297	4649	4648		
Median (p25, p75)	36.2 (33.5, 39.2)	42.5 (38.4, 44.0)	46.8 (42.7, 49.3)		
Incident diabetes (cases)	16	45	148		
Person-years of follow-up	121,391	60,820	57,561		
Crude rate ($\times 10^{-3}$)	0.13	0.74	2.57		
Crude HR	1 (ref.)	2.81 (1.57, 5.04)	7.53 (4.38, 12.95)	<0.001	1.16 (1.10, 1.21)
Multivariate-adjusted HR[2] Model 1	1 (ref.)	2.65 (1.47, 4.80)	5.74 (3.25, 10.13)	<0.001	1.50 (1.40, 1.61)
Multivariate-adjusted HR[3] Model 2	1 (ref.)	2.59 (1.44, 4.68)	3.77 (2.08, 6.80)	<0.001	1.46 (1.33, 1.62)
Repeated measures					
Crude HR	1 (ref.)	2.06 (0.89, 4.80)	8.19 (3.74, 17.93)	<0.001	1.13 (1.06, 1.22)
Multivariate-adjusted HR[2] Model 1	1 (ref.)	2.08 (0.92, 4.72)	8.56 (4.05, 18.08)	<0.001	1.61 (1.47, 1.76)
Multivariate-adjusted HR[3] Model 2	1 (ref.)	2.07 (0.92, 4.67)	6.48 (3.03, 13.85)	<0.001	1.70 (1.47, 1.97)

[1] Values are HR estimated with Cox regression and 95% confidence intervals (CI).
[2] Model 1: HR adjusted for sex, marital status, body weight changes, years of university education, smoking, pack-year, physical activity, television watching, family history of diabetes, total energy intake, adherence to Mediterranean diet, sugar-sweetened beverages, between-meal snacking, adoption of special diet, dietary potassium, dietary magnesium, hypercholesterolemia, hypertriglyceridemia, hypertension, cancer, year of entrance to the cohort.
[3] Model 2: HR adjusted for factors in Model 1 plus BMI higher than $30\,kg/m^2$.

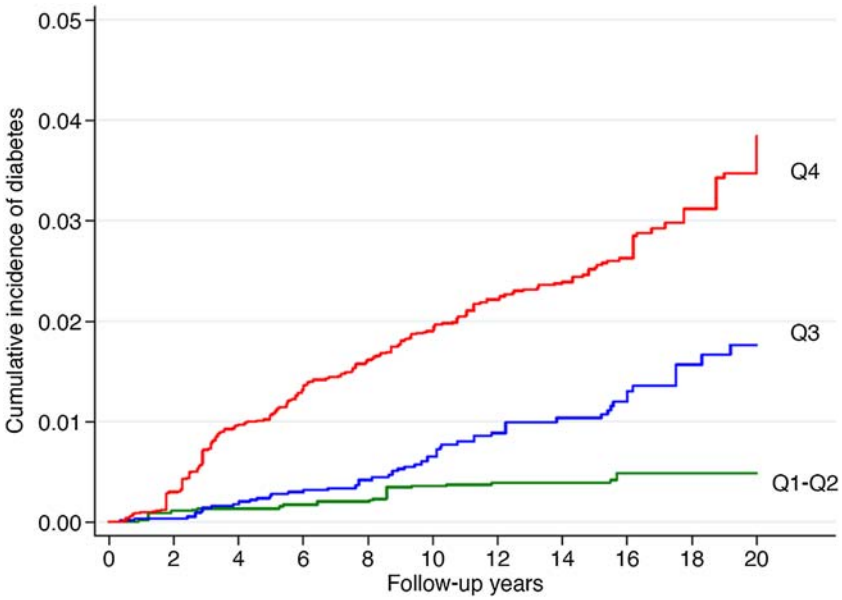

Fig. 1. Nelson-Aalen estimates of cumulative incidence of T2D according to quartiles of body fat assessed with CUN-BAE index among men and women in the SUN ("Seguimiento Universidad de Navarra") cohort, 1999–2022. Adjusted (using inverse probability weighting) for age, sex, marital status, body weight changes, years of university education, smoking, pack-year, physical activity, television watching, family history of diabetes, total energy intake, adherence to Mediterranean diet, sugar-sweetened beverages, between-meal snacking, adoption of special diet, dietary potassium, dietary magnesium, hypercholesterolemia, hypertriglyceridemia, hypertension, cancer, BMI higher than 30 kg/m^2 and year of entrance to the cohort.

incident T2D independently of numerous potential confounders after a long follow-up and a better predictor of T2D risk than BMI. The risk of developing T2D was independently associated with CUN-BAE even after adjusting for obesity (BMI $\geq$ 30 kg/m^2) suggesting that the association was independent of being obese. We also observed that the updated CUN-BAE modifications during follow-up (repeated evaluation every two years) resulted in similarly strong association with the risk of T2D as well as after various sensitivity analyses. This is the first study investigating longitudinally the association of BF assessed with the CUN-BAE index and the risk of T2D in a Mediterranean population.

Increased BF manifested as obesity is a major risk factor for T2D risk at all ages worldwide [1–3]. Former studies in the Nurses' Health Study [25] and in the US male Health Professionals cohort [26] reported a 49-fold and 42-fold higher T2D risk for participants with BMI > 35 kg/m^2, respectively. In previous analyses from the SUN cohort we observed a 64-fold increased risk of T2D for BMI > 35 kg/m^2 vs. BMI < 22 kg/m^2, and a 4-fold increase even in persons with BMI 22.1–24.9 kg/m^2 vs. those with BMI < 22 kg/m^2 [27].

The pathogenesis of T2D involves genetics, biology, healthcare availability and access, mental status, sociocultural factors, personal lifestyle, circadian rhythms, gut microbiota, and other environmental influences. Lifestyle interventions favoring weight loss showed to delay T2D incidence [28,29], while obesity and unfavorable lifestyle were associated with increased risk of incident T2D regardless of genetic risk [30].

The most widely used biometric parameter for defining normal, under or overweight/obesity is BMI, which may correlate with BF but has a low predictive ability [6,31]; its use in isolation is debated because it does not consider body composition, sex or age. BMI may increase as adiposity rises, but body composition modifications make the correlation weak. As such, greater muscle mass or larger bones may be associated with a higher BMI without being linked to a pathological condition. Recent analyses from the Nurses' Health Study and the US male Health Professionals cohort found that predicted fat mass was a stronger predictor of T2D risk than BMI (HR for T2D comparing the highest vs. the lowest quintile of fat mass was 8.38 for men and 12.1 for women, while for BMI HR was 6.94 for men and 9.88 for women [32]. BMI has been a useful indicator in epidemiological research, but may be an inaccurate instrument for determining health outcomes in an individual basis. Because instruments to measure BF directly are not readily available in routine clinical practice, indirect methods have proven to correlate well with adiposity [32,33]. Among these ready-to-use methods to calculate adiposity, the CUN-BAE index showed a stronger correlation with the actual amount of BF compared to other anthropometric indicators [9].

Previous studies have shown appropriate accuracy and validity of the CUN-BAE index in the assessment of metabolic conditions [8,11,13–15,33–37]. Regarding metabolic syndrome, cross-sectional studies in populations from Spain [11,13,34], UK [35], South Africa [36], Poland [8,37], and China [33] have shown significant associations of adiposity calculated with the CUN-BAE index and metabolic syndrome. The original study conceiving the CUN-BAE index showed a significant correlation with insulin sensitivity [9]. Though these cross-sectional studies support that this index has proven useful in different populations for the prediction of metabolic syndrome, there is a scarcity of prospective studies.

For T2D, two cross-sectional studies in populations from Spain [13] and China [38], and one prospective study from Norway [14], as well as one retrospective study from Japan [15], reported significant positive associations of CUN-BAE index in relation to T2D. Specifically, among 3888 Spaniards, the attributable fraction for T2D was over 50% higher when assessed with CUN-BAE as compared to BMI [13] concluding that T2D may be underestimated if assessed using the BMI vs. CUN-BAE index. In 69 388 Chinese participants aged $\geq$60 years the associations of CUN-BAE index and BMI with T2D were similar [38]. Among 6796 participants of a prospective cohort study from Norway the correlation between CUN-BAE and BF (r = 0.88) was stronger than between BMI and BF (r = 0.56). Compared with BMI, the CUN-BAE index showed a stronger association with T2D risk over a 6-year follow-up (in men OR = 2.13 [95%CI: 1.64–2.83] for BMI and OR = 4.33 [95%CI: 2.80–6.71] for CUN-BAE; in women OR = 2.11 [95%CI: 1.76–2.53] for BMI and OR = 5.45 [95%CI: 3.87–7.67] for CUN-BAE) [14]. A retrospective longitudinal study involving 15,464 Japanese participants found that CUN-BAE had a better

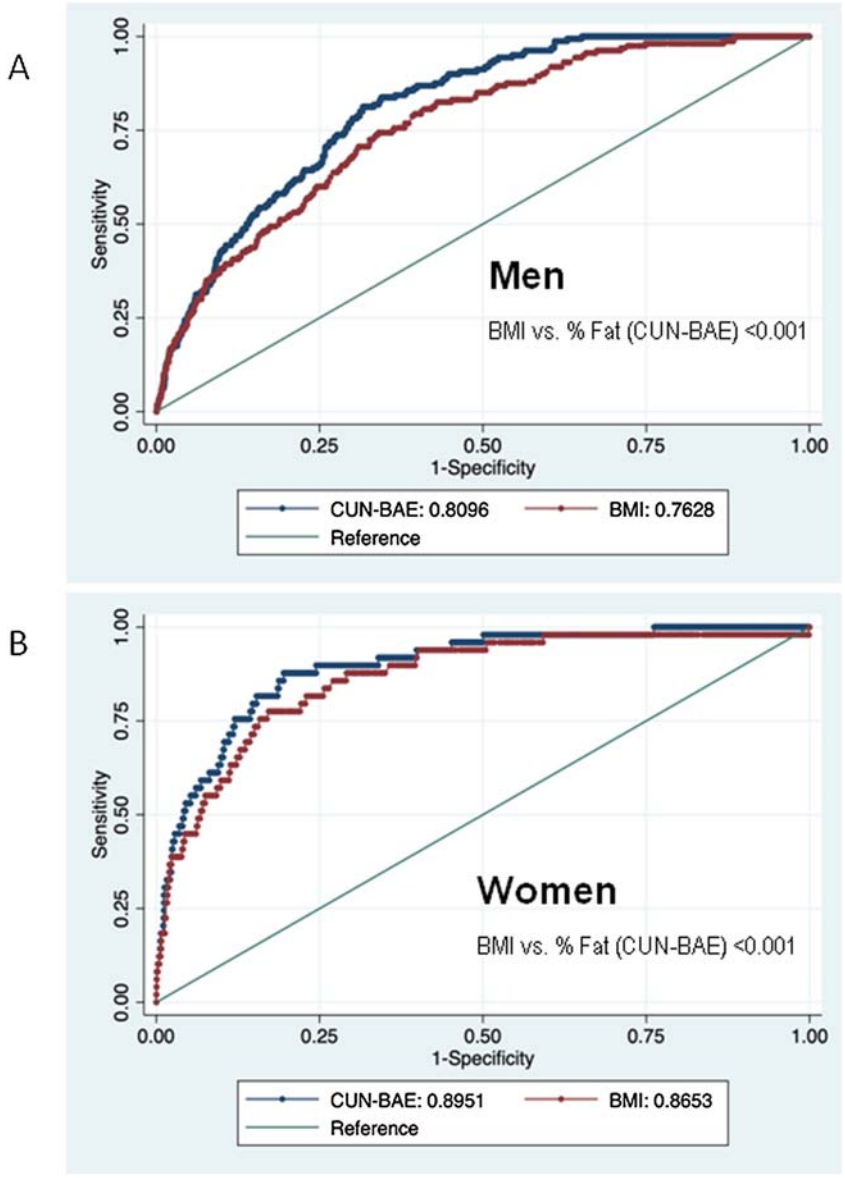

Fig. 2. ROC analysis curves of BMI and body fat assessed with CUN-BAE index for the prediction of T2D in men (*panel A*) and women (*panel B*).

capacity for T2D prediction than both BMI and waist circumference in both sexes after an average follow-up of 5.4 years [15]. These results are consistent with ours, this time with a prospective design in a large Mediterranean cohort with follow-up for several years and multiple repeated measurements throughout the follow-up.

Knowledge on adipose tissue has profoundly changed in the past decades, from considering it only as a full reserve to recognizing it as an endocrine organ producing hormones and other bioactive compounds [39]. The strong link between progressively higher BF and incident T2D that we observed, may be explained by various mechanisms comprising insulin resistance (IR) [40,41], β-cell dysfunction [42], chronic inflammation [39], lipotoxicity [43], and hormonal imbalance [39,41]. It is well-known that excessive BF, mainly abdominal and visceral fat with increased intrahepatic and intramuscular triglycerides, is strongly associated with IR [40,43]. A key role for the generation of IR is attributed to the release of lipids and other circulating factors that alter intracellular levels of crucial intermediates, such as ceramide and other lipids, which inhibit components in the signaling cascade [40]. Recent research has highlighted the role of altered adipose-tissue glucose transport, as a key regulator of systemic insulin sensitivity and whole-body energy balance [41]. Fasting and post-prandial insulin secretion is higher in non-diabetic obese vs. lean people helping overcoming IR and maintenance of normal blood glucose levels. However, the progressive β-cell function decline causes altered glycemic control leading to T2D [42]. Infiltration of immune cells in excess adipose tissue leads to the secretion of proinflammatory cytokines, which may initially be a physiological stress response but maladaptive in the long-term [39]. Adipose tissue failure to continue expanding leads to overspill and deposition of triglycerides throughout the body, with ectopic liver and skeletal muscle accumulation generating lipotoxicity, metabolic dysregulation and T2D [43]. Various hormones, such as adiponectin, leptin, resistin, hepcidin, retinol binding protein 4, and estrogen can become dysregulated with excess adipose tissue accumulation, contributing to IR and progression to T2D [39].

Strengths of the present study include the large sample, extensive follow-up, prospective design, and the possibility of adjustments for multiple potential confounders. Another strengths are the high retention rate and the possibility of repeated measurements of the CUN-BAE index

Table 3
Sensitivity analyses: Multivariable-adjusted Hazard Ratios of incident diabetes associated with Body Fat, as captured by the CUN-BAE index, among men and women in the SUN ("Seguimiento Universidad de Navarra") cohort, 1999-2022[1].

	n	Cases of incident hypertension n	HR (95% CI)[2,3]
Main analysis[2,3]	18594	209	3.48 (1.91, 6.33)
Changing allowable energy limits (percentiles 1–99)[2,3,4]	20099	217	3.89 (2.12, 7.14)
Including only participants <50 y in tertiles[2,3]	15302	82	3.84 (1.64, 8.99)
Excluding participants with prevalent cancer[2,3,*]	18103	198	3.22 (1.76, 5.90)
Excluding participants with prevalent hypertension[2,3,*]	16631	113	4.84 (2.25, 10.40)
Excluding participants with prevalent hypertriglyceridemia[2,3,*]	17393	136	4.03 (1.95, 8.35)
Excluding participants with prevalent hypercholesterolemia[2,3,*]	15446	114	4.0 (1.78, 8.96)

CVD: cardiovascular disease.
[1] Values are HR estimated with Cox regression and 95% confidence intervals (CI) between extreme quartiles.
[2] Model 1: HR adjusted for sex, marital status, body weight changes, years of university education, smoking, pack-year, physical activity, television watching, family history of diabetes, total energy intake, adherence to Mediterranean diet, sugar-sweetened beverages, between-meal snacking, adoption of special diet, dietary potassium, dietary magnesium, hypercholesterolemia, hypertriglyceridemia, hypertension, cancer, year of entrance to the cohort.
[3] Model 2: HR adjusted for factors in Model 1 plus BMI higher than 30 kg/m^2.
[4] The sample size of this sensitivity analysis (changing allowable energy limits) was larger than the sample size of the main analysis because changing these allowable limits inherently led to a different sample size.
[*] When excluding prevalent cancer, hypertension, hypertriglyceridemia, or hypercholesterolemia the specific disease was excluded from Models 1 and 2.

during biennially follow-up. Possible limitations include: (i) the use of self-reported information, however, variables such as self-reported weight and BMI as well as FFQ have been previously validated in subsamples of our cohort [24,44,45]; (ii) the cohort is composed of highly educated participants, with reduced prevalence of overweight/obesity and high physical activity levels, which helps explain the relatively low number of incident T2D and the consequent width of some confidence intervals. Nevertheless, we found stronger associations of BF assessed with CUN-BAE index and incident T2D than with BMI; (iii) Some relevant confounding factors such as socioeconomic status, education, disease, and access to medical care were reduced in our study. However, notwithstanding the characteristics of our cohort, the application of our results in other populations must be based on biological mechanisms and not only on statistical representativeness. Our findings should be confirmed in other population with different characteristics.

5. Conclusion

Increased BF assessed with CUN-BAE index, a validated method to appraise adiposity, was positively, strongly, and independently associated with a higher risk of incident T2D in our Mediterranean cohort showing stronger discrimination than BMI. After further adjustments for obesity, defined by BMI, the results remained robustly significant, which suggests that diabetes risk starts long before excessive weight gain is achieved. Our results highlight the crucial need to control the accumulation of BF tissue, even for persons not usually considered obese, in order to prevent diabetes. It is urgent to contrast these syndemics that continue to spread and cause so much morbidity, mortality, and declining quality of life.

CRediT authorship contribution statement

Study conceptualization and design: L.J.D., E.T. and M.A.M.-G.; acquisition, analysis, and interpretation of data: E.T, C.S.-O, A.G., L.J.D., M.A.M.-G., M.B. M.B.-R.; intellectual content: L.J.D., C.S.-O., E.T., A.G., M.B.-R, M.B., and M.A.M.-G. All authors contributed to the interpretation of the results and the development of the manuscript and agreed to the published version of the manuscript.

Declaration of Generative AI and AI-assisted technologies in the writing process

We confirm that we have not used AI and AI-assisted technologies in the writing process.

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Data availability statement

The data that support the findings of this study are available from the SUN Project at sun@unav.es, upon reasonable request.

Declaration of competing interest

The authors declared no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jnha.2025.100545.

References

[1] Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism 2022;133:155217, doi:http://dx.doi.org/10.1016/j.metabol.2022.155217.
[2] Bluher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol 2019;15:288–98, doi:http://dx.doi.org/10.1038/s41574-019-0176-8.
[3] Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level Diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022;183:109119, doi:http://dx.doi.org/10.1016/j.diabres.2021.109119.
[4] Piche ME, Tchernof A, Despres JP. Obesity phenotypes, diabetes, and cardiovascular diseases. Circ Res 2020;126:1477–500, doi:http://dx.doi.org/10.1161/CIRCRESAHA.120.316101.
[5] Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The concept of normal weight obesity. Prog Cardiovasc Dis 2014;56:426–33, doi:http://dx.doi.org/10.1016/j.pcad.2013.10.003.

[6] Visaria A, Setoguchi S. Body mass index and all-cause mortality in a 21st century U.S. Population: a national health interview survey analysis. PLoS One 2023;18:e0287218, doi:http://dx.doi.org/10.1371/journal.pone.0287218.
[7] Borga M, West J, Bell JD, Harvey NC, Romu T, Heymsfield SB, et al. Advanced body composition assessment: from body mass index to body composition profiling. J Investig Med 2018;66:1–9, doi:http://dx.doi.org/10.1136/jim-2018-000722.
[8] Suliga E, Ciesla E, Gluszek-Osuch M, Rogula T, Gluszek S, Koziel D. The usefulness of anthropometric indices to identify the risk of metabolic syndrome. Nutrients 2019;11:2598, doi:http://dx.doi.org/10.3390/nu11112598.
[9] Gomez-Ambrosi J, Silva C, Catalan V, Rodriguez A, Galofre JC, Escalada J, et al. Clinical usefulness of a new equation for estimating body fat. Diabetes Care 2012;35:383–8, doi:http://dx.doi.org/10.2337/dc11-1334.
[10] Dominguez LJ, Sayon-Orea C, Gea A, Toledo E, Barbagallo M, Martinez-Gonzalez MA. Increased adiposity appraised with CUN-BAE is highly predictive of incident hypertension. The SUN project. Nutrients 2021;13:3309, doi:http://dx.doi.org/10.3390/nu13103309.
[11] Gomez-Marcos MA, Gomez-Sanchez L, Patino-Alonso MC, Recio-Rodriguez JI, Gomez-Sanchez M, Rigo F, et al. Capacity adiposity indices to identify metabolic syndrome in subjects with intermediate cardiovascular risk (MARK study). PLoS One 2019;14:e0209992, doi:http://dx.doi.org/10.1371/journal.pone.0209992.
[12] Davila-Batista V, Molina AJ, Vilorio-Marques L, Lujan-Barroso L, de Souza-Teixeira F, Olmedo-Requena R, et al. Net contribution and predictive ability of the CUN-BAE body fatness index in relation to cardiometabolic conditions. Eur J Nutr 2019;58:1853–61, doi:http://dx.doi.org/10.1007/s00394-018-1743-9.
[13] Martin V, Davila-Batista V, Castilla J, Godoy P, Delgado-Rodriguez M, Soldevila N, et al. Comparison of body mass index (BMI) with the CUN-BAE body adiposity estimator in the prediction of hypertension and type 2 diabetes. BMC Public Health 2016;16:82, doi:http://dx.doi.org/10.1186/s12889-016-2728-3.
[14] Vinknes KJ, Nurk E, Tell GS, Sulo G, Refsum H, Elshorbagy AK. The relation of CUN-BAE index and BMI with body fat, cardiovascular events and diabetes during a 6-year follow-up: the Hordaland Health Study. Clin Epidemiol 2017;9:555–66, doi:http://dx.doi.org/10.2147/CLEP.S145130.
[15] Peng Q, Feng Z, Cai Z, Liu D, Zhong J, Zhao H, et al. The relationship between the CUN-BAE body fatness index and incident diabetes: a longitudinal retrospective study. Lipids Health Dis 2023;22:21, doi:http://dx.doi.org/10.1186/s12944-023-01784-5.
[16] Gomez-Sanchez L, Garcia-Ortiz L, Patino-Alonso MC, Recio-Rodriguez JI, Rigo F, Marti R, et al. Adiposity measures and arterial stiffness in primary care: the MARK prospective observational study. BMJ Open 2017;7:e016422, doi:http://dx.doi.org/10.1136/bmjopen-2017-016422.
[17] Martinez-Gonzalez MA, Sanchez-Villegas A, De Irala J, Marti A, Martinez JA. Mediterranean diet and stroke: objectives and design of the SUN project. Seguimiento Universidad de Navarra. Nutr Neurosci 2002;5:65–73, doi:http://dx.doi.org/10.1080/10284150290007047.
[18] Segui-Gomez M, de la Fuente C, Vazquez Z, de Irala J, Martinez-Gonzalez MA. Cohort profile: the' Seguimiento Universidad de Navarra' (SUN) study. Int J Epidemiol 2006;35:1417–22, doi:http://dx.doi.org/10.1093/ije/dyl223.
[19] Willett W. Nutritional epidemiology. 3rd ed New York: Oxford University Press; 2013, doi:http://dx.doi.org/10.1093/acprof:oso/9780199754038.001.0001.
[20] ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Addendum. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. Diabetes Care 2023;46(Suppl. 1):S19–40, doi:http://dx.doi.org/10.2337/dc23-ad08.
[21] Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003;348:2599–608, doi:http://dx.doi.org/10.1191/1358863x04vm552xx.
[22] Martinez-Gonzalez MA, Lopez-Fontana C, Varo JJ, Sanchez-Villegas A, Martinez JA. Validation of the Spanish version of the physical activity questionnaire used in the Nurses' Health Study and the Health Professionals' Follow-up study. Public Health Nutr 2005;8:920–7, doi:http://dx.doi.org/10.1079/phn2005745.
[23] Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:S498–504, doi:http://dx.doi.org/10.1097/00005768-200009001-00009.
[24] Bes-Rastrollo M, Perez Valdivieso JR, Sanchez-Villegas A, Alonso A, Martinez-Gonzalez MA. Validación del peso e índice de masa corporal auto-declarados de los participantes de una cohorte de graduados universitarios. Rev Esp Obes 2005;3:183–9.
[25] Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995;122:481–6, doi:http://dx.doi.org/10.7326/0003-4819-122-7-199504010-00001.
[26] Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282:1523–9, doi:http://dx.doi.org/10.1001/jama.282.16.1523.
[27] Dominguez LJ, Bes-Rastrollo M, Basterra-Gortari FJ, Gea A, Barbagallo M, Martinez-Gonzalez MA. Association of a dietary score with incident type 2 diabetes: the dietary-based diabetes-risk score (DDS). PLoS One 2015;10:e0141760, doi:http://dx.doi.org/10.1371/journal.pone.0141760.
[28] Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–50, doi:http://dx.doi.org/10.1056/NEJM200105033441801.
[29] Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403, doi:http://dx.doi.org/10.1056/NEJMoa012512.
[30] Schnurr TM, Jakupovic H, Carrasquilla GD, Angquist L, Grarup N, Sorensen TIA, et al. Obesity, unfavourable lifestyle and genetic risk of type 2 diabetes: a case-cohort study. Diabetologia 2020;63:1324–32, doi:http://dx.doi.org/10.1007/s00125-020-05140-5.
[31] Prentice AM, Jebb SA. Beyond body mass index. Obes Rev 2001;2:141–7, doi:http://dx.doi.org/10.1046/j.1467-789x.2001.00031.x.
[32] Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Willett WC, et al. Comparison of the association of predicted fat mass, body mass index, and other obesity indicators with type 2 diabetes risk: two large prospective studies in US men and women. Eur J Epidemiol 2018;33:1113–23, doi:http://dx.doi.org/10.1007/s10654-018-0433-5.
[33] Guo X, Ding Q, Liang M. Evaluation of eight anthropometric indices for identification of metabolic syndrome in adults with diabetes. Diabetes Metab Syndr Obes 2021;14:1431–43, doi:http://dx.doi.org/10.2147/DMSO.S294244.
[34] Lopez-Gonzalez AA, Jover AM, Martinez CS, Artal PM, Bote SA, Jane BA, et al. The CUN-BAE, Deurenberg Fat Mass, and visceral adiposity index as confident anthropometric indices for early detection of metabolic syndrome components in adults. Sci Rep 2022;12:15486, doi:http://dx.doi.org/10.1038/s41598-022-19343-w.
[35] Amirabdollahian F, Haghighatdoost F. Anthropometric indicators of adiposity related to body weight and body shape as cardiometabolic risk predictors in British young adults: superiority of waist-to-height ratio. J Obes 2018;2018:8370304, doi:http://dx.doi.org/10.1155/2018/8370304.
[36] Sekgala MD, Opperman M, Mpahleni B, McHiza ZJ. Anthropometric indices and cut-off points for screening of metabolic syndrome among South African taxi drivers. Front Nutr 2022;9:974749, doi:http://dx.doi.org/10.3389/fnut.2022.974749.
[37] Gluszek S, Ciesla E, Gluszek-Osuch M, Koziel D, Kiebzak W, Wypchlo L, et al. Anthropometric indices and cut-off points in the diagnosis of metabolic disorders. PLoS One 2020;15:e0235121, doi:http://dx.doi.org/10.1371/journal.pone.0235121.
[38] Bai K, Chen X, Song R, Shi W, Shi S. Association of body mass index and waist circumference with type 2 diabetes mellitus in older adults: a cross-sectional study. BMC Geriatr 2022;22:489, doi:http://dx.doi.org/10.1186/s12877-022-03145-w.
[39] Cypess AM. Reassessing human adipose tissue. N Engl J Med 2022;386:768–79, doi:http://dx.doi.org/10.1056/NEJMra2032804.
[40] James DE, Stockli J, Birnbaum MJ. The aetiology and molecular landscape of insulin resistance. Nat Rev Mol Cell Biol 2021;22:751–71, doi:http://dx.doi.org/10.1038/s41580-021-00390-6.
[41] Santoro A, Kahn BB. Adipocyte regulation of insulin sensitivity and the risk of type 2 diabetes. N Engl J Med 2023;388:2071–85, doi:http://dx.doi.org/10.1056/NEJMra2216691.
[42] Hudish LI, Reusch JE, Sussel L. Beta cell dysfunction during progression of metabolic syndrome to type 2 diabetes. J Clin Invest 2019;129:4001–8, doi:http://dx.doi.org/10.1172/JCI129188.
[43] Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. N Engl J Med 2014;371:1131–41, doi:http://dx.doi.org/10.1056/NEJMra1011035.
[44] de la Fuente-Arrillaga C, Ruiz ZV, Bes-Rastrollo M, Sampson L, Martinez-Gonzalez MA. Reproducibility of an FFQ validated in Spain. Public Health Nutr 2010;13:1364–72, doi:http://dx.doi.org/10.1017/S1368980009993065.
[45] Fernandez-Ballart JD, Pinol JL, Zazpe I, Corella D, Carrasco P, Toledo E, et al. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. Br J Nutr 2010;103:1808–16, doi:http://dx.doi.org/10.1017/S0007114509993837.