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Association of MRI-based adrenal gland volume and impaired glucose metabolism in a population-based cohort study

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Abstract

Objectives: The aim of this study was to assess adrenal gland volume by using magnetic resonance imaging (MRI) and to study its role as an indirect marker of impaired glucose metabolism and hypothalamic–pituitary–adrenal (HPA) axis activation in a population-based cohort.

Methods: Asymptomatic participants were enrolled in a nested case–control study and underwent a 3-T MRI, including T1w-VIBE-Dixon sequences. For the assessment of adrenal gland volume, adrenal glands were manually segmented in a blinded fashion. Impaired glucose metabolism was determined using fasting glucose and oral glucose tolerance test. Cardiometabolic risk factors were also obtained. Inter- and intrareader reliability as well as univariate and multivariate associations were derived.

Results: Among 375 subjects included in the analysis (58.5% male, 56.1 ± 9.1 years), 25.3% participants had prediabetes and 13.6% had type 2 diabetes (T2DM). Total adrenal gland volume was 11.2 ± 4.2 ml and differed significantly between impaired glucose metabolism and healthy controls with largest total adrenal gland volume in

Abbreviations: BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; HPA, hypothalamic–pituitary–adrenal (axis); ICC, intraclass correlation coefficient; KORA, Cooperative Health Research in the Augsburg Region, Germany; MRI, magnetic resonance imaging; oGTT, oral glucose tolerance test; OR, odds ratio; SD, standard deviation; T2DM, type 2 diabetes mellitus.

T2DM (healthy controls: 10.0 ± 3.9 ml, prediabetes: 12.5 ± 3.8 ml, T2DM: 13.9 ± 4.6 ml; $p < 0.001$). In the multivariate analysis, association of T2DM and increased adrenal gland volume was independent of age, sex, hypertension, triglycerides and body mass index (BMI), but was attenuated in subjects with prediabetes after adjustment for BMI.

Conclusions: T2DM is significantly associated with increased adrenal gland volume by MRI in an asymptomatic cohort, independent of age, sex, dyslipidaemia, hypertension and BMI. Adrenal gland volume may represent an indirect marker of impaired glucose metabolism and HPA axis dysfunction.

KEYWORDS
adrenal gland, impaired glucose metabolism, MRI, prediabetes, segmentation, type 2 diabetes mellitus

1 | INTRODUCTION

Physiological stress such as metabolic diseases has been shown to be accompanied by the activation of the hypothalamic–pituitary–adrenal (HPA) axis.[1,2] Type 2 diabetes (T2DM) as well as its precursor state prediabetes is a major public health problem with increasing prevalence.[3] It is considered to constitute a stressful metabolic state, which induces chronic activation of the HPA axis.[4] Previous studies found that T2DM is associated with hypercortisolism and adrenocortical growth.[5] Furthermore, subclinical hypercortisolism is assumed to be one of the notable causes of insulin resistance associated with the metabolic syndrome, and involvement of the HPA axis in the pathogenesis of T2DM has been discussed.[6,7] Chronic activation of the HPA axis increases the volume of adrenal glands due to trophic effects of adrenocorticotropic hormone on the adrenal glands.[8] Thus, adrenal gland volume measurement seems to be a reliable method to assess HPA axis activation.[9] The feasibility of adrenal gland segmentation in epidemiological studies has been demonstrated in previous studies.[10–12] Hence, an association of increased adrenal gland volume in patients with prediabetes may serve as an early marker of the condition similar to impaired glucose tolerance.

The advantages of magnetic resonance imaging (MRI) towards computed tomography consist in the lack of radiation and its greater capacity of tissue characterisation,[13] but only a few studies conducted adrenal gland segmentation using MRI. Two pilot studies with relatively small sample sizes investigated the feasibility of measuring adrenal gland volume by MRI. While the study cohort of Grant et al.[10] consisted of only four healthy subjects, Freel et al.[14] investigated 20 normotensive men to assess both accuracy and reproducibility of adrenal gland volume measurements using MRI. So far, the primary studies performing adrenal gland volume measurement by MRI have been focussing on the involvement of adrenal gland volume in mental disorders and adipose tissue characterisation.[11,15]

Therefore, the value of adrenal gland volume assessment by MRI in metabolic disease states, particularly prediabetes or T2DM, remains unclear.

Thus, we aimed to study the role of adrenal gland volume as quantified by MRI and determine its role as an indirect marker of impaired glucose metabolism and dysfunction of the HPA axis in prediabetes and T2DM in a population-based Western cohort.

2 | MATERIALS AND METHODS

2.1 | Study design and study population

This case–control study's population was derived from the KORA-MRI sub-study, an MRI study nested within the population-based prospective cohort from the 'Cooperative Health Research in the Augsburg Region, Germany' (KORA), and which was designed as a cross-sectional prospective cohort study with the purpose to investigate the interplay between subclinical metabolic and cardiovascular disease in individuals with impaired glucose metabolism. KORA is a population-based research platform with a series of follow-up studies regarding epidemiology, health economics, and health research. Starting from 1996, four cross-sectional surveys S1–S4 have been performed at 5-year intervals within KORA. Each of these cross-sectional surveys consisted of an independent random sample and served as a cohort for long-term follow-up studies and as a data resource for nested case–control and case–cohort studies.[16] The study population of the KORA-MRI sub-study, from which our study population was derived, was recruited from the second follow-up of the KORA S4 cohort (FF4) and consisted of 400 individuals who performed a comprehensive whole-body MRI study protocol between June 2013 and September 2014. Participation required the absence of known prior cardiovascular disease (e.g., stroke, myocardial infarction and revascularisation) and of contraindications to MRI (e.g., cardiac pacemaker, implantable defibrillator, cerebral aneurysmal clip, neural stimulator, any type of ear implant and ocular foreign body) and/or to gadolinium contrast agent (e.g., known allergy against gadolinium compounds and impaired renal function with serum creatinine ≥1,3 mg/dl). Further exclusion criteria were age >72 years, pregnancy, and breastfeeding.[16,17]

2.2 | MR-imaging protocol

A standardised comprehensive whole-body MRI protocol was applied on a 3-T Magnetom Skyra (Siemens Healthineers) as previously described. For the assessment of adrenal gland volume, a two-point T1-weighted isotropic VIBE-Dixon gradient-echo sequence of the trunk was applied (slice thickness 1.7 mm, spatial resolution: 1.7 × 1.7 mm^2, field of view: 488 × 716 mm using a 256 × 256 matrix, repetition time: 4.06 ms, and echo time: 1.26 & 2.49 ms with a 9° flip angle).[16,17]

2.3 | MR-image analysis for adrenal gland volume

Images were assessed by two independent and blinded readers (EA and CK, radiology trainees with 1–2 years of experience, supervised by CS and EK; EA performed the analysis of the complete study cohort as well as for inter- and intrareader reliability, CK performed the analysis for interreader reliability). Image analysis for the assessment of adrenal gland volume was performed on the water-only phase sequences acquired by the two-point T1-weighted isotropic VIBE-Dixon gradient-echo sequence because of best anatomical identifiability of the adrenal glands. Quality of MRI images was categorised dependent on the absence or presence of motion-related artefacts, technical artefacts, and/or difficult organ delineation due to tight adhesion to adjacent organs (e.g., lower surface of the liver) as: (a) high (good accessability of the adrenal glands without the impairment of organ delineation through artefacts or tight adhesion to adjacent organs), (b) moderate (the presence of artefacts or tight adhesion of the adrenal glands to adjacent organs, but still sufficient identifiability of the adrenal glands), and (c) poor (presence of artefacts or difficult organ delineation due to tight adhesion to adjacent organs with impossible delineation of the adrenal glands). Participants with poor quality of the image sets or with missing T1w-VIBE-Dixon sequences or with adrenal gland masses were excluded. Image segmentations were performed using a local installation of the medical imaging platform, NORA (www.nora-imaging.com). After the identification of right and left adrenal glands on coronal, axial, and sagittal planes in the T1w-VIBE-Dixon sequences, adrenal gland contours were bilaterally traced on coronal slices on a slide-by-slide basis using a manual tool following clearly defined anatomical boundaries. Adrenal gland margins were subsequently adapted on axial and sagittal planes. The volume of each adrenal gland was automatically calculated as the number of voxels multiplied by voxel size.

The main outcome of the present study was total adrenal gland volume, that is, the sum of volumes in the left and right adrenal glands. For completeness, also the average volumes, that is, the average of left and right adrenal glands is reported.

Inter- and intrareader reliability were assessed in a random subset of 30 participants, respectively. To avoid recall bias, the measurements were performed with a time interval of at least 4 months. A delineation of adrenal volume segmentation in axial, coronal, and sagittal reconstructions is supplied in Figure 1.

2.4 | Assessment of impaired glucose metabolism

The assessment of diabetes status was described previously.[17] In brief, participants without known T2DM underwent oral glucose tolerance testing (oGTT), and fasting plasma glucose (FPG) concentration was measured. The 1998 World Health Organization criteria were applied to define prediabetes and T2DM.[18]

2.5 | Other covariates

Clinical and demographic data such as age, sex, height and cardiovascular risk factors such as BMI, triglycerides and hypertension were evaluated by comprehensive interviews and medical examinations in a standardised fashion as detailed elsewhere.[16,17] Cortisol levels of the participants were not recorded.

2.6 | Statistical analysis

For the assessment of inter- and intrareader reliability, relative differences between the two observers/observations were calculated according to the Bland–Altman analysis and presented as means. Additionally, intraclass correlation coefficients (ICC) from two-way random effects ANOVA were calculated. An ICC value close to 1 indicated excellent agreement between the two observers or observations.

Demographics, cardiometabolic risk factors and adrenal gland volume according to the diabetes status are presented as arithmetic mean and standard deviation (SD). Overall differences in these covariates according to diabetes status were evaluated by ANOVA or χ^2 test where appropriate.

To determine associations of adrenal gland volume with demographics and cardiometabolic risk factors, linear regression models with outcome total adrenal gland volume were calculated while adjusting for age, sex, and BMI. Odds ratios (OR) with corresponding 95% confidence intervals (CI) were calculated per standard deviation of the variable of interest to enable comparability between effect estimates.

To determine the diagnostic value of adrenal volume as a marker of diabetes status, associations of adrenal gland volume with diabetes status were assessed by multinomial and binomial logistic regression models with stepwise adjustment. Model 1 was adjusted only for age and sex, Model 2 was additionally adjusted for hypertension, Model 3 was additionally adjusted for hypertension and triglycerides, and Model 4 was additionally adjusted for hypertension, triglycerides and BMI. All analyses were conducted with R v3.6.3.[19] p-Values <0.05 are considered to denote statistical significance.

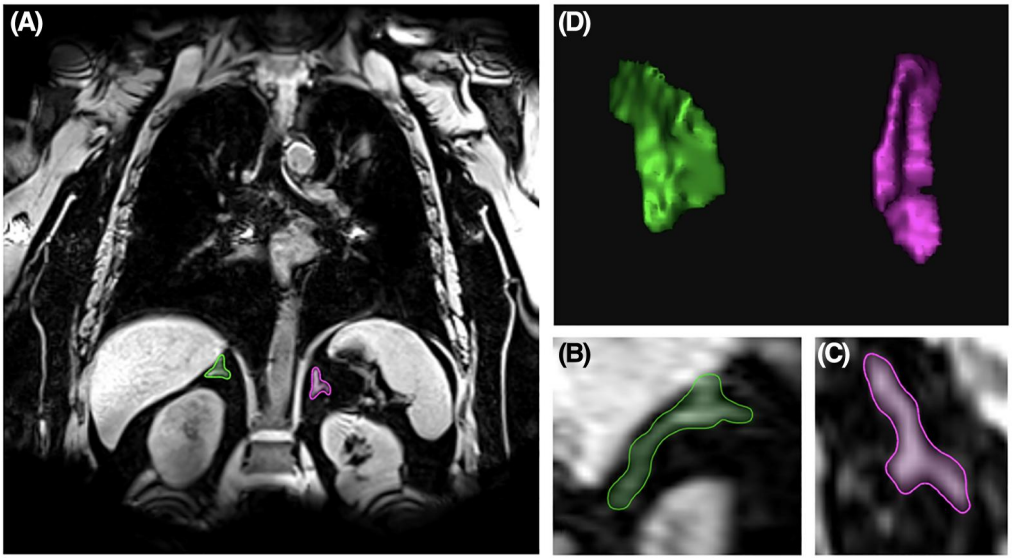

FIGURE 1 Example of adrenal gland boundaries delineation in coronal reconstruction (A), sagittal reconstruction of the right adrenal gland (B) and axial reconstruction of the left adrenal gland (C) on T1w-VIBE-Dixon sequences and in 3D representation (D)

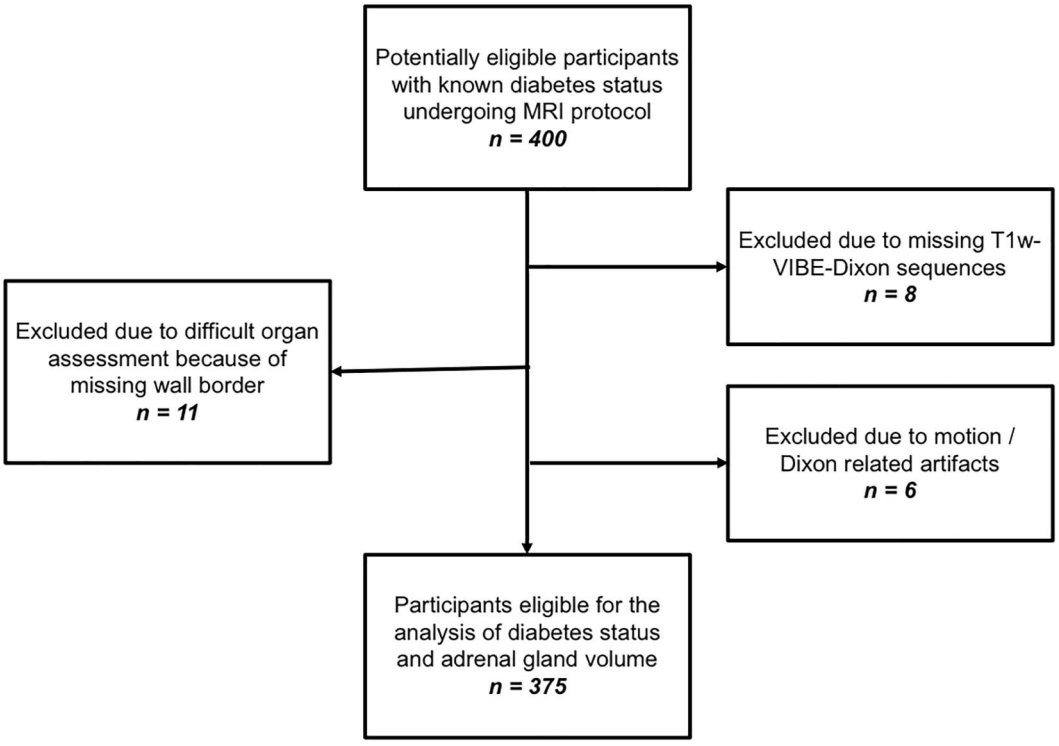

FIGURE 2 Study flowchart of participant inclusion and exclusion

3 | RESULTS

Among a total of 400 participants initially enrolled within the study, 8 (2.0%) were excluded due to missing or incomplete T1w-VIBE-Dixon sequences and 17 (4.3%) were excluded due to poor image quality (Figure 2, Table S1). No adrenal gland mass was detected in the remaining study cohort. Thus, 375 participants (58.5% male, 56.1 ± 9.1 years) were included in our analysis. Fifty-one (13.6%) participants fulfilled the criteria for T2DM, 30 (58.8%) of these were taking antidiabetic medication. Ninety-five participants (25.3%) were categorised as prediabetic and 229 (61.1%) participants were classified as healthy controls. The average of right and left adrenal gland volumes was 5.6 ± 2.1 ml, and the sum of left and right adrenal gland volumes (total adrenal gland volume) was 11.2 ± 4.2 ml. The average of right and left adrenal gland volumes and total adrenal gland volume were perfectly correlated (Pearson's $r = 1$). Participants'

TABLE 1 Participants' demographic and cardiometabolic risk factors according to diabetes status

N	All N = 375	Healthy controls N = 229 (61.1%)	Prediabetes N = 95 (25.3%)	T2DM N = 51 (13.6%)	p-Value
Adrenal gland volume, ml (right)	5.2 ± 2.2	4.6 ± 1.9	5.8 ± 2.0	6.9 ± 2.2	<0.001
Adrenal gland volume, ml (left)	5.9 ± 2.5	5.4 ± 2.3	6.7 ± 2.3	7.0 ± 2.8	<0.001
Total adrenal gland volume, ml (sum of right and left)	11.2 ± 4.2	10.0 ± 3.9	12.5 ± 3.8	13.9 ± 4.6	<0.001
Average adrenal gland volume, ml (average of right and left)	5.6 ± 2.1	5.0 ± 1.9	6.2 ± 1.9	7.0 ± 2.3	<0.001
Age (years)	56.1 ± 9.1	54.2 ± 8.8	57.9 ± 8.8	61.7 ± 8.3	<0.001
Male sex	219 (58.4%)	117 (51.1%)	64 (67.4%)	38 (74.5%)	0.001
Female sex	156 (41.6%)	112 (48.9%)	31 (32.6%)	13 (25.5%)	
2-h Glucose (mg/dl)/oGTT	113.6 ± 41.2	94.6 ± 20.5	140.8 ± 29.4	216.7 ± 64.3	<0.001
FPG (mg/dl)	104.5 ± 22.8	94.8 ± 7.4	107.1 ± 10.0	144.6 ± 38.2	<0.001
HbA1c (%)	5.6 ± 0.7	5.3 ± 0.3	5.6 ± 0.3	6.7 ± 1.3	<0.001
Antidiabetic medication	30 (8.0%)	0 (0.0%)	0 (0.0%)	30 (58.8%)	<0.001
Height (cm)	171.8 ± 9.7	171.3 ± 10.3	173.0 ± 9.0	171.7 ± 7.8	0.322
BMI (continuous, kg/m^2)	28.1 ± 4.8	26.7 ± 4.3	30.7 ± 4.7	29.8 ± 4.9	<0.001
Normal (<25 kg/m^2)	99 (26.4%)	81 (35.4%)	10 (10.5%)	8 (15.7%)	<0.001
Overweight (25–29,9 kg/m^2)	162 (43.2%)	105 (45.9%)	39 (41.1%)	18 (35.3%)	
Obese (≥30 kg/m^2)	114 (30.4%)	43 (18.8%)	46 (48.4%)	25 (49.0%)	
Waist circumference (cm)	98.8 ± 14.2	93.8 ± 12.6	106.7 ± 12.0	106.8 ± 14.1	<0.001
Waist–hip circumference ratio	0.92 ± 0.09	0.89 ± 0.08	0.96 ± 0.07	0.99 ± 0.08	<0.001
Triglycerides (mg/dl)	132.2 ± 85.2	106.8 ± 64.2	156.3 ± 82.2	201.1 ± 118.0	<0.001
Total cholesterol (mg/dl)	217.9 ± 36.6	216.4 ± 36.2	224.3 ± 31.7	212.8 ± 45.1	0.113
Hypertension	128 (34.1%)	49 (21.4%)	43 (45.3%)	36 (70.6%)	<0.001
Systolic blood pressure (mmHg)	120.6 ± 16.6	116.5 ± 14.8	125.1 ± 14.6	130.5 ± 21.0	<0.001
Diastolic blood pressure (mmHg)	75.3 ± 10.0	73.6 ± 9.0	78.3 ± 9.3	77.5 ± 13.1	<0.001

Note: For continuous variables, values are mean ± standard deviation with *p*-values from one-way ANOVA. For categorical variables, values are counts and percentages with *p*-values from X^2 test.

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; oGTT: oral glucose tolerance test; T2DM, type 2 diabetes mellitus.

demographic and cardiometabolic risk factors according to diabetes status are provided in Table 1.

3.1 | Inter- and intrareader reliability

Interreader reliability as well as intrareader reliability were appropriate for both right and left adrenal glands (Table S2). The interreader reliability resulted in an ICC of 0.99 for the right and 0.97 for the left adrenal gland; the intrareader reliability resulted in an ICC of 0.99 for the right and 0.98 for the left adrenal gland (Table S2, Figure S1).

3.2 | Adrenal gland volume and diabetes status

Adrenal gland volume was strongly dependent on diabetes status with the largest volume in subjects with T2DM (total adrenal gland volume in healthy controls: 10.0 ± 3.9 ml, prediabetes: 12.5 ± 3.8 ml, and T2DM: 13.9 ± 4.6 ml; $p < 0.001$; see Table 1 and Figure 3). Similarly, FPG and oGTT were associated with adrenal gland volume (Figure 3).

Associations between cardiometabolic risk factors and adrenal gland volume were observed in a linear regression model after adjustment for age, sex, and BMI for triglyceride levels ($\beta = 0.52$, 95% CI: [0.2, 0.8], and $p < 0.002$) and for hypertension ($\beta = 1.06$, 95% CI: [0.3, 1.8], $p < 0.004$; Table 2).

The association between diabetes status and adrenal gland volume persisted in the linear regression model for T2DM after adjustment for age, sex, and BMI (T2DM: $\beta = 1.74$, 95% CI: [0.8, 2.7], and $p < 0.001$), while the association of prediabetes with adrenal gland volume was attenuated (Table 2).

The results of the logistic regression analysis for the risk of impaired glucose metabolism after adjustment for age and sex (Model 1), hypertension (Model 2), triglyceride levels (Model 3) and

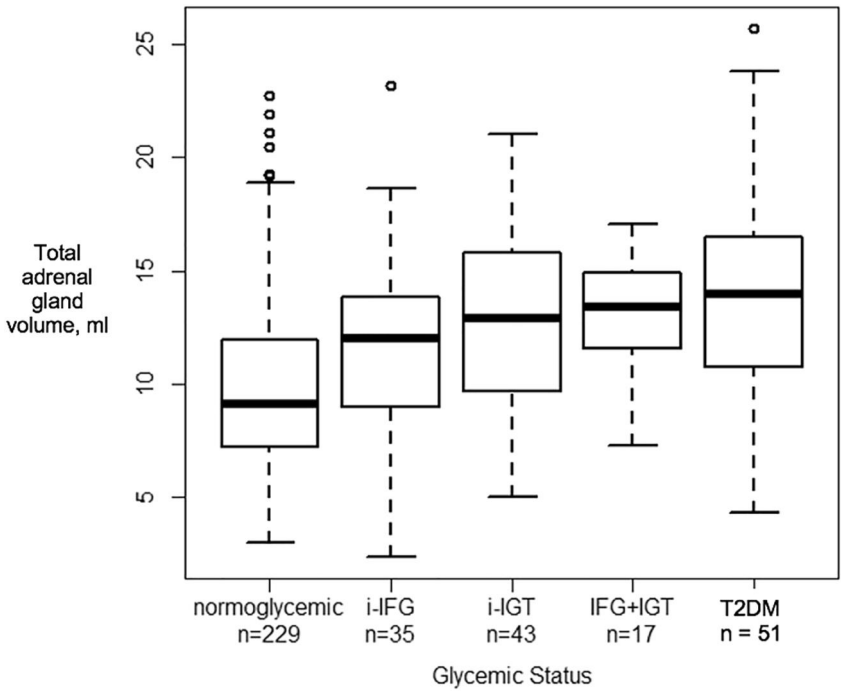

FIGURE 3 Box and whisker plot. Distribution of adrenal gland volume according to diabetes status. *p*-Value <0.001 from one-way ANOVA. i-IFG, isolated – impaired fasting glucose; i-IGT, isolated – impaired glucose tolerance; T2DM, type 2 diabetes mellitus

BMI (Model 4) are provided in Table 3. Specifically, the estimated risk for T2DM increased by 28% per ml adrenal gland volume, independent of age and sex (Model 1: OR: 1.28, 95% CI: [1.16, 1.41], and $p = 0.001$), by 23% per ml adrenal gland volume after additional adjustment for hypertension (Model 2: OR: 1.23, 95% CI: [1.11, 1.36], $p = 0.001$), and by 17% per ml adrenal gland volume after additional adjustment for triglyceride levels (Model 3: OR :1.17, 95% CI: [1.05, 1.3]; $p = 0.004$). The observed risks also persisted after adjustment for BMI (Model 4: OR: 1.13, 95% CI: [1.0, 1.28], and $p = 0.045$). Similarly, the risk for prediabetes (vs. healthy controls) was associated with adrenal gland volume (per ml; results provided in Table 3). Specifically, the increased risk associated with adrenal gland volume (per ml) for prediabetes was 16%, 14%, and 11% for Model 1, Model 2 and Model 3, respectively (Model 1: OR: 1.16, 95% CI: [1.08, 1.25], and $p = 0.001$; Model 2: OR: 1.14, 95% CI: [1.06, 1.24], and $p = 0.001$; and Model 3: OR: 1.11, 95% CI: [1.02, 1.2], and $p = 0.012$). In contrast to T2DM, once adjusted for BMI, the risk for prediabetes associated with adrenal gland volume was attenuated and became non-significant (Model 4: OR: 1.00, 95% CI: [0.91, 1.1], and $p = 0.990$; Table 3).

4 | DISCUSSION

In the present study, we analysed the association between MRI-based adrenal gland volume and impaired glucose metabolism in a well-characterised population-based cohort study. Our results indicate that an increased adrenal gland volume is a marker of impaired metabolic state, and higher adrenal gland volume was found to be associated with higher levels of BMI, triglycerides, hypertension and impaired glucose metabolism. In particular, our results show that while increased adrenal gland volume in T2DM is independent of age, sex, BMI, hypertension and triglyceride level, the association of prediabetes and adrenal gland volume is strongly confounded by BMI. Methodologically, we demonstrate that MRI-based quantification of adrenal gland volume incurs high reproducibility and may thus serve as an indirect marker of cardiometabolic disease, impaired glucose metabolism and dysfunction of the HPA axis.

Studies on the feasibility of measurement of adrenal gland volume by MRI have been conducted previously,[10,14] but their number is scarce, and sample sizes have been modest. Our results demonstrate that MRI is an appropriate non-invasive modality for the assessment of adrenal gland volume with appropriate intra- and interrater reliability. However, manual segmentation is elaborate and automatic segmentation of adrenal gland volume, especially in epidemiological study settings, is highly desirable.

Future prospectives strongly suggest an increasing incorporation of artificial intelligence into radiology practice, and automatic segmentation has become an important target for deep learning approaches.[20] Advantages of artificial intelligence-based automatic segmentation include the potential to extract data from a large number of studies and use data to identify markers that may indicate patient risk profiles. Simultaneously, artificial intelligence can also aid the reporting workflows and help the linking between words, images and quantitative data.[21] In our case, we envision a comprehensive inclusion of adrenal gland volume in standard MR abdominal exam reports as an indirect marker of HPA axis dysfunction. Altogether, this would take clinical routine one step further in the direction of personalised medicine.

Given our setting, we first provide results on adrenal gland volume by MRI in participants with prediabetes, T2DM, and normoglycemic controls. Adrenal gland volume has been suggested as a

TABLE 2 Analysis of associations between demographics, cardiometabolic risk factors and adrenal gland volume, adjusted for age + sex + BMI

Predictor	Estimate (β)	95% CI	p-Value
Age (continuous, years)	0.02	[−0.0, 0.1]	0.262
Female sex (categorical, REF: male sex)	−4.37	[−5.0, −3.7]	<0.001
Diabetes status (categorical, REF: normoglycemic)			
Prediabetes	0.24	[−0.5, 1.0]	0.546
i-IFG	−0.26	[−1.3, 0.8]	0.637
i-IGT	0.53	[−0.5, 1.5]	0.307
IFG + IGT	0.64	[−0.9, 2.2]	0.409
T2DM	1.74	[0.8, 2.7]	<0.001
2-h glucose (continuous, mg/dl)/oGTT	0.41	[0.1, 0.8]	0.021
FPG (continuous, mg/dl)	0.46	[0.1, 0.8]	0.005
HbA1c (continuous, %)	0.41	[0.1, 0.7]	0.009
Antidiabetic medication (categorical, REF: no)	1.58	[0.5, 2.7]	0.006
BMI (continuous, kg/m^2)	1.95	[1.6, 2.3]	<0.001
Waist circumference (continuous, cm)	2.54	[1.8, 3.3]	<0.001
Waist–hip circumference ratio (continuous)	1.76	[1.3, 2.2]	<0.001
Triglyceride levels (continuous, mg/dl)	0.52	[0.2, 0.8]	0.002
Total cholesterol (continuous, mg/dl)	0.09	[−0.2, 0.4]	0.558
Blood pressure			
Hypertension (categorical, REF: no)	1.06	[0.3, 1.8]	0.004
Systolic blood pressure (continuous, mmHg)	0.55	[0.2, 0.9]	0.002

Note: Presented are results from a linear regression with outcome of adrenal gland volume. All models were adjusted for age, sex, and BMI. Continuous predictor variables were standardised before modelling; therefore, beta coefficients are per standard deviation of the predictor, except age (which is per year).

Abbreviations: BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; i-IFG, isolated impaired fasting glucose; i-IGT, isolated impaired glucose tolerance; oGTT: oral glucose tolerance test; T2DM, type 2 diabetes.

marker of HPA axis activity[9] and has been utilised in several studies as such.[12,15,22]

In line with our observations, increased adrenal gland volume in subjects with DM has been observed previously, and we confirm earlier efforts and emphasise the role of adrenal gland volume in metabolic and diabetic states.[23,24] In fact, the relation of the HPA axis and impaired glucose metabolism is complex and has to be looked at from two sides. One side is the assumption that as a consequence of T2DM, neuropathy may affect the endocrine system and lead to an imbalance of the autonomic nervous system resulting in an increased HPA axis activity, which in turn would lead to hypercortisolism and adrenocortical growth.[25,26] The extent of HPA axis dysfunction in T2DM seems to depend on the damage of the neuronal pathway of the HPA axis and a weakening response to negative feedback.[27] Moreover, it has been discussed that continuous hyperinsulinemia by itself may stimulate adrenal steroid hormone production and HPA axis secretory capacity.[2] The other side to be considered is the huge impact glucocorticoids have on energy metabolism.[28] In this light, the prevalence of diabetes has been observed to increase in the function of circulating cortisol levels.[29] Furthermore, glucocorticoids seem to induce insulin resistance.[30] Thus, further prospective studies are necessary to highlight the molecular biological interplays of impaired glucose metabolism and HPA axis activation.

We provide initial evidence that BMI is a strong confounder in the interplay between impaired glucose metabolism and increased adrenal gland volume due to HPA axis activation, especially in participants with prediabetes. T2DM is associated with obesity in about 80% of cases[4] so that strong connections are unquestionable as shown in the present data in view of the higher BMI, which participants with T2DM and prediabetes presented. Interestingly, in our sample, participants with prediabetes had a higher BMI than participants with T2DM. This finding is also in line with the observation that BMI seemed to be a strong confounder especially in participants with prediabetes. In addition, hyperactivity of the HPA axis has been related to being associated with the metabolic syndrome, suggesting

TABLE 3 Multiple logistic regression analysis of association of adrenal gland volume and diabetes status

Model 1: Association of AGV and diabetes status, adjusted for age and sex												
	Outcome healthy controls versus T2DM			Outcome healthy controls versus prediabetes			Outcome prediabetes versus T2DM			Outcome healthy controls versus prediabetes + T2DM		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
AGV	1.28	[1.16, 1.41]	<0.001	1.16	[1.08, 1.25]	<0.001	1.11	[1.01, 1.22]	0.039	1.19	[1.12, 1.28]	<0.001
Model 2: Model 1 + adjusted for hypertension												
	Outcome healthy controls versus T2DM			Outcome healthy controls versus prediabetes			Outcome prediabetes versus T2DM			Outcome healthy controls versus prediabetes + T2DM		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
AGV	1.23	[1.11, 1.36]	<0.001	1.14	[1.06, 1.24]	0.001	1.08	[0.98, 1.2]	0.125	1.16	[1.08, 1.24]	<0.001
Model 3: Model 2 + adjusted for triglycerides												
	Outcome healthy controls versus T2DM			Outcome healthy controls versus prediabetes			Outcome prediabetes versus T2DM			Outcome healthy controls versus prediabetes + T2DM		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
AGV	1.17	[1.05, 1.3]	0.004	1.11	[1.02, 1.2]	0.012	1.06	[0.95, 1.18]	0.280	1.11	[1.03, 1.2]	0.006
Model 4: Model 3 + adjusted for BMI												
	Outcome healthy controls versus T2DM			Outcome healthy controls versus prediabetes			Outcome prediabetes versus T2DM			Outcome healthy controls versus prediabetes + T2DM		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
AGV	1.13	[1, 1.28]	0.045	1.00	[0.91, 1.1]	0.990	1.12	[0.99, 1.26]	0.067	1.03	[0.94, 1.12]	0.534

Note: Results of a logistic regression model with outcome diabetes status and exposure total adrenal gland volume (range 2.4–25.7 ml). First two columns from a multinomial logistic regression with outcomes 'prediabetes' and 'T2DM' (reference normoglycaemic), last two columns from a binomial regression with respective outcomes. ORs denote change per 1 ml of adrenal gland volume.

Abbreviation: AGV, adrenal gland volume.

a causative role for glucocorticoids in obesity,[31] and patients with both diabetes and obesity have been linked to more pronounced disturbances of the HPA axis than patients with obesity alone.[32] Moreover, dysregulation of the HPA axis is thought to play an important role in the pathogenesis of high blood pressure[33] and lipometabolic disorders.[34] This is in line with our study results as we found a significant association between increased adrenal gland volume and higher levels of triglycerides as well as hypertension. Interestingly, our results indicate that a significant correlation between T2DM and increased volume of the adrenal glands is independent of BMI, hypertension and dyslipidemia.

A few limitations of our study have to be considered. The first underlying limitation is linked to the initial cross-sectional design of the present study, inhibiting observations or conclusions on the development of T2DM depending on HPA axis activation in the form of increased adrenal gland volume. However, we used prediabetes as an early state of impaired glucose metabolism to overcome this difficulty. Also, the predominantly Caucasian and asymptomatic population without prior known cardiovascular diseases from the region of Augsburg diminishes the generalisability of our results to other ethnicities, geographical regions, or patients with cardiovascular diseases. Notably, the MRI-based quantification of adrenal gland volume lacks a gold standard to confirm the accuracy, and our manual segmentation may be prone to subjective errors. However, technical feasibility and accuracy have been previously shown,[10,14] and inter- and intrareader reliabilities were appropriate. Moreover, results of adrenal gland volume showed an overlap of average adrenal gland volumes between the different diabetic conditions. Consequently, the definition of a pathological threshold was not realisable, limiting the clinical application of our findings to single individual patients. Observations on larger study cohorts are warranted to study the clinical utility of our findings.

In conclusion, our results indicate that increased adrenal gland volume is linked with higher levels of triglycerides, hypertension, BMI, and impaired glucose metabolism. In particular, DM is significantly associated with increased adrenal gland volume as quantified by MRI, independently of age, sex, BMI, hypertension, and elevated triglycerides, whereas the association of prediabetes and adrenal gland volume is confounded by BMI. Given its non-ionising nature, segmentation of adrenal gland volume by MRI may be used as an indirect marker of impaired glucose metabolism and dysfunction of the HPA axis, and may thus merit further dedicated research to advance knowledge on metabolic disease development and HPA axis activity.

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CONFLICT OF INTERESTS

No conflict of interest was reported by the authors.

ETHICS STATEMENT

The KORA-MRI study was approved by the Institutional Research Ethics Board of the Medical Faculty of Ludwig-Maximilian University Munich and met the requirements of the Helsinki declaration on human research. Written informed consent was obtained from all the participants.

AUTHOR CONTRIBUTIONS

Study concept and design were provided by Esther Askani and Corinna Storz. Acquisition, analysis or interpretation of data were done by Esther Askani, Corinna Storz, Susanne Rospleszcz, Roberto Lorbeer, Elias Kellner, Marco Reisert and Charlotte Kulka. Drafting of the manuscript was done by Esther Askani and Corinna Storz. Critical revision of the manuscript for important intellectual content was done by Esther Askani, Susanne Rospleszcz, Roberto Lorbeer, Charlotte Kulka, Ricarda von Krüchten, Katharina Müller-Peltzer, Dunja Hasic, Wolfgang Rathmann, Annette Peters, Christopher L. Schlett, Fabian Bamberg and Corinna Storz. Statistical analysis was conducted by Susanne Rospleszcz, Roberto Lorbeer, Esther Askani and Corinna Storz. Administrative, technical, or material support was provided by Esther Askani, Fabian Bamberg, Christopher L. Schlett and Corinna Storz. Study supervision was done by Corinna Storz. All authors have read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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TRANSPARENT PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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