BMJ Open

Anthropometric markers and their association with incident type 2 diabetes mellitus: which marker is best for prediction? Pooled analysis of four German population-based cohort studies and comparison with a nationwide cohort study

Saskia Hartwig,[1,2] Alexander Kluttig,[1,2] Daniel Tiller,[1] Julia Fricke,[3,4] Grit Müller,[5] Sabine Schipf,[2,6] Henry Völzke,[2,6] Michaela Schunk,[7] Christa Meisinger,[2,8] Anja Schienkiewitz,[9] Christin Heidemann,[9] Susanne Moebus,[10] Sonali Pechlivanis,[10] Karl Werdan,[11] Oliver Kuss,[2,12] Teresa Tamayo,[12] Johannes Haerting,[1] Karin Halina Greiser[1,2,3]

To cite: Hartwig S, Kluttig A, Tiller D, *et al*. Anthropometric markers and their association with incident type 2 diabetes mellitus: which marker is best for prediction? Pooled analysis of four German population-based cohort studies and comparison with a nationwide cohort study. *BMJ Open* 2016;**6**:e009266. doi:10.1136/bmjopen-2015-009266

▸ Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2015-009266).

SH and AK contributed equally.

Received 2 July 2015
Revised 27 November 2015
Accepted 1 December 2015

For numbered affiliations see end of article.

Correspondence to
Saskia Hartwig;
saskia.hartwig@uk-halle.de

ABSTRACT

Objective: To compare the association between different anthropometric measurements and incident type 2 diabetes mellitus (T2DM) and to assess their predictive ability in different regions of Germany.

Methods: Data of 10 258 participants from 4 prospective population-based cohorts were pooled to assess the association of body weight, body mass index (BMI), waist circumference (WC), waist-to-hip-ratio (WHR) and waist-to-height-ratio (WHtR) with incident T2DM by calculating HRs of the crude, adjusted and standardised markers, as well as providing receiver operator characteristic (ROC) curves. Differences between HRs and ROCs for the different anthropometric markers were calculated to compare their predictive ability. In addition, data of 3105 participants from the nationwide survey were analysed separately using the same methods to provide a nationally representative comparison.

Results: Strong associations were found for each anthropometric marker and incidence of T2DM. Among the standardised anthropometric measures, we found the strongest effect on incident T2DM for WC and WHtR in the pooled sample (HR for 1 SD difference in WC 1.97, 95% CI 1.75 to 2.22, HR for WHtR 1.93, 95% CI 1.71 to 2.17 in women) and in female DEGS participants (HR for WC 2.24, 95% CI 1.91 to 2.63, HR for WHtR 2.10, 95% CI 1.81 to 2.44), whereas the strongest association in men was found for WHR among DEGS participants (HR 2.29, 95% CI 1.89 to 2.78). ROC analysis showed WHtR to be the strongest predictor for incident T2DM. Differences in HR and ROCs between the different markers confirmed WC and WHtR to be the best predictors of incident T2DM. Findings were consistent across study regions and age groups (<65 vs ≥65 years).

Conclusions: We found stronger associations between anthropometric markers that reflect abdominal obesity (ie, WC and WHtR) and incident T2DM than for BMI and weight. The use of these measurements in risk prediction should be encouraged.

Strengths and limitations of this study

- We investigated commonly used anthropometric markers to assess their association with incident type 2 diabetes mellitus (T2DM).
- We used a pooled study population consisting of four prospective, population-based cohorts from different regions of Germany and one nationwide survey.
- We used standardised measuring protocols for anthropometric markers measured by specifically trained and certified study nurses in the study centres.
- Self-report of physician-diagnosed T2DM as opposed to physician-verified diagnosis can be considered a limitation.

INTRODUCTION

During the last decades, the prevalence and incidence of type 2 diabetes mellitus (T2DM) globally as well as within Germany has risen dramatically.[1 2] This cannot be explained by demographic change alone.[3] This development is even more worrying when considering the severe complications

and secondary diseases associated with T2DM, leading to higher mortality rates in patients with diabetes compared with non-diabetic individuals.[4] It is estimated that nearly half of T2DM cases are not even diagnosed, and thus remain untreated.[5] The observed rise of T2DM prevalence and incidence leads to considerable increases in costs of healthcare.[2 6]

T2DM is a major public health issue that needs to be explored in terms of aetiology, prevention and early disease detection. In previous analyses, we found large regional differences in the prevalence and incidence of T2DM across Germany,[7 8] as well as disparities in body fat distribution.[9]

There is some evidence that the association of anthropometric measurements with T2DM risk varies across markers. For example, unfavourable body fat distribution has been found to be more strongly associated with T2DM than increased body mass index (BMI) alone.[10] The underlying mechanism is thought to involve visceral adipose tissue, which on one hand serves as an energy reserve, and on the other hand seems to be of importance in endocrine pathways.[11] However, studies investigating this topic often only used cross-sectional data,[12–14] had limitations of methods[15] or investigated only a limited number of anthropometric factors.[16 17] Moreover, their results were not always consistent. The objective of this work was on one hand to describe the relation of each of the established anthropometric markers with incident T2DM, and on the other hand to elucidate whether there is an advantage of using one of these markers above the others when estimating the risk of incident T2DM, as this is still uncertain. Therefore, we investigated the association of each of the currently established standard anthropometric markers with incident T2DM and examined whether the observed results are consistent across different regions and age groups.

METHODS

Study population

We included data of four population-based longitudinal cohort studies from different regions of Germany: the Cardiovascular Disease, Living and Ageing in Halle (CARLA) Study conducted in East Germany in the city of Halle (Saale), the Study of Health in Pomerania (SHIP) in the North-East, the Heinz Nixdorf Recall Study (RECALL) in the western part of Germany and the Cooperative Health Research in the Region of Augsburg (KORA) F4 Survey from the south of Germany. Detailed information on the design and methods of these studies has already been described elsewhere.[18–22] In brief, the baseline investigations were conducted between 1997 and 2006, with baseline responses between 56% and 69%. The follow-up investigations were performed between 2002 and 2010, resulting in observation times between 3.3 and 8.6 years. Participation rate at follow-up, calculated as the ratio of the number of participants at follow-up and the number of participants at baseline minus the number of participants who died or withdrew, varied from 75% to 84%.

In addition, we used data from the national German Health Interview and Examination Survey for Adults (DEGS), which combines a nationally representative health survey and a longitudinal follow-up of participants from the previous German National Health Interview and Examination Survey in 1997–1999 (GNHIES98). For the present analysis, we only included participants from GNHIES98 who also participated in the follow-up examination (called DEGS). The baseline response of GNHIES98 was 61%[23 24] and the average follow-up time 12.1 years, with a follow-up response of 47%. We analysed DEGS separately from the other studies since its nationwide survey design and sampling procedures with a longitudinal element differs methodologically from the regional cohorts described above.

All studies used a standardised computer-assisted, personal interview, self-administered questionnaires and standardised medical examinations at baseline. The study procedures were described in standard operating protocols, and staff was specifically trained and certified prior to conducting the anthropometric measurements: continuous measures of quality control ensured adherence to the standardised examination methods.

Figure 1 shows the reasons for exclusion of participants from the present analyses in the pooled sample and in DEGS. We excluded participants with prevalent diabetes at baseline, participants with incomplete information regarding T2DM at baseline or follow-up and participants aged under 31 years at baseline, to avoid inclusion of cases of type 1 diabetes mellitus.

Definition of T2DM

T2DM at baseline and follow-up was defined based on self-reported physician-diagnosed diabetes or self-reported current intake of antidiabetic medication during the 7 days prior to the examination, which was coded according to the Anatomical Therapeutic Chemical (ATC) Classification system code as A10.

Measurement of anthropometric markers and covariates at baseline

Body height, weight, waist circumference (WC) and hip circumference (HC) were measured with comparable standardised methods in CARLA, SHIP, RECALL and KORA. Data on weight and height were collected using Seca's measuring systems (Seca GmbH & Co, KG, Hamburg, Germany) for CARLA, RECALL, KORA and DEGS. In SHIP, devices from Soehnle (LEIFHEIT AG, Nassau, Germany) were used. WC and HC were measured using a flexible, inelastic tape measure. WC was measured at the narrowest part between the lowest ribs and the highest point of the iliac crest. HC was measured at the largest circumference between the iliac crest and the crotch in CARLA, SHIP, KORA and DEGS. In RECALL, HC was measured at the middle between

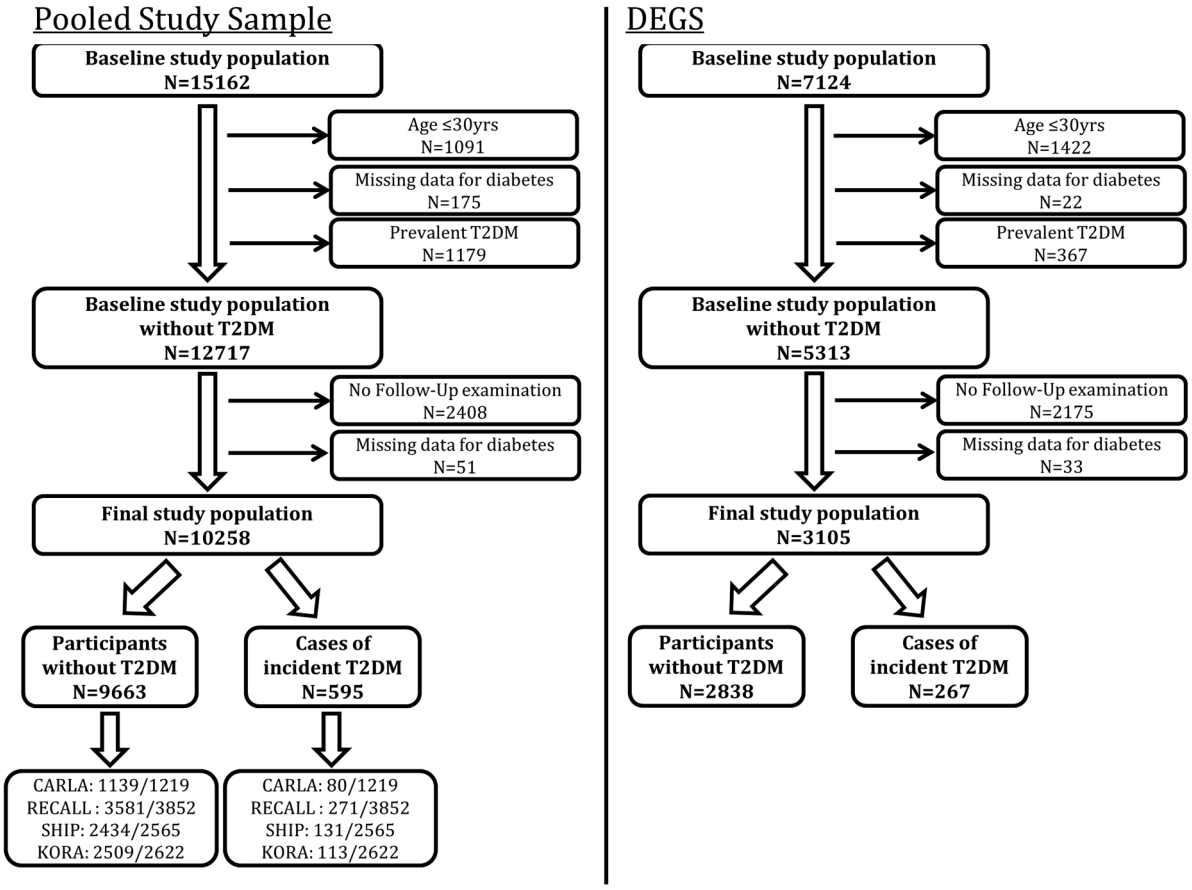

Figure 1 Study population and exclusions (T2DM, type 2 diabetes mellitus).

the iliac crest and the crotch. The indices of BMI, waist-to-hip-ratio (WHR) and waist-to-height-ratio (WHtR) were calculated as follows:

$$\text{BMI} = \frac{\text{weight [kg]}}{\text{height}^2\,[\text{m}^2]}$$

$$\text{WHR} = \frac{\text{waist circumference [cm]}}{\text{hip circumference [cm]}}$$

$$\text{WHtR} = \frac{\text{waist circumference [cm]}}{\text{height [cm]}}$$

Information on lifestyle factors, such as smoking, alcohol consumption and physical activity, as well as on socioeconomic data, was collected during the baseline interview. Socioeconomic status was classified according to the International Standard Classification of Education 1997 (including school and professional education and providing the total number of years of education).[25] Information on current smoking status, duration of smoking and number of cigarettes smoked was combined to calculate pack years of cigarettes (1 pack year ≙20 cigarettes smoked per day for 1 year). Alcohol consumption was dichotomised as no or moderate consumption (♀: 0–10 g/day; ♂: 0–20 g/day) versus consumption above these limits.[26] Sports activities during leisure time were categorised as regular sports activities of at least 1 h per week versus <1 h of sports activities per week. Dietary habits were collected using validated food frequency questionnaires,[27 28] either during the personal interview (in KORA, SHIP and RECALL) or through a self-administered questionnaire (CARLA and DEGS). Based on the German Nutrition Society's recommendations,[29] a simple score was generated based on information regarding brown bread intake, red meat intake, and fruit and vegetable consumption, as these nutritional components are known to be associated with T2DM.[30–32] For each of these components, the participant received one score-point if the intake met the recommendations. The resulting summary score ranged from '0' to '3', with each score-point corresponding to one item that met the recommendations.

Statistical approach

The crude individual data of CARLA, SHIP, RECALL and KORA were pooled into one data set. All described analyses were also conducted for DEGS, where the data had to be weighted to reduce influence of drop-out on the association analyses since 38% of GNHIES98 survey participants did not participate in the follow-up examination during the DEGS study. The study-specific weighting factor was calculated by inverse probability weighting.[33] A stepwise regression approach was used to

model potential predictors of dropout. Furthermore, the weighting factor corrects sample deviations from population structure with regard to age, sex, region, nationality, community and education (as of 31 December 1997).[34]

Missing values in pack years (logarithmically transformed for the imputation process) (n=92), alcohol consumption (n=205), physical activity (n=21) and education (n=11) were replaced by imputed values derived from a series of 10 imputation data sets and age, sex, study region and examination date as additional explanatory variables.[35] Participants with missing values for anthropometric variables were excluded from the specific analyses using these variables. For calculation of incidence rates, we used the complete observation time for participants without incident T2DM, and one-half of the individual recorded observation time between baseline and follow-up for participants with incident T2DM, as we did not always know the exact date of diagnosis.

We estimated HRs and the corresponding 95% CIs for the association of the respective anthropometric measurement with incidence of T2DM. To be able to compare the effects of the diverse markers with each other despite the use of different scales, we standardised anthropometric markers to a mean of 0 and a SD of 1, before estimating the association of the diverse markers and incidence of T2DM. In addition, we calculated the differences of HR and receiver operator characteristic (ROC) area under the curve (AUC) between the respective anthropometric markers and weight in order to provide a measure for the comparison of their predictive ability.

Owing to lack of information on the exact diagnosis date of T2DM, we used a method for interval-censored time-to-event data. Age was used as time scale with age at the baseline as entry time. In a so-called delayed entry study, participants are not observed until they are included in the study. Assuming that age at diabetes onset follows a Weibull distribution, we set up a proportional hazards model. This is similar to a generalised linear model, but includes a non-linear term in the Weibull distribution for individual ages at baseline and at follow-up, as described by Jain *et al*.[36] The proportional hazard assumptions were checked by visual inspection of residuals.

Analyses were adjusted for a variety of confounders that were selected using directed acyclic graphs.[37]

In addition, we stratified the data set (1) by study region and (2) by age (<65 vs ≥65 years) to examine the consistency of the effects. To compare the pooled effects derived from the pooled data analyses of the four regional studies with the results of the nationwide DEGS study, we conducted an age-stratified meta-analysis using Review Manager 5.3 (Cochrane Collaboration, Oxford, England).

Furthermore, we calculated ROC curves individually for all anthropometric measures and compared the AUC by calculating AUC differences (±95% CI).

All analyses except for the meta-analyses, were conducted using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Study population

The final pooled study population consisted of 10 258 individuals, 50.9% of whom were women. In DEGS, 53.4% of the 3.105 participants were female.

Table 1 summarises the baseline characteristics of the study population including important risk and protective factors for T2DM. The mean age in the pooled sample was 55.5 years, ranging from 50.5 years in KORA to 62.2 years in CARLA. The mean BMI was 27.5 kg/m², and 24.4% of all participants were obese (BMI≥30 kg/m²) as classified by WHO 2000. In DEGS, mean BMI was 26.9 kg/m² (ie, in the overweight category according to WHO definition), but fewer participants were obese (20.3%). Participants with incident T2DM showed a more unfavourable risk factor profile than those without T2DM in all studies, and among men and women. For example, they showed higher values for all anthropometric measures (except for baseline height), reported a higher number of pack years and were less physically active as compared with participants without incident T2DM.

Differences across the study regions were found for age, anthropometric measures and lifestyle characteristics. Participants in CARLA had the highest WC (98.1 cm), although weight and BMI were comparable between the studies. In the DEGS study, participants were slightly younger (mean age 48.1 years) and were less likely to play sports for >1 h/week (39.6%) compared with participants in the pooled sample. Education levels and anthropometric measurements were comparable between the pooled sample and DEGS.

Of all participants included in the pooled study sample, 595 developed T2DM during the follow-up, resulting in an incidence rate of 10.8/1000 person years (py) (95% CI 9.9 to 11.6). In DEGS, 267 participants developed T2DM resulting in an incidence rate of 7.5/1000 py (95% CI 6.6 to 8.3).

Association between anthropometric markers and incidence of T2DM

Table 2 shows the standardised effects of the different anthropometric markers on the incidence of T2DM with adjustment for education, study region and the lifestyle factors alcohol consumption, pack years of cigarettes, sports activities and nutritional score. We found consistent moderate associations for each anthropometric marker with incident T2DM. When comparing the standardised anthropometric markers, in the pooled analyses, the measurements reflecting abdominal obesity (WC, WHtR) showed stronger associations with incident T2DM compared with body weight and BMI (table 2) in both sexes. An exception was WHR, which showed the weakest association with incidence of T2DM in women and in men. The observed differences of HR and ROC AUC with the respective CIs support this interpretation.

In women, an increase of 1 SD (=12.4 cm) in WC resulted in a HR of 1.97 (95% CI 1.75 to 2.22), whereas

Table 1 Characteristics of the study population

Women		Pooled sample		DEGS	
		Non-diseased N=4984	Incident T2DM N=237	Non-diseased N=1523	Incident T2DM N=136
Age (years)	Mean (SD)	54.76 (±11.33)	60.66 (±9.63)	47.40 (±10.85)	53.79 (±10.70)
Observation period (years)	Mean (SD)	5.57 (±1.06)	5.46 (±1.05)	12.09 (±1.00)	12.14 (±0.91)
Anthropometry					
Height (m)	Mean (SD)	1.62 (±0.06)	1.61 (±0.07)	1.63 (±0.06)	1.62 (±0.07)
Weight (kg)	Mean (SD)	70.82 (±12.86)	80.26 (±16.04)	69.39 (±12.40)	81.64 (±17.99)
BMI (kg/m²)	Mean (SD)	26.96 (±4.85)	30.96 (±5.72)	26.00 (±4.68)	31.18 (±6.18)
Waist circumference (cm)	Mean (SD)	85.82 (±12.18)	97.12 (±13.01)	83.75 (±11.59)	97.29 (±13.97)
Hip circumference (cm)	Mean (SD)	103.75 (±10.52)	110.79 (±11.90)	104.85 (±9.80)	114.12 (±12.98)
WHR	Mean (SD)	0.83 (±0.07)	0.88 (±0.06)	0.80 (±0.06)	0.85 (±0.06)
WHtR	Mean (SD)	0.53 (±0.08)	0.60 (±0.08)	0.51 (±0.07)	0.60 (±0.09)
Lifestyle					
Smoking (pack years)	Mean (SD)	6.69 (±12.67)	7.63 (±16.10)	5.90 (±10.77)	5.60 (±11.40)
No or moderate alcohol consumption (≤10 g/day)	n (%)	3955 (81.08)	207 (89.61)	1278 (85.31)	121 (90.98)
Sports activities (≥1 h/week)	n (%)	2392 (48.04)	85 (36.02)	611 (40.63)	25 (18.80)
Education (years)					
9/10	n (%)	712 (14.29)	22 (6.15)	219 (14.55)	42 (31.34)
13	n (%)	2717 (54.54)	117 (32.68)	871 (57.87)	73 (54.48)
16	n (%)	863 (17.32)	138 (38.55)	216 (14.35)	8 (5.97)
18	n (%)	690 (13.85)	81 (22.63)	199 (13.22)	11 (8.21)
Nutritional score					
0 Points	n (%)	89 (1.79)	5 (2.11)	47 (3.13)	2 (1.50)
1 Points	n (%)	1099 (22.05)	56 (23.63)	303 (20.20)	33 (24.81)
2 Points	n (%)	1916 (38.44)	99 (41.77)	662 (44.13)	52 (39.10)
3 Points	n (%)	1880 (37.72)	77 (32.49)	488 (32.53)	46 (34.59)

Men		Pooled sample		DEGS	
		Non-diseased N=4679	Incident T2DM N=358	Non-diseased N=1315	Incident T2DM N=131
Age (years)	Mean (SD)	55.55 (±11.59)	61.54 (±8.65)	47.73 (±10.87)	53.06 (±9.85)
Observation period (years)	Mean (SD)	5.51 (±1.07)	5.37 (±0.98)	12.03 (±0.99)	12.11 (±0.99)
Anthropometry					
Height (m)	Mean (SD)	1.75 (±0.07)	1.74 (±0.07)	1.76 (±0.07)	1.75 (±0.07)
Weight (kg)	Mean (SD)	84.59 (±12.65)	92.80 (±14.74)	83.96 (±11.97)	92.71 (±13.86)
BMI (kg/m²)	Mean (SD)	27.59 (±3.65)	30.63 (±4.23)	27.04 (±3.37)	30.35 (±3.89)
Waist circumference (cm)	Mean (SD)	98.02 (±10.26)	107.17 (±10.82)	97.07 (±9.82)	106.73 (±10.32)
Hip circumference (cm)	Mean (SD)	102.57 (±7.29)	107.77 (±9.46)	105.32 (±6.44)	109.42 (±6.81)
WHR	Mean (SD)	0.95 (±0.06)	0.99 (±0.05)	0.92 (±0.06)	0.97 (±0.06)
WHtR	Mean (SD)	0.56 (±0.06)	0.62 (±0.06)	0.55 (±0.06)	0.61 (±0.06)

Continued

Table 1 Continued

Men		Pooled sample Non-diseased N=4679	Pooled sample Incident T2DM N=358	DEGS Non-diseased N=1315	DEGS Incident T2DM N=131
Lifestyle					
Smoking (pack years)	Mean (SD)	16.29 (±21.24)	22.79 (±27.09)	12.25 (±16.39)	19.22 (±24.32)
No or moderate alcohol consumption (≤20 g/day)	n (%)	3113 (67.81)	259 (73.37)	904 (69.75)	85 (65.89)
Sports activities (≥1 h/week)	n (%)	2125 (45.55)	125 (35.01)	543 (41.90)	32 (25.00)
Education (years)					
9/10	n (%)	185 (3.96)	16 (4.48)	90 (6.95)	12 (9.52)
13	n (%)	2193 (46.95)	188 (52.66)	620 (47.88)	60 (47.62)
16	n (%)	1040 (22.27)	83 (23.25)	269 (20.77)	23 (18.25)
18	n (%)	1253 (26.83)	70 (19.61)	316 (24.40)	31 (24.60)
Nutritional score					
0 Points	n (%)	384 (8.21)	22 (6.13)	140 (10.91)	15 (11.63)
1 Points	n (%)	1639 (35.03)	118 (32.87)	482 (37.57)	53 (41.09)
2 Points	n (%)	1787 (38.19)	138 (38.44)	468 (36.48)	45 (34.88)
3 Points	n (%)	869 (18.57)	81 (22.56)	193 (15.04)	16 (12.40)

BMI, body mass index; T2DM, type 2 diabetes mellitus; WHR, waist-to-hip-ratio; WHtR, waist-to-height-ratio.

Table 2 Association between different anthropometric measurements and T2DM in the pooled sample and DEGS

		Women				Men			
		HR*† (95% CI) standardised	HR difference‡ (95% CI)	ROC AUC (95% CI)	ROC AUC difference‡ (95% CI)	HR*† (95% CI) standardised	HR difference‡ (95% CI)	ROC AUC (95% CI)	ROC AUC difference‡ (95% CI)
Pooled Sample	Weight	1.69 (1.53 to 1.88)	–	0.68 (0.65 to 0.72)	–	1.65 (1.54 to 1.78)	–	0.67 (0.64 to 0.70)	–
	BMI	1.68 (1.52 to 1.86)	−0.01 (−0.22 to 0.19)	0.71 (0.68 to 0.75)	0.03 (−0.02 to 0.08)	1.71 (1.59 to 1.85)	0.06 (−0.12 to 0.24)	0.72 (0.69 to 0.74)	0.04 (0.00 to 0.09)
	Waist	1.97 (1.75 to 2.22)	0.28 (−0.01 to 0.57)	0.74 (0.71 to 0.77)	0.06 (0.01 to 0.11)	1.81 (1.67 to 1.96)	0.15 (−0.04 to 0.34)	0.74 (0.71 to 0.76)	0.07 (0.03 to 0.11)
	WHR	1.55 (1.40 to 1.71)	−0.14 (−0.38 to 0.09)	0.72 (0.68 to 0.75)	0.03 (−0.01 to 0.08)	1.64 (1.46 to 1.83)	−0.02 (−0.24 to 0.20)	0.69 (0.66 to 0.71)	0.02 (−0.02 to 0.06)
	WHtR	1.93 (1.71 to 2.17)	0.23 (−0.06 to 0.52)	0.75 (0.71 to 0.78)	0.06 (0.01 to 0.11)	1.81 (1.66 to 1.97)	0.15 (−0.04 to 0.35)	0.75 (0.72 to 0.77)	0.07 (0.04 to 0.11)
DEGS§	Weight	1.84 (1.59 to 2.12)	–	0.72 (0.67 to 0.76)	–	1.78 (1.53 to 2.07)	–	0.69 (0.64 to 0.74)	–
	BMI	1.78 (1.56 to 2.03)	−0.06 (−0.40 to 0.28)	0.76 (0.72 to 0.80)	0.04 (−0.02 to 0.10)	2.00 (1.72 to 2.33)	0.23 (−0.17 to 0.62)	0.75 (0.70 to 0.79)	0.06 (−0.01 to 0.13)
	Waist	2.24 (1.91 to 2.63)	0.40 (−0.04 to 0.84)	0.77 (0.73 to 0.81)	0.05 (−0.01 to 0.12)	2.06 (1.74 to 2.43)	0.28 (−0.14 to 0.70)	0.75 (0.71 to 0.80)	0.07 (0.00 to 0.13)
	WHR	1.83 (1.57 to 2.13)	−0.01 (−0.39 to 0.37)	0.74 (0.69 to 0.78)	0.02 (−0.04 to 0.08)	2.29 (1.89 to 2.78)	0.52 (0.01 to 1.02)	0.75 (0.71 to 0.79)	0.06 (0.00 to 0.13)
	WHtR	2.10 (1.81 to 2.44)	0.26 (−0.14 to 0.66)	0.78 (0.74 to 0.82)	0.06 (0.00 to 0.12)	2.03 (1.71 to 2.40)	0.25 (−0.17 to 0.67)	0.77 (0.73 to 0.81)	0.08 (0.02 to 0.14)

*HRs are adjusted for study region (only in the pooled sample), education, alcohol consumption, smoking (pack-years), sports activities and nutritional score.
†Data of exposure variables are standardised to a mean of 0 and a SD of 1 for these analyses. The calculated HRs relate to a difference of 1 SD.
‡Compared with weight (reference).
§Results are weighted for dropout.
AUC, area under the curve; BMI, body mass index; ROC, receiver operator characteristic; T2DM, type 2 diabetes mellitus; WHR, waist-to-hip-ratio; WHtR, waist-to-height-ratio.

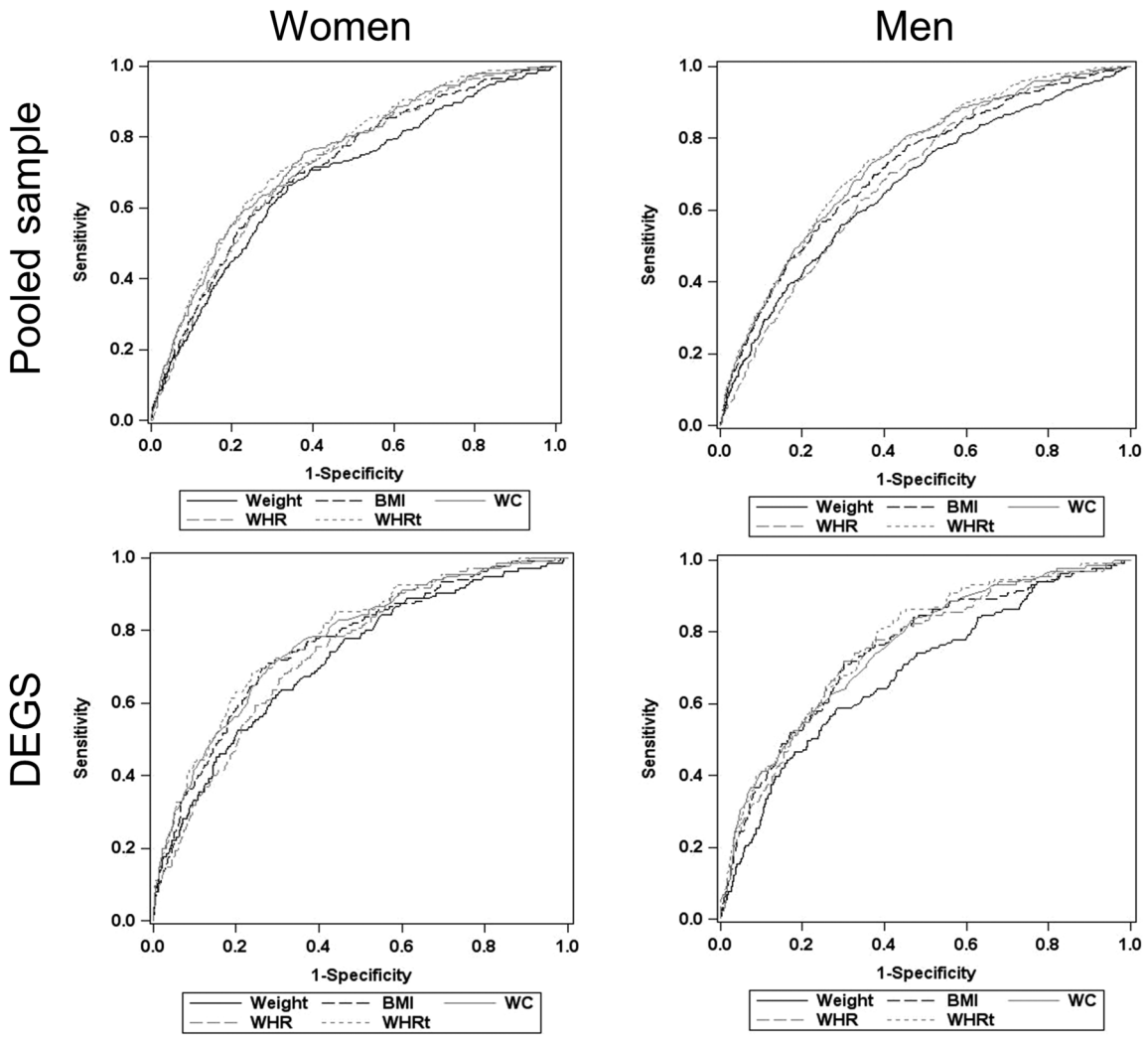

Figure 2 ROC curves of five anthropometric markers with respect to incident T2DM (BMI, body mass index; ROC, receiver operator characteristic; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHR, waist-to-hip-ratio; WHtR, waist-to-height-ratio).

a 1 SD difference in weight (≙ 13.2 kg) resulted in a HR of 1.69 (95% CI 1.53 to 1.88). Likewise, in men, a 1 SD difference in WC (≙10.6 cm) led to a HR of 1.81 (95% CI 1.67 to 1.96), whereas a 1 SD difference in weight (≙ 13.0 kg) resulted in a HR of 1.66 (95% CI 1.54 to 1.78).

In the DEGS sample, in men, WHR showed the strongest association with incident T2DM of all anthropometric markers, whereas in women, WC and WHtR again were superior to the other markers (lower part of table 2). The finding for WHR is contrary to the results observed in the pooled sample.

When we calculated the ROC AUC for different anthropometric measurements, we also found comparable predictive values for women and men for each indicator of obesity (table 2 and figure 2). In the pooled data set in both sexes, WHtR was the strongest predictor for incident T2DM (AUC women=0.75 (95% CI 0.71 to 0.78); AUC men=0.75 (95% CI 0.72 to 0.77)) with an AUC difference of 0.06 (95% CI 0.01 to 0.11) and 0.07 (0.04 to 0.11) for women and men, respectively, compared with weight. Predictive values for the other markers were similar, apart from weight in women, and weight and WHR in men, which had a lower discriminative ability. In the DEGS study sample, the ROC AUC values and HRs as such were slightly higher than in the pooled sample, but the comparison of predictive ability between the anthropometric markers was consistent with the ranking found in the pooled sample.

Looking at the associations observed within the individual study regions of the pooled data set (table 3), standardised HRs were highest for indices that reflected abdominal obesity as well. WC and WHtR had the strongest associations with incident T2DM. For women, HRs ranged from 1.56 (95% CI 1.10 to 2.20) to 2.33 (95% CI 1.81 to 3.00) for WC, and from 1.58 (95% CI 1.10 to 2.25) to 2.36 (95% CI 1.81 to 3.08) for WHtR. For men, the HR ranged from 1.60 (95% CI 1.35 to 1.91) and 2.25 (95% CI 1.73 to 2.92) for WC to 1.64 (95% CI 1.33 to 2.01) and 2.40 (95% CI 1.81 to 3.19) for WHtR.

In age-stratified analyses we found smaller effects in participants ≥65 years compared with younger participants (figure 3). However, the pattern of larger

Table 3 HRs of different anthropometric markers for incident T2DM, stratified by study region

	HR* (95% CI) standardised†									
	Women					Men				
	CARLA	SHIP	KORA	RECALL		CARLA	SHIP	KORA	RECALL	
Weight	1.47 (1.10 to 1.98)	1.67 (1.30 to 2.13)	1.98 (1.59 to 2.48)	1.62 (1.39 to 1.89)		1.98 (1.58 to 2.47)	1.70 (1.42 to 2.03)	1.44 (1.24 to 1.67)	1.67 (1.48 to 1.89)	
BMI	1.55 (1.14 to 2.10)	1.64 (1.28 to 2.12)	2.05 (1.65 to 2.56)	1.58 (1.36 to 1.82)		2.31 (1.84 to 2.90)	1.73 (1.46 to 2.06)	1.52 (1.29 to 1.79)	1.65 (1.47 to 1.85)	
Waist	1.56 (1.10 to 2.20)	2.14 (1.62 to 2.83)	2.33 (1.81 to 3.00)	1.81 (1.53 to 2.14)		2.25 (1.73 to 2.92)	1.92 (1.58 to 2.33)	1.60 (1.35 to 1.91)	1.72 (1.53 to 1.93)	
WHR	1.97 (0.80 to 4.82)	1.56 (1.33 to 1.82)	2.15 (1.62 to 2.87)	1.45 (1.23 to 1.71)		1.49 (1.10 to 2.01)	1.72 (1.37 to 2.16)	1.70 (1.36 to 2.13)	1.48 (1.27 to 1.73)	
WHtR	1.58 (1.10 to 2.25)	2.00 (1.52 to 2.63)	2.36 (1.81 to 3.08)	1.76 (1.49 to 2.08)		2.40 (1.81 to 3.19)	1.92 (1.57 to 2.35)	1.64 (1.33 to 2.01)	1.69 (1.50 to 1.90)	

*HRs are adjusted for education, alcohol consumption, pack years, sports activities and nutritional score.
†Data of exposure variables are standardised to a mean of 0 and a SD of 1 for these analyses. The calculated HRs relate to a difference of 1 SD.
BMI, body mass index; T2DM, type 2 diabetes mellitus; WHR, waist-to-hip-ratio; WHtR, waist-to-height-ratio.

estimated effects for WC and WHtR was consistent across age groups in the pooled sample and the DEGS study as well as in the meta-analyses, except for the highest HR for WHR in older participants in DEGS (HR for WHR in women 2.15 (95% CI 1.47 to 3.13); HR men 3.50 (95% CI 1.64 to 7.46)).

DISCUSSION

We investigated the association between different anthropometric measurements and the incidence of T2DM in a study population consisting of four prospective population-based cohorts located in different regions of Germany, as well as in a nationwide population. Overall, we found consistently stronger associations with incident T2DM for markers reflecting abdominal obesity (ie, WC and WHtR) except for WHR. We also found advantages in discriminative ability between diabetic and non-diabetic participants for the same markers (WC and WHtR), for example, in the pooled sample at a specificity of 70%, 5 more T2DM cases of the 100 would be identified when using WHtR compared with BMI. However, the differences in the AUCs are small and need to be further validated in independent international cohorts.

Other investigation groups have conducted similar analyses with comparable results regarding the strength of association as well as the discriminative ability. Schneider *et al*[12] found WHtR to have the best discriminative ability compared with WHR, WC, HC and BMI in a cross-sectional analysis. In another cross-sectional study, Bhowmik *et al*[13] calculated ROCs and found the AUC of WHR, WC and WHtR to be superior to BMI. Folsom *et al*[16] conducted a prospective study and found the strongest association of WC with incident T2DM as compared with WHR and BMI, using quintiles of anthropometric measures. Findings from several meta-analyses were inconsistent. A meta-analysis of longitudinal studies was performed by Kodama *et al*,[15] while Lee *et al*[14] performed a meta-analysis of mainly cross-sectional studies in Asian populations. Both meta-analyses found WHtR to be more strongly associated with T2DM than WC, WHR or BMI. Contrary to these results, Vazquez *et al*[17] found no difference between the anthropometric markers when they studied WHR, WC and BMI in another meta-analysis of longitudinal studies.

The finding of an apparent advantage of markers of central obesity over BMI or weight alone observed in most studies can probably be explained by the physiological functions of visceral fat tissue, which is known to have endocrine functions and to be an independent risk factor for T2DM.[17 38] The weaker predictive ability of WHR observed in our study is contrary to some of the prior studies,[13 17] but consistent with findings of some others.[12 15 16] The fact that WHR seems to be inferior in predicting diabetes could be explained by the weaker correlation of WHR and visceral fat as compared with

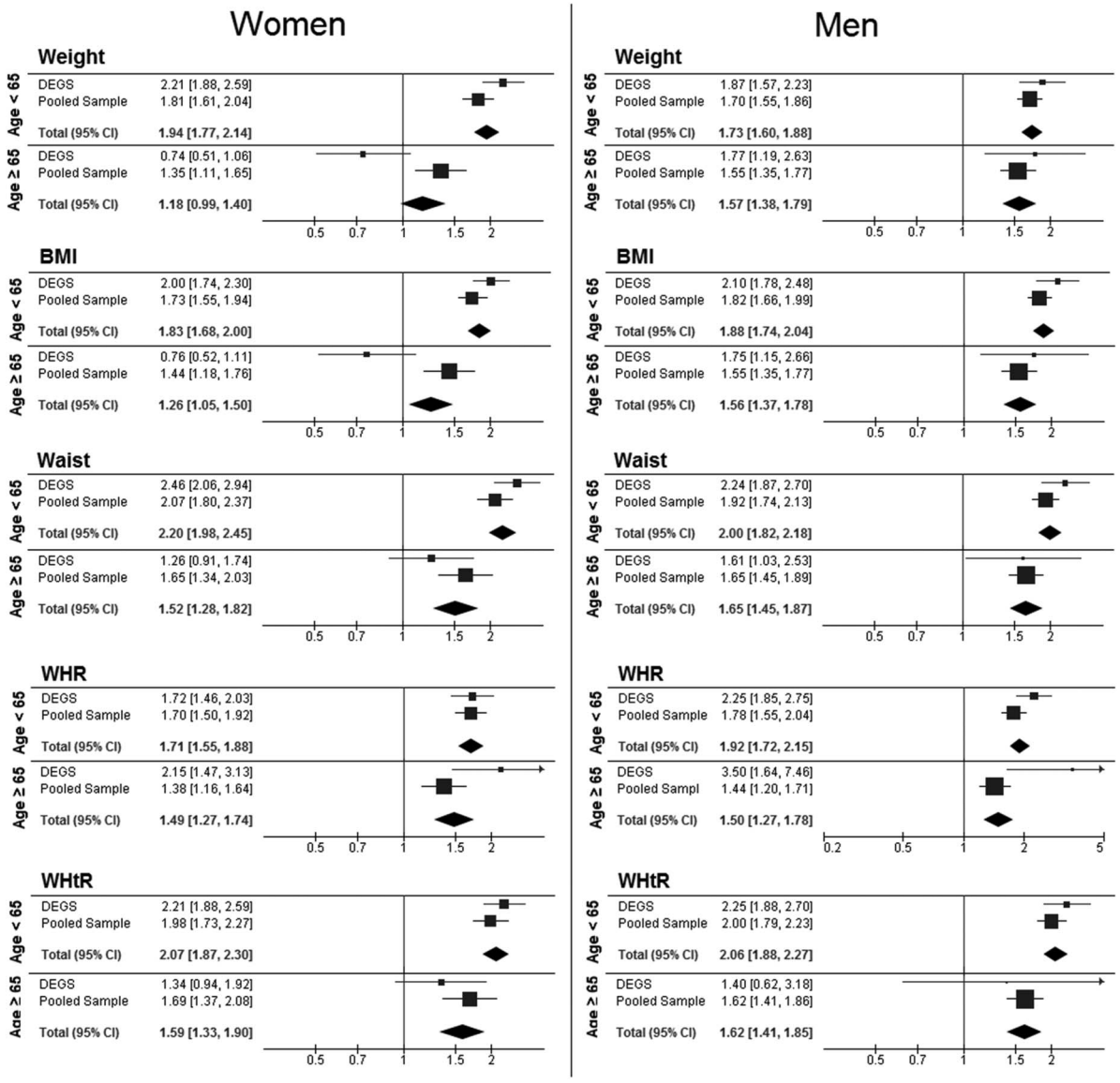

Figure 3 Meta-analyses of HRs for the association between anthropometric markers and T2DM, stratified by age (BMI, body mass index; T2DM, type 2 diabetes mellitus; WC, waist circumference; WHR, waist-to-hip-ratio; WHtR, waist-to-height-ratio).

the correlation between WC and visceral fat, thus being a weaker marker of visceral fat tissue.[39] HC—which is an inherent component of WHR—can reflect different components, such as muscle mass, fat mass and skeletal features, while WC mainly reflects visceral organs and abdominal fat and thus is a better surrogate marker of visceral fat tissue.[40]

Comparing our results with those of the studies aforementioned, caution is needed because of differences in design and cohort characteristics. Schneider *et al*[12] used a cross-sectional design so their results cannot be directly compared with those of our study; Bhowmik *et al*[13] conducted their study in an Asian cohort, where they found considerably lower cut-off values for risk of T2DM than were found in our Western populations. However, different thresholds of risk for different ethnicities have already been suggested; for example, the threshold for WC is lower for South Asians, Chinese and Japanese than for Europeans.[41]

When we compared the study regions among each other, the advantage of markers of abdominal adiposity over other anthropometric indices was consistent across most studies. Men in KORA and DEGS are the exceptions because in these groups, the strongest associations were observed for WHR, possibly due to cohort differences. Persistence of the estimated associations was also found when stratifying the sample by age (<65 vs ≥65 years) in the pooled sample except for the older group in DEGS, which was very small (n=112 women and 110 men) and showed imprecise results. In a meta-analysis of DEGS and the pooled sample in both age groups, WC and WHtR showed the strongest associations.

In the age stratified meta-analyses, we found consistently smaller effects of anthropometric markers on

diabetes risk in individuals aged ≥65 years. Although the difference is small, this finding indicates a lower importance of anthropometric markers in predicting diabetes in the elderly. This finding needs to be confirmed in independent samples.

Considering all the results observed, we recommend paying greater attention to those markers that represent visceral obesity, such as WC and WHtR. Although all investigated markers show an association with incident T2DM, WC and WHtR show the most consistent associations in all analyses for the studied population.

Our study offers strengths and limitations in terms of study design and methods. Among the strengths, we can list the following: we used data from four prospective planned population-based[42] studies from different regions in Germany, as well as data from a nationwide survey, resulting in a large study sample. The prospective design of our original studies is a main advantage, as certain research question cannot be answered by cross-sectional studies because of unclear temporality between anthropometric markers such as exposure and occurrence of T2DM. The comparable design and methods as well as the availability of raw data from CARLA, KORA, RECALL and SHIP, allowed us to pool the data instead of conducting a meta-analysis. Using the DEGS sample, we had the opportunity to compare a nationwide survey to the pooled data set. We used several statistical instruments such as the transformation of measurements to units of SD in order to make HRs comparable, as well as comparison of AUCs to investigate the consistency of the results. Furthermore, we corrected for the interval-censored character of the data and the possibility of late entry with the help of the Weibull model. Another strength is the selection of covariates applying the theory of directed acyclic graphs.[37]

However, there are some limitations to our study. For example, information on family history of T2DM, which is a potential confounder of the association of anthropometric markers and diabetes, was lacking in some studies and thus could not be used for our analyses. Other limitations include the definition of T2DM and medication use via self-reported information instead of using physician-verified diagnoses or the results from an oral glucose tolerance test. Therefore, it is likely that the incidence of self-reported T2DM is an underestimation of the true incidence due to undetected and unknown cases of T2DM. In general, the specificity of self-reported T2DM can be considered as high, whereas its sensitivity is relatively low.[43] This means that a bias due to undetected cases could be possible in this study. However, Xu *et al*'s[44] investigation showed WC and WHtR as having stronger associations than other anthropometric markers with undiagnosed T2DM as well.

Although examination methods used in the participating studies were very similar, small differences exist regarding HC, as described in the method section. To reduce the effect of variability in the examination methods, we adjusted all regression models for the study region.

Furthermore, loss to follow-up could have influenced our results, because drop outs could be systematically different from participants who attended the follow-up investigation. However, loss to follow-up in the regional studies was small and analyses in the nationwide DEGS study, where follow-up non-response was more substantial, were adjusted for drop outs via inverse weighting from propensity score models.

Overall, our results may be affected by heterogeneity between studies that could not be captured by the explicit adjustment for the study effects that we performed. To investigate this, we assessed heterogeneity by estimating I^2 (and the corresponding χ^2 test) before and after correcting for the study sides in our analyses. Heterogeneity ranged from I^2=0% to I^2=67% ($p>0.05$ except for analysis of BMI in men ($p=0.03$)) between effects of regional studies and I^2=0% to I^2=89% ($p>0.05$ except for analysis of WHR in men ($p=0.003$)) between effects in the meta-analyses of pooled regional studies and nationwide DEGS study. This means that, both between regional studies and between the pooled data set and DEGS, heterogeneity was present in varying degrees.

Another limitation is the fact that we had to work with interval-censored data because the exact date of diagnosis was not available. There might be slight variations in the studies' anthropometric measuring methods, but we corrected for this by adjusting for the study.

In order to encourage use of measures of abdominal obesity in clinical settings, a lack of confidence in measuring body circumferences[45] could be overcome by using alternative measurement methods such as photonic scanning rather than flexible tape. These methods are more precise,[46] but the instruments are expensive and therefore only suitable for specific applications. A first step to achieve better comparability could be standardisation of measuring methods. An implication of our study results for clinical practice might be that, based on our findings, general practitioners should be encouraged to pay close attention to the distribution of body fat of their patients when assessing the risk for T2DM, since visceral fat is more hazardous than evenly distributed body fat. Although there is a high level of evidence for the importance of WC, this knowledge is not often applied in clinical practice by using the respective measurements.

Author affiliations
[1]Institute of Medical Epidemiology, Biostatistics, and Informatics, Martin-Luther-University Halle-Wittenberg, Halle, Germany
[2]German Center for Diabetes Research (DZD), München-Neuherberg, Germany
[3]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
[4]Institute for Social Medicine, Epidemiology and Health Economics, Charité-Universitätsmedizin Berlin, Berlin, Germany
[5]Institute of Epidemiology and Social Medicine, University of Muenster, Muenster, Germany

[6]Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany
[7]Institute of Health Economics and Health Care Management, Helmholtz Zentrum München, Neuherberg, Germany
[8]Institute of Epidemiology II, Helmholtz Zentrum München, Neuherberg, Germany
[9]Department of Epidemiology and Health Monitoring, Robert Koch Institute, Berlin, Germany
[10]Institute for Medical Informatics, Biometry, and Epidemiology, University Hospital of Essen, University Duisburg-Essen, Essen, Germany
[11]Department of Medicine III, Martin-Luther-University Halle-Wittenberg, Halle, Germany
[12]Institute of Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich-Heine-University, Düsseldorf, Germany

Parts of this study were presented in abstract form and orally at the 8th Annual Meeting of the German Society for Epidemiology (DGEpi) e.V., Leipzig-Germany, 25–27 September 2013.

Contributors SH conducted analyses and wrote the manuscript. AK helped to coordinate the CARLA study, participated in the statistical analyses and helped to write and draft the manuscript. DT helped to coordinate the CARLA study and reviewed the manuscript. JF contributed to the discussion and reviewed the manuscript. GM took part in the discussion and the statistical analyses, and reviewed the manuscript. SS reviewed the manuscript. HV provided data and reviewed the manuscript. MS contributed to the discussion and reviewed the manuscript. CM provided data and reviewed the manuscript. AS provided data, contributed to the discussion and reviewed the manuscript. CH contributed to the discussion and reviewed the manuscript. SM provided data and reviewed the manuscript. SP reviewed the manuscript. KW researched data and reviewed the manuscript. OK participated in the statistical analyses and the discussion, and reviewed the manuscript. TT contributed to the data pooling and reviewed the manuscript. JH helped to design the CARLA study and to draft the manuscript. KHG designed major parts of the CARLA Study, coordinated the study and reviewed the manuscript. All the authors read and approved the final manuscript. SH takes responsibility for the contents of the manuscript.

Funding This work was supported by the Competence Network Diabetes Mellitus of the German Federal Ministry of Education and Research (BMBF, grant 01GI1110C) and the Competence Network Obesity (BMBF, grant 01GI1121B). The Cardiovascular Disease, Living and Ageing in Halle (CARLA) Study was supported by a grant from the Deutsche Forschungsgemeinschaft as part of the Collaborative Research Center 598 "Heart failure in the elderly—cellular mechanisms and therapy" at the Medical Faculty of the Martin-Luther-University Halle-Wittenberg, by a grant of the Wilhelm-Roux Programme of the Martin-Luther-University Halle-Wittenberg; by the Ministry of Education and Cultural Affairs of Saxony-Anhalt, and by the Federal Employment Office. The Study of Health in Pomerania (SHIP) is part of the Community Medicine Research net (http://www.community-medicine.de) at the University of Greifswald, Germany. Funding was provided by grants from the German Federal Ministry of Education and Research (BMBF, grant 01ZZ0403); the Ministry for Education, Research, and Cultural Affairs; and the Ministry for Social Affairs of the Federal State of Mecklenburg–West Pomerania. The Heinz Nixdorf Recall Study (RECALL) was generously supported by the Heinz Nixdorf Foundation (Germany). The study is also supported by the German Ministry of Education and Science. The KORA research platform (KORA, Cooperative Health Research in the Region of Augsburg) was initiated and financed by the Helmholtz Zentrum München—German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Local Ethics Committees.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Anthropometric markers and their association with incident type 2 diabetes mellitus: which marker is best for prediction? Pooled analysis of four German population-based cohort studies and comparison with a nationwide cohort study

Saskia Hartwig, Alexander Kluttig, Daniel Tiller, Julia Fricke, Grit Müller, Sabine Schipf, Henry Völzke, Michaela Schunk, Christa Meisinger, Anja Schienkiewitz, Christin Heidemann, Susanne Moebus, Sonali Pechlivanis, Karl Werdan, Oliver Kuss, Teresa Tamayo, Johannes Haerting and Karin Halina Greiser

BMJ Open 2016 6:
doi: 10.1136/bmjopen-2015-009266