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

Short Title: Adrenal gland and glucose metabolism

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Abstract

Objectives

The aim of this study was to asses adrenal gland volume by 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 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 T2DM (healthy controls: 10.0 ± 3.9 ml, prediabetes: 12.5 ± 3.8 ml, T2DM: 13.9 ± 4.6 ml; $p<0.001$). In 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, dyslipidemia, hypertension and BMI. Adrenal gland volume may represent an indirect marker of impaired glucose metabolism and HPA axis dysfunction.

Keywords

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

Keypoints

- Assessment of adrenal gland volume by megnatic resonance imaging is feasible.
- Our results indicate that type 2 diabetes is significantly associated with increased adrenal gland volume as quantified by magnetic resonance imaging, independently of age, sex, body mass index, hypertension, and elevated triglycerides.
- Adrenal gland volume may represent an indirect marker of impaired glucose metabolism and hypothalamic-pituitary-adrenal axis dysfunction.

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*

Introduction

Physiological stress such as metabolic diseases has been shown to be accompanied by 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 volume of adrenal glands due to trophic effects of adrenocorticotrope 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 MRI towards computed tomography consist in lack of radiation and its greater capacity of tissue characterization,[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. (1987) consisted of only four healthy subjects,[10] Freel et al. (2013) investigated twenty normotensive men to assess both accuracy and reproducibility of adrenal gland volume measurements using MRI.[14] So far, the primary studies performing adrenal gland volume measurement by MRI have been focusing on the involvement of adrenal gland volume in mental disorders and adipose tissue characterization.[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.

Materials and Methods

Study design and study population

This case-control study's population was derived from the KORA-MRI sub-study, a 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 interplays 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 to S4 have been performed at five year interval within KORA. Each of these cross-sectional surveys consisted of an independent random sample and served as 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, revascularization) and of contraindications to MRI (e.g. cardiac pacemaker, implantable defibrillator, cerebral aneurysmal clip, neural stimulator, any type of ear implant, ocular foreign body) and/or to gadolinium contrast agent (e.g. known allergy against gadolinium compounds, impaired renal function with serum creatinine ≥ 1,3 mg/dl). Further exclusion criteria were age > 72 years, pregnancy and breastfeeding.[16,17] 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 participants.

MR-imaging protocol

A standardized comprehensive whole-body MRI protocol was applied on a 3-T Magnetom Skyra (Siemens Healthineers, Erlangen, Germany), 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 x 1.7 mm^2, field of view: 488 x 716 mm using a 256 x 256 matrix, repetition time: 4.06 ms, echo time: 1.26 & 2.49 ms, with a 9° flip angle).[16,17]

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 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 categorized dependent on the absence or presence of motion-related artifacts, technical artifacts, and/or difficult organ delineation due to tight adhesion to adjacent organs (e.g. lower surface of the liver) as: (a) high (good assessability of the adrenal glands without impairment of organ delineation through artifacts or tight adhesion to adjacent organs), (b) moderate (presence of artifacts or tight adhesion of the adrenal glands to adjacent organs, but still sufficient identifiability of the adrenal glands, and (c) poor (presence of artifacts 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 identification of right and left adrenal gland on coronal, axial and sagittal plane 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 plane. 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, i.e. the sum of volumes in the left and right adrenal gland. For completeness, also the average volumes, i.e. the average of left and right adrenal gland 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 four months. A delineation of adrenal volume segmentation in axial, coronal, and sagittal reconstruction is supplied in Figure 1.

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]

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 standardized fashion as detailed elsewhere.[16,17] Cortisol levels of the participants were not recorded.

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, intra-class 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 to 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.

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, Supplemental Table 1). No adrenal gland mass was detected in the remaining study cohort. Thus, 375 participants (58.5% male, 56.1±9.1years) were included in our analysis. 51 (13.6%) participants fulfilled the criteria for T2DM, 30 (58.8%) of these were taking antidiabetic medication. 95 participants (25.3%) were categorized as prediabetic, and 229 (61.1%) participants were classified as healthy controls. The average of right and left adrenal gland volume was 5.6±2.1 ml, and the sum of left and right adrenal gland volume (total adrenal gland volume) was 11.2±4.2ml. The average of right and left adrenal gland volume and total adrenal gland volume were perfectly correlated (Pearson's r=1). Participant's demographic and cardiometabolic risk factors according to diabetes status are provided in Table 1.

Inter- and intrareader reliability

Interreader reliability as well as intrareader reliability were appropriate for both right and left adrenal gland (Supplemental Table 2). 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 (Supplemental Table 2, Supplemental Figure 1).

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, 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 (β=0.52, 95%CI:[0.2, 0.8], $p<0.002$) and for hypertension (β=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: β=1.74, 95%CI:[0.8, 2.7], $p<0.001$), 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 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], 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], 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], p=0.001; Model 2: OR:1.14, 95%CI:[1.06, 1.24], p=0.001; Model 3: OR:1.11, 95%CI:[1.02, 1.2]; 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], p=0.990; Table 3).

Discussion

In the present study, we analyzed the association between MRI-based adrenal gland volume and impaired glucose metabolism in a well-characterized 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 inter-rater 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 personalized medicine.

Given our setting, we firstly provide results on adrenal gland volume by MRI in participants with prediabetes, T2DM, and normoglycemic controls. Adrenal gland volume has been suggested as a marker of HPA axis activity[9] and has been utilized in several studies as such.[12,15,22]

In line with our observations, increased adrenal gland volume in subjects with T2DM has been observed previously, and we confirm earlier efforts and emphasize 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 function of the 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 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 generalizability 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 reliability 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 realizable, 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, T2DM 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-ionizing 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.

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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Conflict of interests

No conflict of interest was reported by the authors.

Author's contribution

Study concept and design were performed by EA and CS. Acquisition, analysis or interpretation of data were performed by EA, CS, SR, RL, EK, MR and CK. Drafting of the manuscript was performed by EA and CS. Critical revision of the manuscript for important intellectual content was performed by EA, SR, RL, CK, RVK, KMP, DH, WR, AP, CLS, FB and CS. Statistical analysis was performed by SR, RL, EA and CS. Administrative, technical or material support was performed by EA, FB, CLS and CS. Study supervision was performed by CS.

All authors have read and approved the final manuscript.

References

1. Björntorp P, Rosmond R. Obesity and cortisol. *Nutrition* 2000; **16**(10): 924-36.

2. Fruehwald-Schultes B, Kern W, Bong W, et al. Supraphysiological hyperinsulinemia acutely increases hypothalamic-pituitary-adrenal secretory activity in humans. *J Clin Endocrinol Metab* 1999; **84**(9): 3041-6.

3. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998; **21**(9): 1414-31.

4. Diz-Chaves Y, Gil-Lozano M, Toba L, et al. Stressing diabetes? The hidden links between insulinotropic peptides and the HPA axis. *J Endocrinol* 2016; **230**(2): R77-94.

5. Elahi-Moghaddam Z, Behnam-Rassouli M, Mahdavi-Shahri N, Hajinejad-Boshroue R, Khajouee E. Comparative study on the effects of type 1 and type 2 diabetes on structural changes and hormonal output of the adrenal cortex in male Wistar rats. *J Diabetes Metab Disord* 2013; **12**(1): 9.

6. Vicennati V, Pasquali R. Abnormalities of the hypothalamic-pituitary-adrenal axis in nondepressed women with abdominal obesity and relations with insulin resistance: evidence for a central and a peripheral alteration. *J Clin Endocrinol Metab* 2000; **85**(11): 4093-8.

7. Godoy-Matos AF, Vieira AR, Moreira RO, et al. The potential role of increased adrenal volume in the pathophysiology of obesity-related type 2 diabetes. *J Endocrinol Invest* 2006; **29**(2): 159-63.

8. Imaki T, Naruse M, Takano K. Adrenocortical hyperplasia associated with ACTH-dependent Cushing's syndrome: comparison of the size of adrenal glands with clinical and endocrinological data. *Endocr J* 2004; **51**(1): 89-95.

9. Golden SH, Wand GS, Malhotra S, Kamel I, Horton K. Reliability of hypothalamic-pituitary-adrenal axis assessment methods for use in population-based studies. *Eur J Epidemiol* 2011; **26**(7): 511-25.

10. Grant LA, Napolitano A, Miller S, Stephens K, McHugh SM, Dixon AK. A pilot study to assess the feasibility of measurement of adrenal gland volume by magnetic resonance imaging. *Acta Radiol* 2010; **51**(1): 117-20.

11. Kahl KG, Schweiger U, Pars K, et al. Adrenal gland volume, intra-abdominal and pericardial adipose tissue in major depressive disorder. *Psychoneuroendocrinology* 2015; **58**: 1-8.

12. Ludescher B, Najib A, Baar S, et al. Gender specific correlations of adrenal gland size and body fat distribution: a whole body MRI study. *Horm Metab Res* 2007; **39**(7): 515-8.

13. Hussain HK, Korobkin M. MR imaging of the adrenal glands. *Magn Reson Imaging Clin N Am* 2004; **12**(3): 515-44, vii.

14. Freel EM, Nicholas RS, Sudarshan T, et al. Assessment of the accuracy and reproducibility of adrenal volume measurements using MRI and its relationship with corticosteroid phenotype: a normal volunteer pilot study. *Clin Endocrinol (Oxf)* 2013; **79**(4): 484-90.

15. Kessing LV, Willer IS, Knorr U. Volume of the adrenal and pituitary glands in depression. *Psychoneuroendocrinology* 2011; **36**(1): 19-27.

16. Holle R, Happich M, Lowel H, Wichmann HE, Group MKS. KORA--a research platform for population based health research. *Gesundheitswesen* 2005; **67 Suppl 1**: S19-25.

17. Bamberg F, Hetterich H, Rospleszcz S, et al. Subclinical Disease Burden as Assessed by Whole-Body MRI in Subjects With Prediabetes, Subjects With Diabetes,

and Normal Control Subjects From the General Population: The KORA-MRI Study. *Diabetes* 2017; **66**(1): 158-69.

18. Organization WH, Federation ID. Definition and Diagnosis od Diabetes Mellitus and Intermediate Hyperglycemia: Report of a WHO/IDF Consultation. *Geneva, Switzerland, World Health Organization* 2006: p.13-28.

19. R Core Team. R: A language and environment for statistical computing. *R Foundation Statistical Computing, Vienna, Austria* 2020.

20. Lundervold AS, Lundervold A. An overview of deep learning in medical imaging focusing on MRI. *Z Med Phys* 2019; **29**(2): 102-27.

21. What the radiologist should know about artificial intelligence - an ESR white paper. *Insights Imaging* 2019; **10**(1): 44.

22. Ludescher B, Najib A, Baar S, et al. Increase of visceral fat and adrenal gland volume in women with depression: preliminary results of a morphometric MRI study. *Int J Psychiatry Med* 2008; **38**(3): 229-40.

23. Serifoglu I, Oz, II, Bilici M. The Adrenal Gland Volume Measurements in Manifestation of the Metabolic Status in Type-2 Diabetes Mellitus Patients. *Int J Endocrinol* 2016; **2016**: 7195849.

24. Carsin-Vu A, Oubaya N, Mulé S, et al. MDCT Linear and Volumetric Analysis of Adrenal Glands: Normative Data and Multiparametric Assessment. *Eur Radiol* 2016; **26**(8): 2494-501.

25. Edwards JL, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. *Pharmacol Ther* 2008; **120**(1): 1-34.

26. Barber M, Kasturi BS, Austin ME, Patel KP, MohanKumar SM, MohanKumar PS. Diabetes-induced neuroendocrine changes in rats: role of brain monoamines, insulin and leptin. *Brain Res* 2003; **964**(1): 128-35.

27. Chan O, Inouye K, Riddell MC, Vranic M, Matthews SG. Diabetes and the hypothalamo-pituitary-adrenal (HPA) axis. *Minerva Endocrinol* 2003; **28**(2): 87-102.

28. van Raalte DH, Ouwens DM, Diamant M. Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? *Eur J Clin Invest* 2009; **39**(2): 81-93.

29. Di Dalmazi G, Pagotto U, Pasquali R, Vicennati V. Glucocorticoids and type 2 diabetes: from physiology to pathology. *J Nutr Metab* 2012; **2012**: 525093.

30. Ferris HA, Kahn CR. New mechanisms of glucocorticoid-induced insulin resistance: make no bones about it. *J Clin Invest* 2012; **122**(11): 3854-7.

31. Vegiopoulos A, Herzig S. Glucocorticoids, metabolism and metabolic diseases. *Mol Cell Endocrinol* 2007; **275**(1-2): 43-61.

32. Appel MC, Schibly BA, Kamara JA, Sorenson RL. Adrenal gland involvement in mice with hereditary obesity and diabetes mellitus. Morphological studies. *Diabetologia* 1979; **16**(6): 391-8.

33. Whitworth JA, Mangos GJ, Kelly JJ. Cushing, cortisol, and cardiovascular disease. *Hypertension* 2000; **36**(5): 912-6.

34. Si MW, Yang MK, Fu XD. Effect of hypothalamic-pituitary-adrenal axis alterations on glucose and lipid metabolism in diabetic rats. *Genet Mol Res* 2015; **14**(3): 9562-70.

Tables

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

	All	**Healthy controls**	**Prediabetes**	**T2DM**	**p-value**
N	N=375	N=229 (61.1%)	N=95 (25.3%)	N=51 (13.6%)	
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%)	
2h 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	75.3 ± 10.0	73.6 ± 9.0	78.3 ± 9.3	77.5 ± 13.1	<0.001

(mmHg)					

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.

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

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

Presented are results from a linear regression with outcome adrenal gland volume. All models were adjusted for age, sex and BMI. Continuous predictor variables were standardized before modeling, therefore beta coefficients are per standard deviation of the predictor, except age (which is per year). CI: confidence interval, i-IFG: isolated impaired fasting glucose, i-IGT: isolated impaired glucose tolerance, T2DM: type 2 diabetes mellitus, oGTT: oral glucose tolerance test, FPG: fasting plasma glucosis, BMI: body mass index.

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 vs T2DM			Outcome Healthy controls vs Prediabetes			Outcome Prediabetes vs T2DM			Outcome Healthy controls vs 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 vs T2DM			Outcome Healthy controls vs Prediabetes			Outcome Prediabetes vs T2DM			Outcome Healthy controls vs 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 vs T2DM	Outcome Healthy controls vs Prediabetes	Outcome Prediabetes vs T2DM	Outcome Healthy controls vs 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 vs T2DM			Outcome Healthy controls vs Prediabetes			Outcome Prediabetes vs T2DM			Outcome Healthy controls vs 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

Results of a logistic regression model with outcome diabetes status and exposure total adrenal gland volume (range 2.4ml to 25.7 ml). First two columns from a multinomial logistic regression with outcomes “prediabetes” and “T2DM” (reference normoglycemic), last two columns from a binomial regression with respective outcomes. ORs denote change per one ml of adrenal gland volume. AGV: adrenal gland volume.

Tables

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	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 vs T2DM	Outcome Healthy controls vs Prediabetes	Outcome Prediabetes vs T2DM	Outcome Healthy controls vs Prediabetes + T2DM

	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
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	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
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Figure Legends

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).

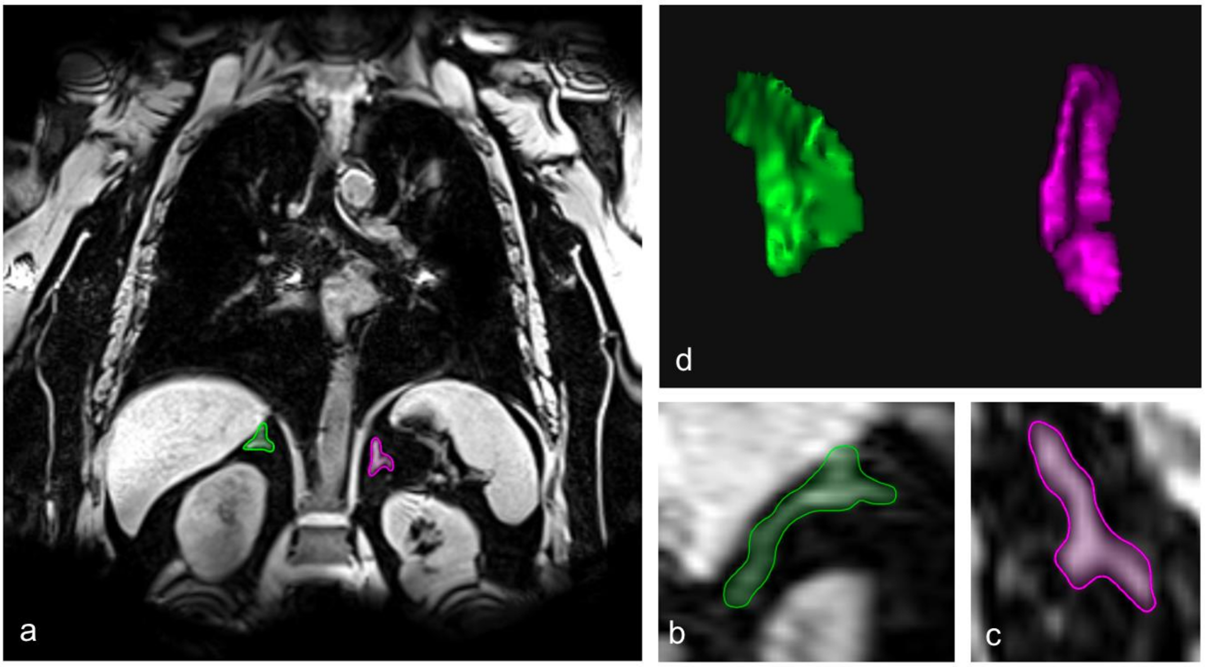

Figure 2. Study flowchart of participant inclusion and exclusion.

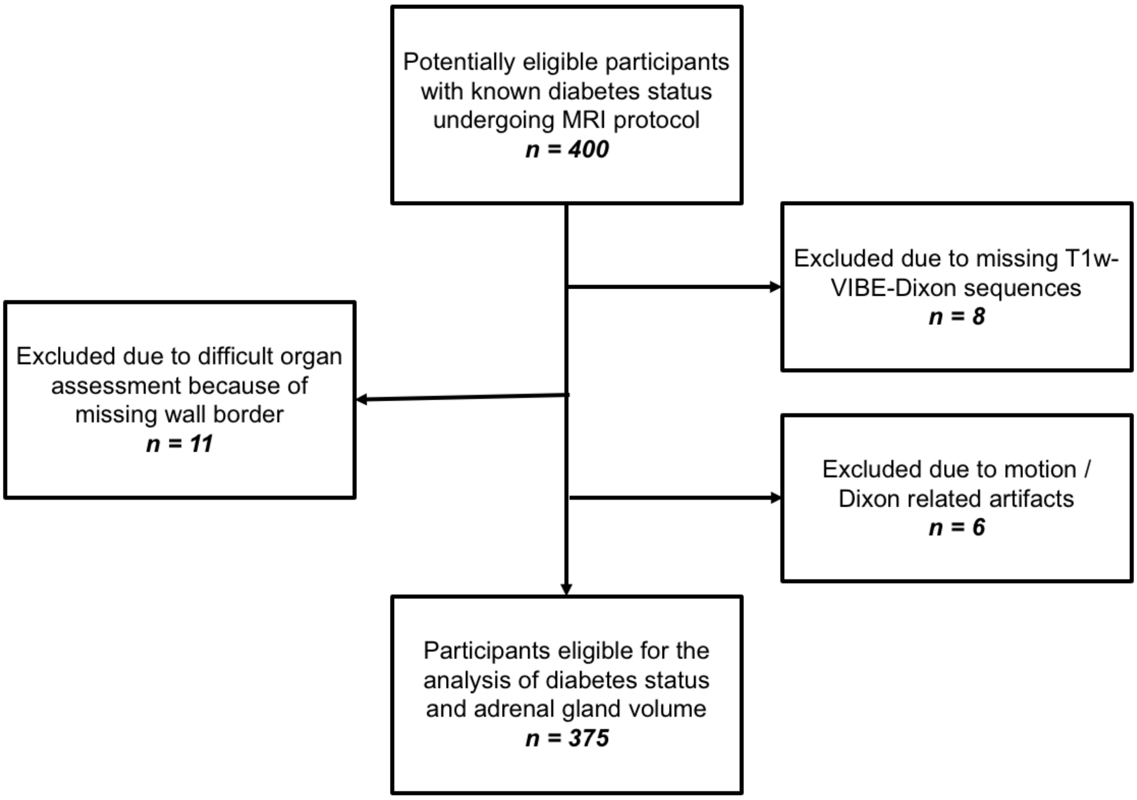

Figure 3. Box and whisker plot. Distribution of adrenal gland volume according to diabetes status. (i-IFG: isolated – impaired fasting glucose, i-IGT: isolated – impaired glucose tolerance, T2DM: type 2 diabetes mellitus). p- value < 0.001 from one-way ANOVA.