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Original article

Basal metabolic rate using indirect calorimetry among individuals living with overweight or obesity: The accuracy of predictive equations for basal metabolic rate

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SUMMARY

Background & aims: Weight reduction programs in people with overweight or obesity can be informed by indirect calorimetry (IC) which is the gold standard to measure basal metabolic rate (BMR). Since IC is labor intensive and expensive, predictive equations are often used as an alternative. In this study the accuracy rate was assessed and bias statistics of predictive equations were compared to IC among subjects with overweight or obesity. Secondly, differences in clinical features between individuals with over-, accurate or underestimation of their BMR were evaluated.

Methods: This cross sectional study included 731 subjects from the outpatient obesity clinic of the Antwerp University Hospital, Belgium. Fourteen equations were evaluated. Overestimation and underestimation was defined as >10 % and <10 % of measured BMR.

Results: In the total population, mean age was 43 ± 13 years, mean BMI 35.6 ± 5.8 kg/m^2 and 79.5 % were female. The highest accuracy rates were reached by the Henry (73 %), Ravussin (73 %) and Mifflin St. Jeor (73 %) equations. In the total population, the Mifflin St. Jeor and Henry equation were unbiased. The Akern, Livingston and Ravussin equations were biased to underestimation. All other equations were biased to overestimation.

Subjects with an underestimation of BMR had significantly higher waist-hip ratio (1.02 ± 0.13 vs 0.91 ± 0.11; P < 0.001), higher visceral adipose tissue (239 ± 96 vs 162 ± 93; P < 0.001), lower fat free mass (kg) (67.6 (45.4–95.9) vs 54.0 (39.6–95.5); P < 0.001) and a higher prevalence of the Metabolic Syndrome (24 (77.4) vs 112 (37.5); P < 0.001). Individuals with an overestimation of BMR had significantly higher subcutaneous adipose tissue (545 ± 149 vs 612 ± 149; P < 0.05), lower fasting plasma insulin (81 (10–2019) vs 67 (27–253); P < 0.001) and lower 2-h plasma glucose (132 (30–430) vs 116 (43–193); P < 0.001) during OGTT.

Conclusions: In this study, the Henry and Mifflin St. Jeor equations have the highest accuracy and lowest bias to estimate the basal metabolic rate in a Caucasian, predominantly female, population living with overweight or obesity. Visceral and subcutaneous adipose tissue and presence of metabolic syndrome were significantly different in individuals with over- or underestimation of BMR.

1. Introduction

Worldwide, more than 1.9 billion adult people have overweight, of whom 650 million have obesity [1]. These are daunting figures, since obesity is linked to, amongst others, increased risk for diabetes, cardiovascular disease, cancer, arthrosis, obstructive sleep apnea, non-alcoholic fatty liver disease [2,3]. Obesity is an

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important common consequence of energy imbalance, where energy intake chronically exceeds energy expenditure [4]. Regulation of energy metabolism varies, with body composition as a major determinant that accounts for 65–90 % of basal metabolic rate (BMR) [5–7]. Assessment of body composition by Bioelectrical Impedance Vector Analysis (BIVA) can distinguish fat mass (FM), being all body lipids that are predominantly located in adipose tissue, from fat-free mass (FFM), being nonlipid components of skeletal muscle and vital organs. Adipose tissue is considerably less metabolically active than FFM, but not metabolically inert [6]. Indirect calorimetry (IC) is seen as the gold standard to measure BMR [4,5]. Human oxygen consumption and carbon dioxide production in expired air are directly measured and then used for the calculation of BMR by the formula of Weir [4,5]. IC is an extremely valid method. However, the high cost, the time needed to perform IC and the specialized personnel make it a technique that is mainly performed in dedicated weight clinics [5]. Thus, the estimation of basal metabolic rate (BMR) via prediction equations and BIVA-derived body composition data is a common practice in clinical practice, among dieticians and for research [5–7]. Most interventions for weight loss advocate a 500 kcal deficit. If however the error of the predictive equation approaches 15 % or approximately 300 kcal, the flawed accuracy of the equation might result in inadequate nutritional recommendations for weight loss.

As most commonly used BMR equations were developed in populations with few people with obesity, the risk for a clinically significant error is real [6].

This study has 3 objectives:

1. To focus on the accuracy rate of estimation equations compared to Indirect Calorimetry (IC) among adults with overweight or obesity.
2. To report statistics for bias.
3. To report differences in clinical characteristics between individuals who showed overestimation, accurate estimation and underestimation of their BMR.

2. Material and methods

2.1. Study population

Individuals with overweight or obesity were consecutively included from the outpatient clinic of the Department of Endocrinology, Diabetology and Metabolism of the Antwerp University Hospital, a Belgian weight clinic. None of these patients were involved in a weight reduction program at the time of enrolment. Every patient underwent a standard metabolic work-up, approved by the Ethics Committee of the Antwerp University Hospital (reference 1/10/32 and 6/25/125) and provided written informed consent. Inclusion of patients was based on age ($\geq$18 years), body mass index (BMI) $\geq$ 25 kg/m^2 and completion of BIVA and indirect calorimetry.

2.2. Collection of data

The collection of data for this cross sectional study was performed from August 2012 to April 2021. A metabolic work-up was performed in fasting conditions.

BMI was calculated as weight (measured with digital scale to 0.2 kg) over height (measured to 0.5 cm) squared. Waist circumference was measured between the lower rib margin and the iliac crest, while hip circumference was measured at the trochanter major's level. Waist-hip ratio (WHR) was calculated dividing waist circumference by hip circumference. BIVA was performed early in the morning to determine body composition. The BIVA measurements were executed using the equipment of Akern® (BIA 101 RJL, Akern Bioresearch, Florence, Italy). Resistance and reactance were measured by a single-frequency 50 kHz bioelectrical impedance analyzer [8]. Body composition was calculated from bioelectrical measurements and anthropometric data by applying the software provided by the manufacturer, which incorporated validated predictive equations for total body water, FM and FFM [9]. Cross-sectional areas of total abdominal adipose tissue (TAT), visceral abdominal adipose tissue (VAT) and subcutaneous abdominal adipose tissue (SAT) were measured by computerized tomography (CT) at L4-L5 level according to previously described methods [10].

Systolic and diastolic blood pressure were measured on the patient's arm using a mercury sphygmomanometer after a least 5 min rest. A fasting blood analysis included lipid profile [total cholesterol, high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG)]. An OGTT with 75 g glucose was performed, with glucose and insulin sampling at 0 (FPG) and 120 (2hPG) minutes. Insulin resistance was calculated, using the homeostasis model assessment (HOMA-IR) as [insulin (mU/L) * [glucose (mg/dl) * 0.0555]/22.5 [11].

Plasma glucose, total cholesterol, High density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL C) and TG were measured on Atellica® Solution 1 (Siemens, Germany). HbA1c was determined by high performance liquid chromatography (Roche, Switserland; reference range: 4.8–6.0 %). C-peptide was determined by electrochemiluminescence immunoassay on Cobas 8000 e801 (Roche, Switzerland). All patients had Thyroid-stimulating hormone (TSH) levels within the reference range.

Metabolic syndrome (MetS) was defined following the harmonized definition by Alberti et al. (2009) [12]. Glucose tolerance status was defined based on the criteria of the American Diabetes Association [13].

2.3. Indirect calorimetry

Subjects stayed overnight at the metabolic ward of the University Hospital Antwerp, and BMR was measured in the morning on awakening after an overnight fast. Indirect calorimetry (IC) measurements were obtained in a fasting, semi-supine, and non-sedated state with the use of a canopy hood and a breathing valve apparatus and the Vmax Encore 29 metabolic cart. Oxygen consumption and carbon dioxide production in expired air were measured each minute for 40 min after a 10-min equilibration period.

The BMR was calculated using the Weir formula: BMR = 1440 $\times$ (3.94 VO2 [l/minute]+1.11 $\times$ VCO2 [l/minute]) kcal/day [14].

2.4. Equations used for estimating BMR

Equations that were examined among people living with overweight or obesity, and with the highest accuracy according to the literature, were selected for this study (see Table 1). More complex equations using fat mass or lean mass were excluded with the exception of the Ravussin equation because of its high accuracy. The Nachmani equation was selected because of its recent development. As discussed previously, body composition was measured

Table 1
Overview of BMR equations.

Author		Formula
Harris-Benedict [15]	male	66.4730 + 13.7516 x weight (kg) + 5.0033 x height (cm) − 6.7550 x age = kcal/day
	female	655.0955 + 9.5634 x weight (kg) + 1.8496 x height (cm)− 4.6756 x age (y) = kcal/day
Henry weight/height [16]	Male	Age 18–30 y: (MJ) = 0.0600 weight (kg)+ 1.31 height (m) + 0.473
		Age 30–60 y: (MJ) = 0.0476 weight (kg)+ 2.26 height (m) − 0.574
		Age ≥60 y: (MJ) = 0.0478 weight + 2.26 height (m) − 1.07
	Female	Age 18–30 y: (MJ) = 0.0433 weight + 2.57 height (m) − 1.18
		Age 30–60 y: (MJ) = 0.0342 weight + 2.10 height (m) - 0.0486
		Age ≥60 y: (MJ) = 0.0356 weight + 1.76 height (m) + 0.0448
Lazzer	Male [17]	(MJ) = 0.048 weight + 4.655 height (m) − 0.020 age − 3.605
	Female [18]	(MJ) = 0.042 weight + 3.619 height (m) − 2.678
Lührman et al. [19]	(diab pop)	757 + 11.9*weight - 3.7*age + 178*gender = kcal/day
Livingston & Kohlstadt [20]	male	293 x Weight^{-}0.4330 - Age (5.92) = kcal/day
	female	248 x Weight^{-}0.43356 - Age (5.09) = kcal/day
Mifflin St. Jeor [21]	Male	(9.99 × weight (kg))+(6.25 × height (cm))–(4.92 × age (y))+ 5 = kcal/day
	Female	(9.99 × weight (kg))+(6.25 × height (cm))–(4.92 × age (y)) − 161 = kcal/day
Muller et al. [22]		(MJ day-1) = 0.047 weight + 1.009 sex 0.01452 age +3.21 (male = 1; female = 0)
Muller et al. [22]	BMI 25–30 kg m^2	(MJ day-1) = 0.04507 weight + 1.006 sex - 0.01553 age +3.407 (male = 1; female = 0)
	BMI >30 kg m^2	(MJ day-1) = 0.05 weight + 1.103 sex - 0.01586 age +2.924 (male = 1; female = 0)
Nachmani et al., 2020 [23]	Male	1328.2 + 28.37 weight −205.59 height + 9.46 FFM - 2.87 A −25.93 FM = kcal/day
	female	553.97 + 16.60 weight +1033.84 height - 13.73 FFM - 10.93 A −19.67 FM = kcal/day
Owen et al.	Male [24]	795 + 7.18 weight
	Female [25]	879 + 10.2 weight
Schofield Weight/height [26]	male	Age 18–30 y: (MJ) = 0.063 weight − 0.042 height (m) + 2.953
		Age 30–60 y: (MJ) = 0.048 weight − 0.011 height (m) + 3.670
		Age ≥60 y: (MJ) = 0.038 weight + 4.068 height (m) − 3.491
	female	Age 18–30 y: (MJ) = 0.057 weight + 1.84 height (m) + 0.411
		Age 30–60 y: (MJ) = 0.034 weight + 0.006 height (m) + 3.530
		Age ≥60 y: (MJ) = 0.033 weight + 1.917 height (m) + 0.074
Ravussin & Ferraro [27]		671 + 14.6 (FFM in kg) + 7.3 (fm in kg) − 3.2(age)
Weijs & Vansant [28]		14.038 weight + 4.498 height (cm) + 137.566 sex − 0.977 age (years) −221.631 = kcal/day
		(male = 1; female = 0)
WHO [29]	male	18-29 y: (15.4 × weight (kg))-(0.27 × height (cm))+717 = kcal/day
		30-60 y: (11.3 × weight (kg))+(0.16 × height (cm))+901 = kcal/day
		>60 y: (8.8 × weight (kg))+(11.28 × height (cm))-1071 = kcal/day
	female	18-29 y: (13.3 × weight (kg))+(3.34 × × height (cm))+35 = kcal/day
		30-60 y: (8.7 × weight (kg))-(0.25 × height (cm))+865 = kcal/day
		>60 y: (9.2 × weight (kg))+(6.37 × height (cm))-302 = kcal/day
BIVA Akern		BMR Estimates were calculated with Akern's copyrighted proprietary equations (Bodygram PLUS Software Vers. 1.18.1)

Kg kilogram, cm centimeter, kcal kilocalories, MJ MegaJoule, m meter, diab pop, diabetes population, BMI Body Mass Index, FFM Fat Free Mass, FM Fat Mass, World Health Organisation, BIVA Bioelectrical Impedance Vector Analysis.

with AKern's equipment. The Akern device provides an equation for BMR which was also included in the study.

2.5. Statistical analysis

All data were analyzed using statistical package for the social sciences (SPSS 27.0) software. A p-value ≤0.05 was accepted as statistically significant.

Data were presented as mean values with their standard deviation (SD) for normally distributed variables and median values with minimum and maximum (min - max respectively) for not normally distributed variables. Normality was checked using the Kolmogorov Smirnov test.

Violin plots were used to illustrate the mean difference (striped line) between measured and estimated BMR and the upper and lower quartile (dotted lines). Wider sections of the violin plot represent a higher probability that individuals of the study population will take on the given value.

Between two independent groups, categorical and dichotomous variables were tested using the chi-squared (χ^2) or Fisher exact test; differences in continuous variables were tested using independent sample Student's t-test (parametric variables) or Mann–Whitney U-test (non-parametric variables). For more than 2 independent groups, differences in continuous variables were tested using ANOVA with Tukey post hoc tests (parametric variables) and Kruskal–Wallis (non-parametric variables). Group differences were analyzed according to gender, BMI categories, MetS and accuracy (accurate, under- and overestimation). All differences were corrected for age and gender when appropriate.

Bias is a quantative term describing the difference between the average of the calculated BMR with a certain formula on the one hand and the average of all measurements with indirect calorimetry on the other hand. The closer the difference is to 0, the least bias is present. To report bias, a one sample t-test was performed based on a 95 % confidence interval (CI) between measured and estimated values. Asterisks above the violins in the violin plot indicate which equation do not significantly deviate.

Accuracy was defined as the percentage of participants whose predicted BMR was within 10 % difference of the measured value of indirect calorimetry (IC). Overestimation and underestimation were defined as a calculated BMR that differed more than 10 % of measured BMR.

Bland–Altman plots offer the advantage of providing a measure on population level. So Bland–Altman plots were created for the 4 most accurate predictive equations, thus visually reflecting the accuracy of the estimated BMR compared to the measured BMR. The Bland–Altman plots display the calculated mean of the estimated and measured BMRs on the X-axis against the calculated

difference (Δ) between the estimated and measured BMR for each subject on the Y-axis. The mean difference (estimated BMR − measured BMR) is represented by a solid red horizontal line. On the y-axis, the distance of the mean difference line from the zero-difference point visually represents bias. Data points are thus plotted closest to the zero-difference point for participants whose measured BMR was most closely predicted by the calculated BMR.

Limits of agreement indicate the interval within which a proportion of the differences between measurements lie, and provide a useful measure for comparing the likely differences between individual results measured by two methods, in this case BMR estimation equations and IC. To define limits of agreement, Bland and Altman recommend that at least 95 % of the data points should lie within ±2SD of the mean difference. In the figures, 2solid horizontal green lines, located 2 standard deviations (SD) above and below the mean difference line, correspond to these limits of agreement.

3. Results

3.1. Patients characteristics

Patient characteristics are provided in Table 2. In total, 731 subjects (79.5 % female) with a mean age of 43 ± 13 years and a mean BMI of 35.6 ± 5.8 kg/m^2 were included, of whom 93 (12.7 %) had type 2 diabetes.

3.2. Accuracy rates and bias of estimated equations

The accuracy of all equations in the total population, according to BMI, gender and MetS are provided in Fig. 1. The mean difference, P25, P75 and bias of all equations in the total population, according to BMI, gender and MetS are shown on the violin plots in Fig. 2.

3.2.1. Total population

In the total population, accuracy varied between 73 % (Henry) and 25 % (Owen) (Fig. 1A).

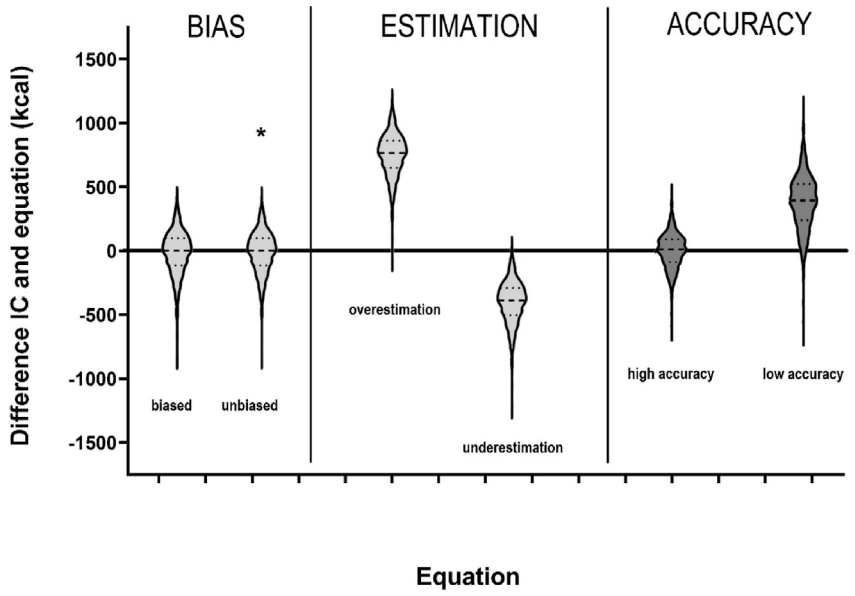
The Henry and Mifflin St Jeor equation were unbiased (Fig. 2 A). The Akern, Livingston and Ravussin equations were biased to underestimation and all other equations were biased to overestimation. Bias ranged from 21 kcal (−95 kcal; 116 kcal) for the unbiased equations to −46 kcal (range −191 to 71 kcal) for the equations that are biased to underestimation and 251 kcal (range 93 kcal–444 kcal) for the equations that were biased to overestimation.

3.2.2. According to BMI

In the overweight group, accuracy varied between 84 % (Ravussin) and 3 % (Nachmani) (Fig. 1B). The Livingston and Ravussin equation were unbiased, while all other equations were biased to overestimation (Fig. 2B). Bias ranged from 12 kcal (−61 to 76 kcal) for the unbiased equations to 443 kcal (364–574 kcal) for the biased equations.

In the BMI 30–34.9 kg/m^2 group, Accuracy varied between 73 % (Henry; Mifflin St. Jeor) and 21 % (Nachmani) (Fig. 1B). The Akern, Henry and Mifflin St Jeor equation were unbiased (Fig. 2B). The Livingston and Ravussin equation were biased to underestimation while all other values were biased to overestimation. Bias ranged from 9 kcal (−93 to 104 kcal) for the unbiased equations to −36 kcal (147–65 kcal) for the equations that are biased to underestimation and 275 kcal (180–433 kcal) for the equations that are biased to overestimation.

In the BMI 35–39.9 kg/m^2 group accuracy varied between 74 % (Ravussin) and 24 % (Owen) (Fig. 1B). The Henry and Mifflin St Jeor equation were unbiased (Fig. 2B). The Akern, Livingston and Ravussin equation were biased to underestimation while all other values were biased to overestimation. Bias ranged from −1 kcal (−122 to 116 kcal) for the unbiased equations to −81 kcal (−218 to



Legenda of the information derived from the violin plots. • Violin plots illustrate the mean difference (striped line) between measured and estimated BMR and the upper and lower quartile (dotted lines). Wider sections of the violin plot represent a higher probability that individuals of the study population will take on the given value. • BIAS: absence of a * indicates the equation is biased, * above the violin chart indicates the equation is unbiased ($p < 0.05$). • ESTIMATION: if the violin plot is situated mainly above the 0-line, the equation is prone to overestimation of the BMR. If the violin plot is situated mainly below the 0-line, the equation is prone to underestimation of the BMR. • ACCURACY: if the body of the violin plot is close to the 0-line, the equation is higly accurate. If the body of the violin plot is located away from the 0-line, this indicates low accuracy.

Table 2
Baseline characteristics according to BMI.

Variable	total population	BMI 25.0–29.9	BMI 30.0–34.9	BMI 35.0–39.99	BMI ≥40.0	statistics	Corrected for age and Gender
number	731	121	256	196	158		
women. n (%)	581 (79.5)	107 (88.4)	215 (84)	149 (76)	110 (69.6)	<0.001[b,c,d,e]	
age (years)	43 ± 13	39 ± 13	44 ± 14	43 ± 14	44 ± 13	0.013[a,b,c]	
weight (kg)	101.6 ± 20.7	78.89 ± 7.55	91.5 ± 10.0	107.2 ± 11.5	128.3 ± 18.2	<0.001[a,b,c,d,e,f]	<0.001
BMI (kg/m^2)	35.6 ± 5.8	28.09 ± 1.28	32.6 ± 1.4	37.4 ± 1.5	44.2 ± 3.3	<0.001[a,b,c,d,e,f]	<0.001
waist (cm)	108.7 ± 15.3	91.77 ± 7.40	102.0 ± 9.1	113.7 ± 9.4	126.7 ± 11.8	<0.001[a,b,c,d,e,f]	<0.001
VAT (cm^2)	160.84 ± 88.83	94.91 ± 52.46	141.1 ± 69.0	177.56 ± 85.59	221.17 ± 98.92	<0.001[a,b,c,d,e,f]	<0.001
Fat free mass (kg)	55.3 (39.1–98.6)	49.3 (39.6–78.4)	52.5 (39.4–88.0)	57.0 (43.6–91.2)	61.7 (39.1–98.6)	<0.001[a,b,c,d,e,f]	<0.001
fat mass (kg)	40.9 (16.8–97.7)	28.3 (16.8–44.9)	36.4 (17.4–55.3)	45.9 (23.1–72.0)	60.2 (39.1–98.6)	<0.001[a,b,c,d,e,f]	<0.001
FPG (mg/dl)	85 (62–288)	83 (62–104)	84 (63–270)	86 (70–156)	88 (69–288)	<0.001[b,c,e]	0.009
2 h PG (mg/dl)	134 (30–1358)	120 (33–234)	133 (35–470)	137 (30–1358)	147 (43–430)	<0.001[b,c]	0.007
Diabetes (%)	93 (12.7)	3 (2.5)	30 (11.7)	33 (16.8)	27 (17.1)	0.055[a,b,c,e]	<0.001
Diabetes med (%)	46 (6.3)	2 (1.7)	14 (5.5)	17 (8.7)	13 (8.2)	<0.001[b,c]	0.145
HDL (mg/dl)	53 (21–111)	59 (28–111)	56 (22–104)	49 (21–102)	48 (27–102)	<0.001[a,b,c,d,e]	<0.001
TG (mg/dl)	122 (29–513)	95 (29–271)	125 (46–513)	129 (46–374)	125 (42–440)	<0.001[a,b,c]	<0.001
systolic BP (mmHg)	125 ± 15	118 ± 11	125 ± 14	126 ± 15	131 ± 18	<0.001[a,b,c,e,f]	<0.001
diastolic BP (mmHg)	74 ± 10	72 ± 9	75 ± 9	74 ± 11	76 ± 11	0.012[a,c]	0.035
BP medication	179 (24.6)	14 (11.6)	50 (19.5)	55 (28.2)	60 (38.0)	<0.001[b,c,d,e]	<0.001
MetS yes (%)	292 (39.9)	12 (9.9)	95 (37.1)	97 (49.5)	88 (55.7)	<0.001[a,b,c,d,e]	<0.001

Data are expressed as mean ± SD or as median (min–max), if appropriate.
BMI body mass index, WHR waist-hip ratio, VAT visceral abdominal adipose tissue, FP fasting plasma, G glucose, MED medication, HDL-C high-density lipoprotein-cholesterol, TG triglycerides, Bp blood pressure, MetS Metabolic Syndrome.
Tukey post hoc test/Mann–Whitney U test.
a) comparing overweight to grade 1 ($p < 0.05$).
b) comparing overweight to grade 2 ($p < 0.05$).
c) comparing overweight to grade 3 ($p < 0.05$).
d) comparing grade 1 to grade 2 ($p < 0.05$).
e) comparing grade 1 to grade 3 ($p < 0.05$).
f) comparing grade 2 to grade 3 ($p < 0.05$).

25 kcal) for the equations that are biased to underestimation and 252 kcal (94 kcal–359 kcal) for the equations that are biased to overestimation.

In the BMI >40 kg/m^2 group, accuracy varied between 70 % (Henry; Mifflin St. Jeor) and 23 % (Owen) (Fig. 1B). The Henry, Mifflin St Jeor and Owen equation were unbiased (Fig. 2B). The Akern, Livingston and Ravussin equation were biased to underestimation while all other values were biased to overestimation. Bias ranged from −1 kcal (−130 to 119 kcal) for the unbiased equations to −228 kcal (−388 to −96 kcal) for the equations that are biased to underestimation and 315 kcal (178–463 kcal) for the equations that are biased to overestimation.

Overall, bias differed significantly between all BMI categories for the Akern, Nachmani and Weijs equation ($P < 0.001$). Significant differences between overweight and other categories ($P < 0.05$) were found for the Luhrman, Livingston, Muller BMI, Owen and Ravussin. No significant differences between BMI categories were found for the Harris and benedict, Henry, Lazzer, Mifflin St. Jeor, Muller, Schofield and WHO equation.

3.2.3. According to gender

Among women, Accuracy varied between 78 % (Ravussin) and 29 % (Owen) (Fig. 1C). The Henry, Mifflin St. Jeor and Ravussin equations were unbiased, based on a 95 % CI of the difference between estimated and measured values (Fig. 2C). The Akern and Livingston were biased to underestimation, while all other equations were biased to overestimation. Bias ranged from 11 kcal (−85 to 106 kcal) for the unbiased equations to −30 kcal (−95 to 55 kcal) for the equations that are biased to underestimation and 255 kcal (139–343 kcal) for the equations that are biased to underestimation.

Among men, accuracy varied between 70 % (Henry) and 10 % (Owen) (Fig. 1C). The Luhrman and Muller equations were unbiased (Fig. 2C). The Akern and Livingston, Mifflin St Jeor, Owen, Ravussin were biased to underestimation, while all other equations were biased to overestimation. Bias ranged from 55 kcal (−113 to 205 kcal) for the unbiased equations to −469 kcal (−686 to −328 kcal) for the equations that are biased to underestimation and 493 kcal (339–691 kcal) for the equations that are biased to overestimation.

Overall, bias differed significantly between male and female groups for all equations ($P < 0.001$), with the exception of the Lazzer, Muller based on BMI and Weijs equation.

3.2.4. According to metabolic syndrome

Among subjects without MetS, accuracy varied between 78 % (Ravussin) and 23 % (Nachmani) (Fig. 1D). The Ravussin was the sole unbiased equation, based on a 95 % CI of the difference between estimated and measured values (Fig. 2D). The Akern and Livingston were biased to underestimation, while all other equations were biased to overestimation. Bias ranged from 25 kcal (−74 to 105 kcal) for the unbiased equations to −10 kcal (−106 to 70 kcal) for the equations that are biased to underestimation and 318 kcal (145–452 kcal) for the equations that are biased to overestimation.

Among subjects with MetS, accuracy varied between 69 % (Henry) and 25 % (Owen) (Fig. 1D). the Owen and Schofield were unbiased (Fig. 2D). The Akern and Livingston, Henry, Mifflin St Jeor and Ravussin were biased to underestimation, while all other equations were biased to overestimation. Bias ranged from 22 kcal (−132 to 132 kcal) for the unbiased equations to −134 kcal (−286 to 26 kcal) for the equations that are biased to underestimation and 206 kcal (51–322 kcal) for the equations that are biased to overestimation.

Overall, bias differed significantly between subjects with and without MetS for all equations ($P < 0.05$).

3.2.5. According to diabetes classification

Among subjects without diabetes, accuracy varied between 77 % (Ravussin) and 23 % (Nachmani) (Fig. 1E). The Ravussin was the sole unbiased equation, while all other equations were biased

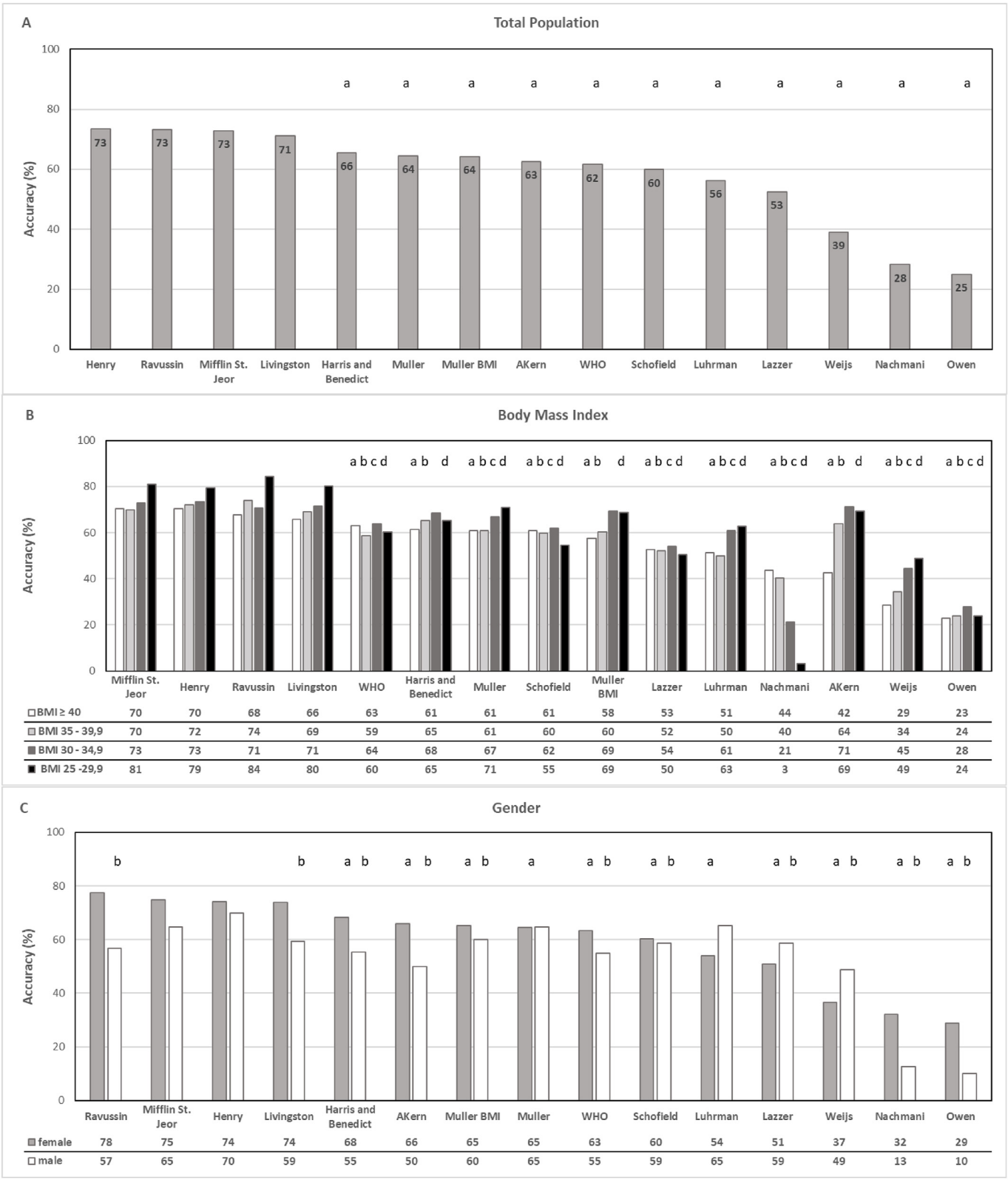


Fig. 1. Accuracy of prediction equations for measurements of BMR within ±10 % using each equation in 731 subjects (A) and according to gender (B), metabolic syndrome (C), body mass index (D) and diabetes (E), respectively. a) $P < 0.05$ vs. Henry equation. b) $P < 0.05$ vs. equation with respectively the highest accuracy within each subcategory in descending order. c) $P < 0.05$ vs. equation with respectively the highest accuracy within each subcategory in descending order. d) $P < 0.05$ vs. equation with respectively the highest accuracy within each subcategory in descending order.

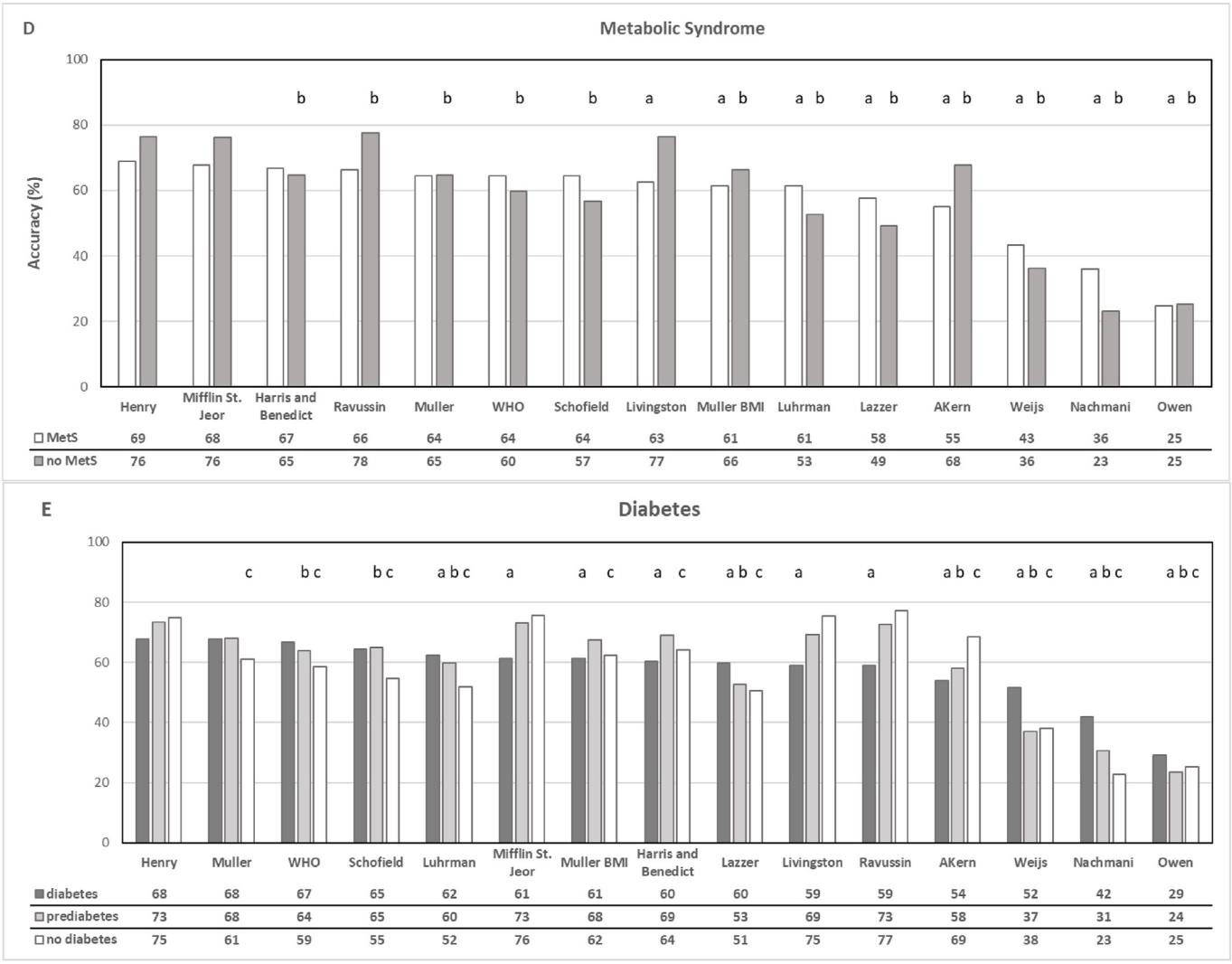


Fig. 1. (*continued*).

to overestimation (Fig. 2E). Bias ranged from −23 kcal (−72 to 107 kcal) for the unbiased equations to −8 kcal (−135 to 94 kcal) for the equations that are biased to underestimation and 333 kcal (160–452 kcal) for the equations that are biased to overestimation.

Among subjects with prediabetes, accuracy varied between 73 % (Henry, Mifflin St. Jeor and Ravussin) and 24 % (Owen) (Fig. 1E). The Henry and Owen were unbiased (Fig. 2E). The Akern and Livingston, Mifflin St Jeor and Ravussin were biased to underestimation, while all other equations were biased to overestimation. Bias ranged from 8 kcal (−118 to 103 kcal) for the unbiased equations to −80 kcal (−235 to 59 kcal) for the equations that are biased to underestimation and 223 kcal (58 kcal–442 kcal) for the equations that are biased to overestimation.

Among subjects with diabetes, accuracy varied between 68 % (Henry; Muller) and 25 % (Owen) (Fig. 1E). The Harris and Benedict, Mulle, Owen, Schofield and WHO were unbiased (Fig. 2E). The Akern, Henry, Livingston, Mifflin St. Jeor and Ravussin were biased to underestimation, while all other equations were biased to overestimation. Bias ranged from 13 kcal (−131 to 157 kcal) for the unbiased equations to −138 kcal (−317 to −3 kcal) for the equations that are biased to underestimation and 173 kcal (2–299 kcal) for the equations that are biased to overestimation.

Overall, bias differed significantly between the 3 diabetes categories for the Harris and Benedict, Henry, Luhrman, Livingston, Mifflin, Muller, Muller BMI, Nachmani and Ravussin ($P < 0.05$). Significant differences between the no-, pre- and/OR diabetes and other categories ($P < 0.05$) were found for the Akern, Lazzer, Owen, Schofield, Weijs and WHO equation.

3.3. Bland Altman plots to assess bias and limits of agreement among most accurate equations

Fig 3 is showing the bias between IC and, consecutively, the Henry equation (3 A) the Livingston equation (3 B) the Ravussin equation (3C) and the Mifflin St. Jeor equation (3D). Using the cut-off of at least 95 % as proposed by Bland and Altman, there is an agreement between IC and the Henry, Livingston and Mifflin St. Jeor equation. With an agreement of 94.8, the Ravussin equation fails agreement.

3.4. Metabolic differences between individuals with accurate and inaccurate estimates

Metabolic differences between individuals with accurate and inaccurate estimates are provided in Table 3. After adjusting for

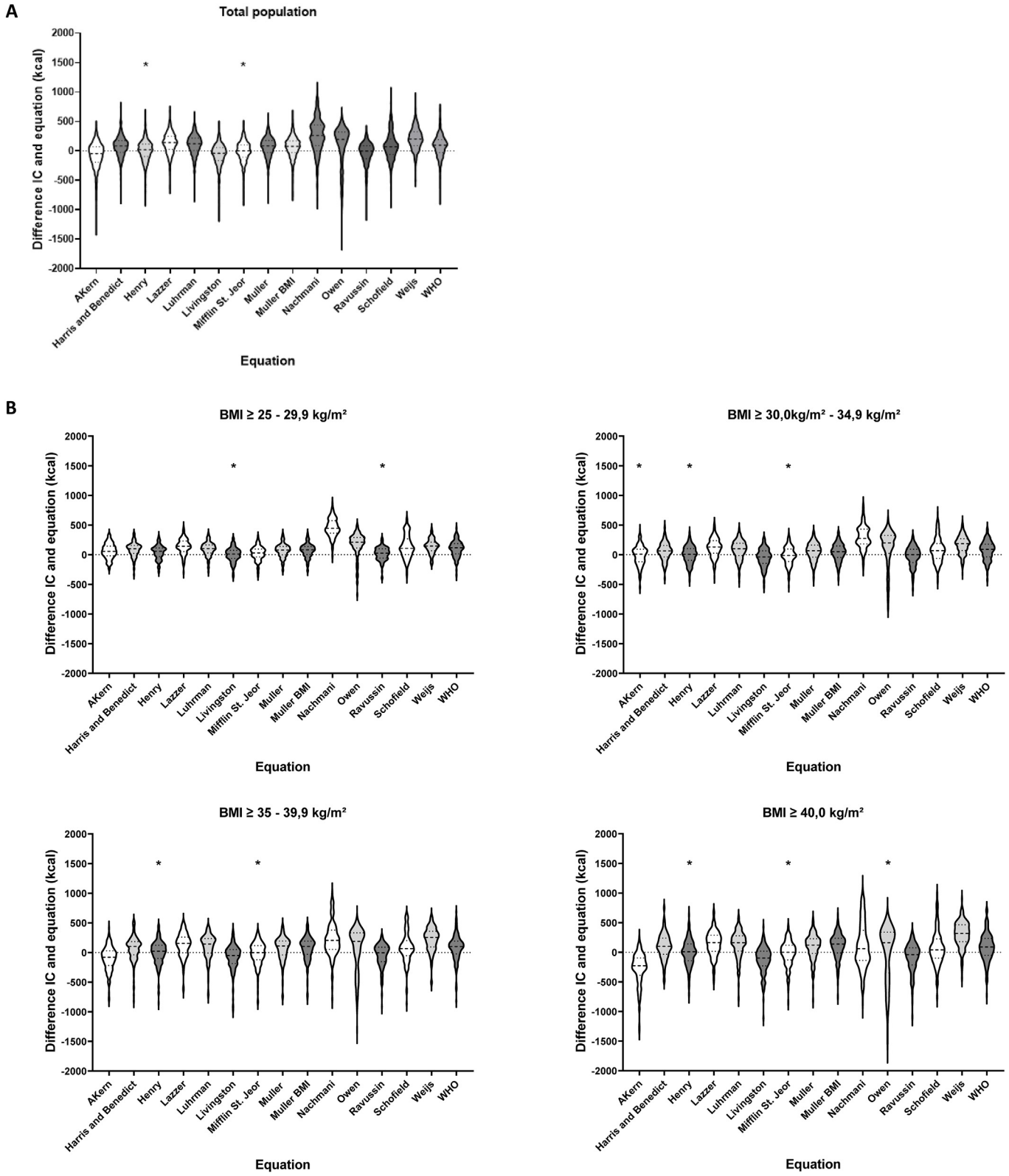


Fig. 2. Violin plot for each equations in the total population (A), according to BMI (B), gender (C), metabolic syndrome(D), and classification of diabetes (E). Each equation is found on the X-axis. The difference between IC and predictive equations expressed in kcal is found on the Y- axis. A negative difference (expressed in kcal) means underestimation of the BMR, while a positive difference means an overestimation of the BMR. The lower dotted line is P25, the higher dotted line P75 and the striped line is P50. The width of the violin plot represent the distribution of the values. Asterisks on the chart indicate which equations are unbiased with a p > 0,05.

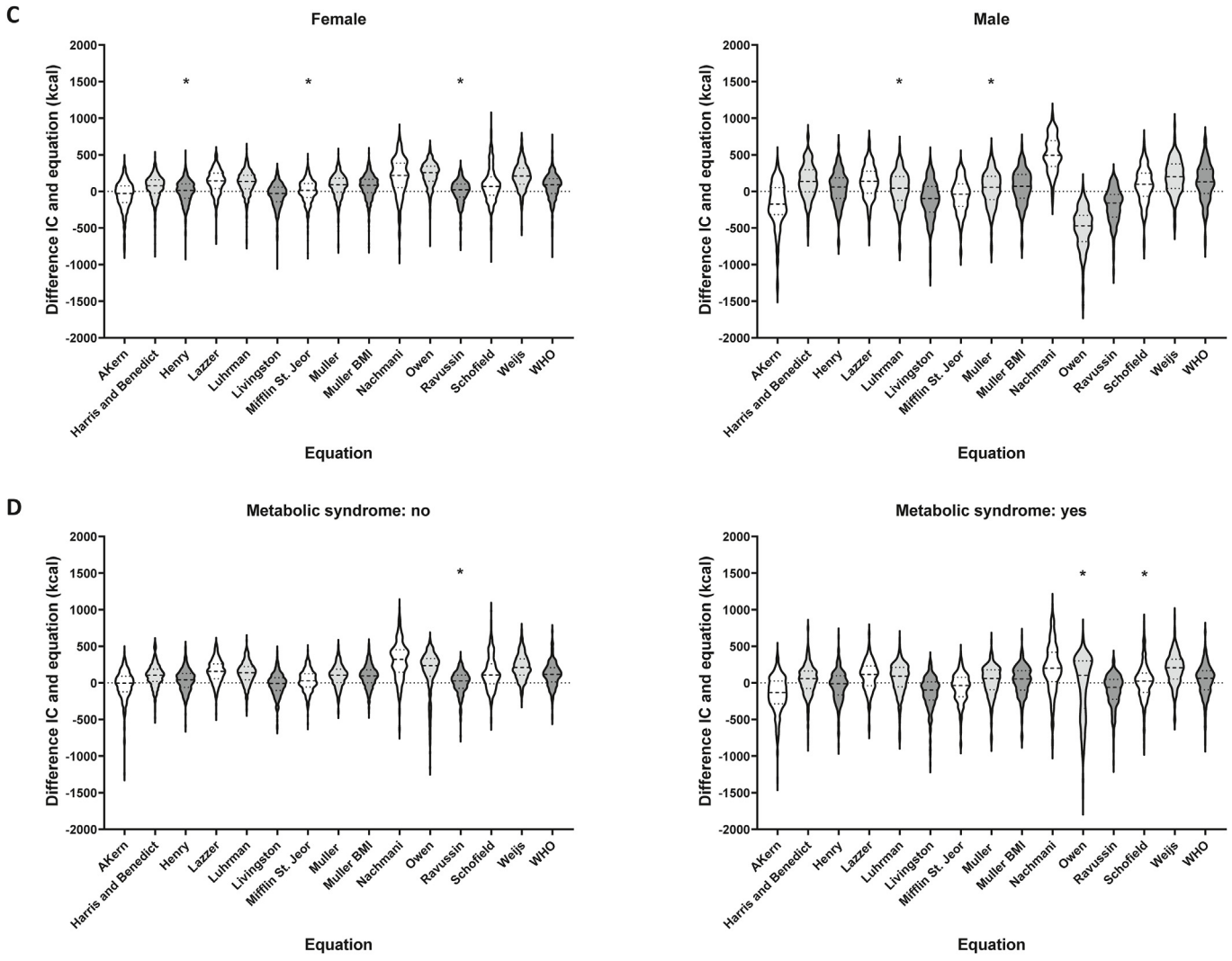


Fig. 2. (*continued*).

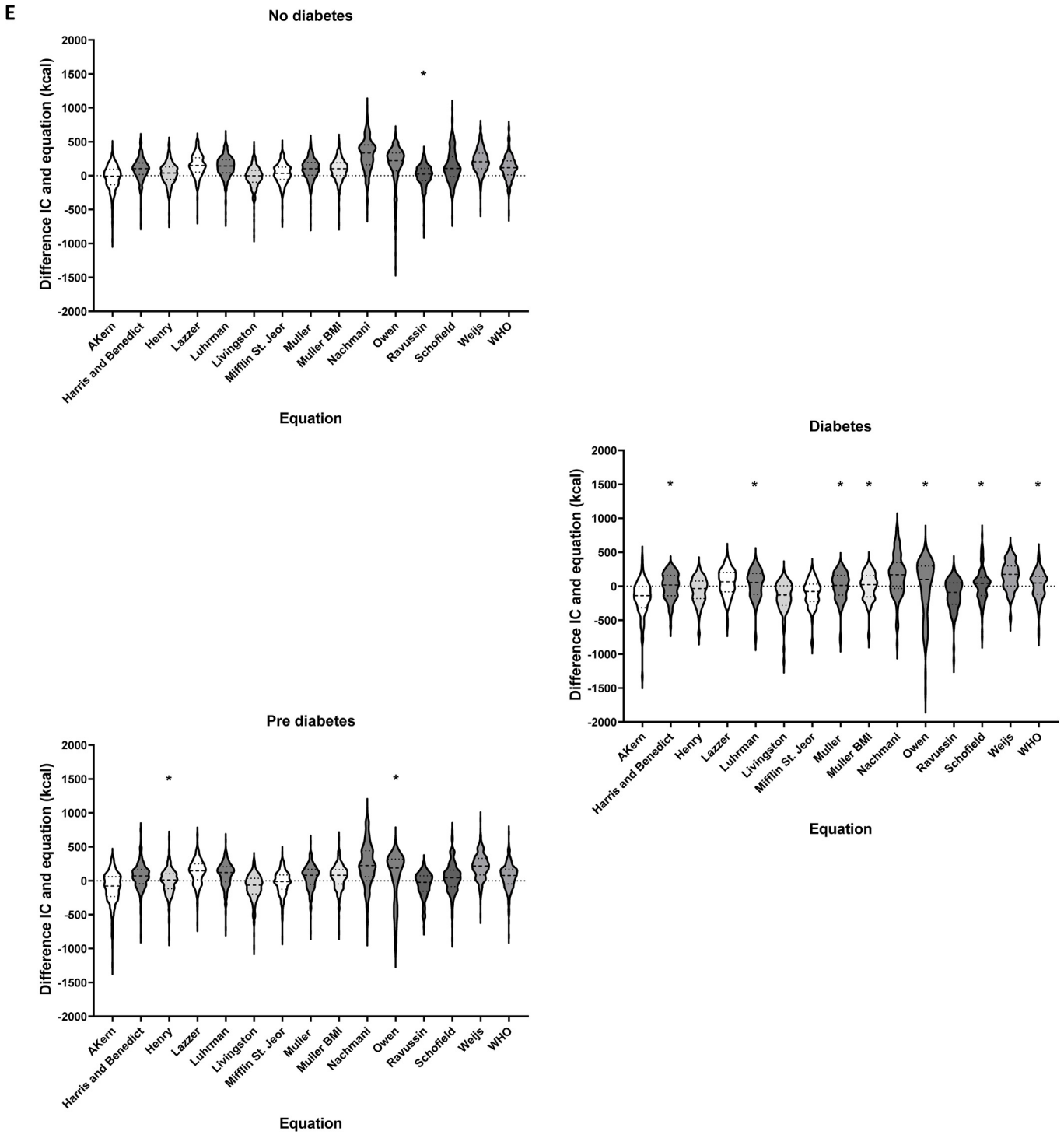


Fig. 2. (*continued*).

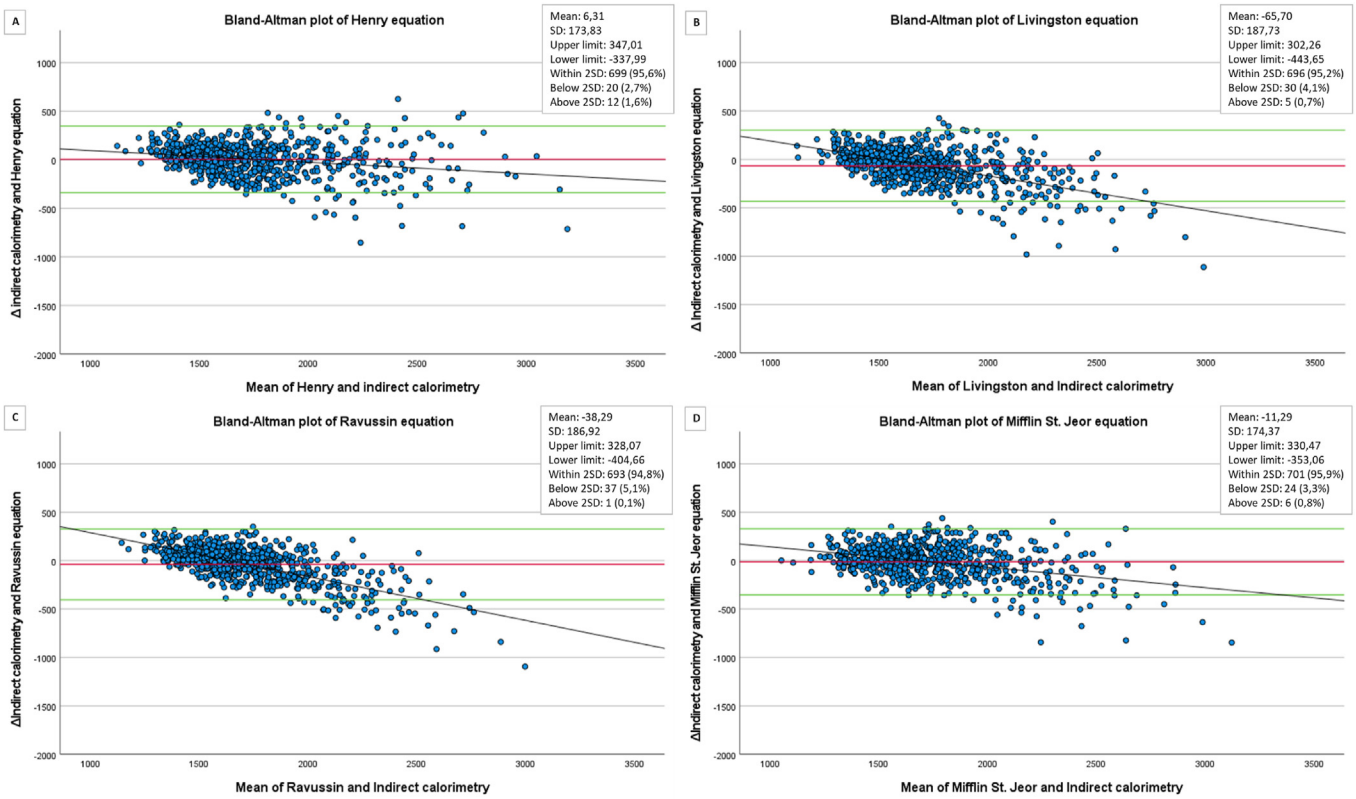


Fig. 3. Bland Altman Plots of least biased equations.

Table 3
Baseline characteristics according to accuracy.

Variable	underprediction	accurate	overprediction	statistics	Corrected for age and gender
number	31	299	42		
women. n (%)	20 (64.5)	245 (81.9)	33 (78.6)	0.067	
age (years)	48 ± 12	44 ± 14	40 ± 12	0.038[b]	
weight (kg)	110.1 ± 24.3	100.0 ± 20.7	103.2 ± 18.5	0.026[a]	0.189
BMI (kg/m^2)	37.1 ± 5.4	35.6 ± 5.8	35.9 ± 5.7	0.346	0.640
waist (cm)	116.6 ± 15.3	107.9 ± 15.6	109.8 ± 15.6	0.012[a]	0.124
VAT (cm^2)	239.1 ± 95.5	162.2 ± 93.4	135.5 ± 62.0	<0.001[a,b]	**<0.001**
Fat free mass (kg)	67.6 (45.4–95.9)	54.0 (39.6–95.5)	54.9 (45.1–85.1)	<0.001[a,b]	**<0.001**
fat mass (kg)	41.1 (21.8–71.3)	39.9 (17.4–97.7)	42.8 (27.9–80.5)	0.191	0.190
FPG (mg/dl)	93 (68–153)	86 (62–288)	84 (70–128)	0.005[a,b]	0.054
2 h PG (mg/dl)	167 (83–293)	132 (30–430)	116 (43–193)	<0.001[a,b,c]	**<0.001**
No-Pre-diabetes (%)	6/15/10 (19.4/48.4/32.3)	150/117/32 (50.2/39.1/10.7)	29/12/1 (69.0/28.6/2.4)	<0.001[a,b,c]	**<0.001**
HDL (mg/dl)	42.5 (32–93)	53 (27–11)	56 (21–87)	0.011[a,b]	**0.029**
TG (mg/dl)	169 (82–342)	114 (38–440)	111 (46–236)	<0.001[a,b]	**<0.001**
systolic BP (mmHg)	132 ± 14	125 ± 16	118 ± 13	<0.001 b.c	**0.002**
diastolic BP (mmHg)	78 ± 9	74 ± 10	72 ± 10	0.035[b]	0.060
BP med (%)n	13 (43.3)	70 (23.4)	8 (19.0)	0.037[a,b]	0.192
MetS yes (%)	24 (77.4)	112 (37.5)	9 (21.4)	<0.001[a,b,c]	**<0.001**

Data are expressed as mean ± SD or as median (min–max), if appropriate.
BMI body mass index, WHR waist-hip ratio, VAT visceral abdominal adipose tissue, FP fasting plasma, G glucose, MED medication, HDL-C high-density lipoprotein-cholesterol, TG triglycerides, Bp blood pressure, MetS Metabolic Syndrome.
Tukey post hoc test/Mann–Whitney U test.
a) comparing underprediction to accurate prediction ($p < 0.05$).
b) comparing underprediction to overprediction ($p < 0.05$).
c) comparing accurate prediction to overprediction ($p < 0.05$).

gender and age, subjects with accurate estimates had lower VAT ($p < 0.001$), higher prevalence of HbA1c < 5,6 % ($P < 0.001$) compared to individuals with over- or underestimations.

Compared to individuals with an accurate prediction, subjects with underprediction had higher waist-hip ratio ($P < 0.001$), higher VAT ($P < 0.001$), lower fat free mass ($P < 0.001$), higher HbA1c ($P = 0.005$), higher 2 h plasma glucose (PG) ($P < 0.001$), higher fasting insulin ($P < 0.001$), higher fasting c-peptide ($P < 0.001$), higher HOMA-IR ($P < 0.001$), lower HDL ($P = 0.029$), higher TG ($P < 0.001$), and a higher prevalence of MetS ($P < 0.001$).

Subjects with overprediction had lower waist-hip ratio ($P < 0.001$), lower VAT ($P < 0.001$), higher fat free mass ($P < 0.001$),

lower HbA1c ($P = 0.005$), lower 2 h PG ($P < 0.001$), lower fasting insulin ($P < 0.001$), lower fasting c-peptide ($P < 0.001$), lower HOMA-IR ($P < 0.001$), lower systolic blood pressure ($P < 0.001$), lower hs-CRP ($P = 0.011$), and a lower prevalence of MetS ($P < 0.001$).

4. Discussion

According to our data, prediction equations that provide the most accurate estimates of BMR in adults with overweight or obesity differ with body mass index, with Ravussin being most accurate in the individuals with overweight, while the Henry and Mifflin St. Jeor equations were most accurate in the individuals with obesity.

However, prediction equations that provide the most accurate estimates of BMR in overweight or obese adults also differ according to sex, presence of metabolic syndrome and diabetes status.

Madden et al. (2016) concluded that on a population level, the WHO equation, based on weight and height, offered the most accurate prediction for groups with overweight, whereas Mifflin St. Jeor equation was considered most accurate for groups with a BMI 30–39.9 and Henry (weight and height) or Lazzer for a female population with a BMI $\geq$40 kg/m^2 [6]. According to the American Academy of Nutrition and Dietetics (AND), the Mifflin St. Jeor is considered to be the most adequate equation to estimate BMR in subjects with obesity [30]. Our results are in line with these studies. However, the Mifflin St Jeor does not outperform the Henry equation with respect to accuracy [31]. The differences in accuracy that were found are less than 5 %. Madden et al. (2016) referred to the Lazzer and Henry equations as the most accurate equation in individuals with a BMI$\geq$ 40 kg/m^2 [6]. Our results confirm that the Henry, but not the Lazzer equation is the most predictive equation in individuals with a BMI $\geq$40 kg/m^2. Lazzer et al. derived their equation from a study solely on Caucasian women with a BMI $\geq$40 kg/m^2, whereas in this study approximately 150 men with a BMI $\geq$40 kg/m^2 were also included. This may explain the discrepancy in our results compared to the results from Lazzer et al. [6].

According to our data, prediction equations that provide the most accurate estimates of BMR in adults with overweight or obesity also differ slightly according to gender, with Henry being the most accurate among males and Mifflin St. Jeor and Ravussin being the most accurate in women. Interestingly a higher predictive accuracy is found for BMR prediction in female patients compared to male patients with obesity [32]. According to Marra et al. (2017), the Muller equation gave the best least difference in prediction between both sexes [33]. This can be confirmed by the results of our study. Moreover, Ravussin was the most accurate in metabolically healthy individuals, whereas the Henry and Mifflin StJeor equations were the most accurate in individuals with the metabolic syndrome. In contrast, The Ravussin equation was the most accurate in subjects without diabetes, and the Henry, Mifflin St. Jeor and Ravussin equation being the most accurate in subjects with prediabetes, whereas the Henry and Muller equation were the most accurate in subjects with diabetes. To the best of our knowledge, so far, the usefulness of these predictive equations was investigated to a limited extent in people with and without metabolic syndrome in both men and women. Only few articles were found whereof 1 study was performed among Brazilian women with obesity [34].

Recent studies found that in subjects with diabetes, estimates derived from the FAO/WHO equation were the closest to the measured BMR values [35,36]. Despite what previous studies have suggested, our data indicate that the accuracy of the Henry and Muller equation is higher in subjects with diabetes. The WHO formula is indeed superior to the Mifflin St. Jeor formula, but its accuracy is lower compared to the Henry and Muller formula. This could possibly be explained by the higher prevalence of diabetes among men in our dataset, and why the accuracy of the Muller formula outperforms both the WHO and the Mifflin St. Jeor formulas.

Secondly, equations were subjected to the assessment of bias. According to our analyses, the Henry and Mifflin St Jeor equation were unbiased in the total population. The Akern, Livingston and Ravussin equations were biased to underestimation and all other equations were biased to overestimation. However, while bias also differs according to sex and the presence of metabolic syndrome, the Henry and Mifflin St Jeor equation are most consistent over all subgroups. Thus, we can conclude that the results of our study are in line with previous research [6,31,37].

The Mifflin St Jeor equation was derived from 498 people with normal weight, overweight or obesity [22]. The sex distribution was approximately equal. The distribution of age ranged between 19 and 78 years. The data of our patients were similar, except that our included population was larger. This may reflect the high accuracy and low bias in our results.

The Henry equation was developed using a dataset from 10,552 BMR values that [1] excluded all the Italian subjects (from data from Schofield, Schofield, and James cfr WHO) and [2] included a much larger number (4018) of people from the tropics [22]. Given the large dataset and heterogeneity of subjects in our study, it is not unexpected that the results reproduce high accuracy and low bias with the Henry equation.

An important factor stated by Madden et al., 2016 is that accuracy data allow under and overestimates to cancel each other out. Therefore, they are not useful when a predicted value is required for a single individual where precision is needed to assess the chance of the prediction being within 10 % of measured values [6]. Thus, even with the most precise equations, approximately 25 % of predictions might be either a 10 % over- or underprediction of measured values. Our findings support these results. At least 15 % off all predictions is either a 10 % over- or underestimation of measured values, even with the best performing equations. In less accurate equations, more than half the estimates will be imprecise. As measured energy requirements increase, this difference can be very substantial. For a requirement of 2000 kcal, a 10 % difference is 200 kcal.

In this study, bias ranges from 21 kcal (range −95 to 116 kcal) for the unbiased (Henry) equation to −46 kcal (range −191 to 71 kcal) for the equations that are biased to underestimation and 251 kcal (range 93–444 kcal) (Nachmani) for the equations that were biased to overestimation, which may be a major pitfall for weight interventions. Indeed, the tendency for bias of the BMR could pose difficulties in clinical practice, particularly when counselling individuals aiming for weight loss through dietary measures. If the potential measurement error is close to or larger than the 500-kcal deficit recommended by the NIH for incremental weight loss, the flawed accuracy of the equation might result in inadequate prediction of to-be-expected weight loss [38].

Each equation has a specific set of variables, in which weight plays a central role. Depending on the equation, height, age, sex and body composition (FM and FFM) play an additional role. A study of Bentes et al. (2021) examined the reliability of BIA versus indirect calorimetry to evaluate BMR in Brazilian women with MetS. They found a strong correlation between with BIA device BMR and IC and concluded that BIA is a reliable alternative to estimate BMR in elderly women with MetS [34]. This is not confirmed by our study. Our findings indicate that in subjects with and without MetS, the Henry, Livingston, Mifflin St Jeor, and Ravussin equation are most accurate to estimate BMR, although the accuracy of these equations is lower in subjects with MetS. The accuracy of the BIVA equation

was 13 % lower (from 68 % to 55 %) in people with MetS and inaccurate estimations were biased toward underestimation (−156 ± 250 kcal/day) of BMR. An important note is that this study group used a different BIA device to calculate body composition which may explain in part the difference in results. Nevertheless, despite what previous studies have suggested, our data indicate that equations that include FM or FFM assessed by BIVA, do not significantly improve the accuracy of the equations [33,37,38]. Marra et al. (2017) confirmed that the greater the degree of obesity, the more variance in FM distribution (subcutaneous, visceral, ectopic fat; android vs gynoid) and FFM distribution may occur (intra vs extracellular; edema, lymphedema) [33]. In fact, obesity is associated with a state of general 'overhydration', with an excess of total body water and a dysregulated extracellular to intracellular water ratio. This may result in overestimations of FFM and thereby underestimate FM, resulting in increasingly lower accuracy rates of body composition assessments with higher levels of obesity [33].

Other variables such as ethnicity, age and metabolic parameters such as HbA1c, VAT, HOMA-IR also affect BMR [33,36,37]. Physiological differences likely play a role in the sex-specific accuracy of equations between those including FFM and those which do not. For example men typically carry higher levels of muscle mass, which is included in FFM, while females have higher amounts of FM [37]. In addition, different devices are available for estimating people's body composition that have a different technical approach to estimating body composition. Hence, comparing studies that use different devices might be prone to bias.

Yet our study demonstrates that formulas without body composition data also exhibit significant accuracy and minimal bias in a female population.

Lastly, this work examined whether a phenotype for accurate estimates can be distinguished based on metabolic parameters. Our results indicate that the equations in people with MetS had a higher chance of underestimating true BMR. Furthermore, the BMR expressed in absolute value (kcal/24 h) is significantly higher in these subjects, even when the BMR is adjusted for FFM (kcal/FFM/kg 24 h). This result is in accordance with previous studies that demonstrated an increased BMR in metabolically unhealthy subjects [39,40]. The precise mechanisms that contribute to the higher BMR in subjects with MetS are still unknown, although factors such as chronic low grade inflammation, hyperglycemia, glucose intolerance might upregulate BMR compared to healthy subjects [39]. Energy restriction in combination with healthy food choices is a cornerstone to shift from metabolic unhealthy to healthy. However, a pitfall might occur when healthcare professionals (HCP) underestimate energy requirements causing subjects to follow a very low calorie diet due to an underestimation when it is contraindicated. This may result in undesirable outcomes such as malnutrition and unwanted loss of lean mass [41]. When HCPs overestimate energy requirements, this might result in the prescription of a diet with a smaller than 500 kcal deficit. The ensuing lack of results might cause frustration, both in patient and HCP, and could put a strain on the therapeutic confidence and relation.

According to the ESPEN guidelines, there is evidence that the role for indirect calorimetry to asses BMR is preferred in various circumstances such as liver disease, kidney disease and polymorbidity [42]. Obesity has long been considered a chronic disease [43].Thus, subjects living with obesity who have a poor metabolic profile might benefit from a measured basal metabolism using indirect calorimetry to start a weight reduction program.

The strength of our study lies in the comprehensive inclusion of equations. With these equations, we were able to make comparisons between individuals based on BMI and the presence of absence of the metabolic syndrome. Additionally, we took into account the classification of diabetes, allowing for a more nuanced analysis between different metabolic profiles.

The creation categories of subjects based on their under, accurate, or overestimation of basal metabolic rate is also a strength of this study. This approach provided valuable insights into the potential variations and inaccuracies in estimating metabolic rates, contributing to a more comprehensive understanding of individual metabolic profiles.

A last notable strength of this study is that in this large dataset of 731 individuals, the extensive metabolic workup and performance of indirect calorimetry was performed based on a standardized protocol. A limitation of the study is that our results may not be generalizable to other ethnic groups since this study was conducted on data from Caucasian men and women.

5. Conclusion

In conclusion, The Henry, Mifflin St. Jeor and Ravussin equation are the most accurate equations to estimate the basal metabolic rate in a predominantly caucasian population living with overweight or obesity. The rationale of this study is not to stick to 1 equation. The Ravussin equation can be used in subjects with overweight or subjects with obesity who are metabolic healthy. In people with a BMI>30, it is preferable to use the Mifflin St Jeor in obese women, and prefer the Henry equation in obese men. Subjects with obesity with a suspected metabolic unhealthy profile benefit from indirect calorimetry. Indirect calorimetry is still the most valuable method to assess BMR, particularly in metabolically unhealthy subjects living with obesity. Further studies involving larger, more heterogeneous cohorts, such as subjects with normal BMI, as well as subjects with overweight and or obesity, and racial and ethnic diversity are needed.

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Declaration of competing interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2023.12.024.

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