Serum insulin is associated with right ventricle function parameters and lung volumes in subjects free of cardiovascular disease

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Abstract

Background: Diabetes mellitus is an established risk factor for cardiovascular diseases. Even impaired levels of glucose and insulin might harm organ function prior to diabetes onset. Whether serum glucose or insulin plays a direct role in cardiac dysfunction or lung volume reduction remains unclear. The aim was to investigate the relationship between glucose and insulin with the right ventricle and lung volumes within KORA-MRI FF4 study.

Methods: From the KORA-MRI FF4 cohort study 337 subjects (mean age 55.7 ± 9.1 years; 43% women) underwent a whole-body 3T MRI scan. Cardiac parameters derived from a cine-steady-state free precession sequence using cvi42. MRI-based lung volumes derived semi-automatically using an in-house algorithm. Fasting serum glucose, fasting insulin levels, and HOMA index were calculated in all study subjects. Linear regression analyses were performed to assess the relationships between glucose and insulin levels with right ventricle volumes and lung volumes adjusted for age, sex, BMI, and cardiovascular risk factors.

Results: In univariate and multivariate-adjusted models, high serum insulin was inversely associated with end-diastolic volume ($\beta = -12.43$, $P < 0.001$), end-systolic volume ($\beta = -7.12$, $P < 0.001$), stroke volume ($\beta = -5.32$, $P < 0.001$), but not with ejection fraction. The association remained significant after additional adjustment for lung volumes. Similarly, serum insulin was inversely associated with lung volume ($\beta = -0.15$, $P = 0.04$). Sensitivity analysis confirmed results after excluding subjects with known diabetes.

Conclusions: Serum insulin was inversely associated with right ventricle function and lung volumes in subjects from the general population free of cardiovascular disease, suggesting that increased insulin levels may contribute to subclinical cardiopulmonary circulation impairment.

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Introduction

Impaired glucose and insulin levels represent two major pathophysiological features of type 2 diabetes mellitus that may occur prior to diabetes disease onset (1, 2). Type 2 diabetes mellitus is an established risk factor for cardiovascular diseases (CVD) (3), and dysregulated levels of glucose and insulin have been implicated in the etiology of CVD in general (4). Moreover, under conditions of diabetes mellitus, subclinical cardiopulmonary dysfunction might aggravate (5, 6). In this context, the right ventricle and lungs constitute the main axis of the pulmonary circulation and their functional impairment reflects into cardiac output and may lead to pulmonary hypertension, especially among the elderly population.

Cardiac right ventricle (RV) function in subjects with prediabetes and type 2 diabetes within the Cooperative Health Research in the Region of Augsburg (KORA) cohort study was assessed, and the study reported an impaired right ventricle function in subjects with prediabetes and diabetes compared to controls (7). However, disruptions of levels may occur much earlier before diabetes onset (2) and the main driver of glucose metabolism is insulin (8). In addition, previous studies reported an association between insulin resistance and cardiac left ventricle (LV) dysfunction, particularly worsening of diastolic function (9, 10, 11). The FLEMENGHO (Flemish Study on Environment, Genes, and Health Outcomes) study has shown that higher levels of insulin at baseline and follow-up were associated with the decrease of left ventricular systolic and diastolic function and an increase in left ventricular mass index (12). When matching the population-based cohort studies Study of Health in Pomerania (SHIP) and KORA, a relation between higher glucose and/or insulin levels and greater arterial stiffness, smaller LV chamber size and higher LV thickness with resultant LV concentric remodeling and lower LV stroke volume has been shown (13). The RV function closely related to the pulmonary circulation and lung volumes may represent important parameters for reciprocal function or dysfunction. Nevertheless, research on the RV function and pulmonary circulation, in general, remains underrepresented (14), especially in the context of the role of glucose and/or insulin. To date, no study assessed the relationship between glucose and insulin, RV function and/or lung volumes, and whole-body MRI technology enables reliable assessment of both, cardiac function and pulmonary volumes simultaneously during a single radiation-free MR scan examination (15).

Therefore, this study aimed to investigate the relationship between glucose and insulin with MRI-derived RV and lung volumes in a population-based cohort study without known cardiovascular diseases.

Methods

Study population

The KORA S4 is a prospective population-based cohort study in the region of Augsburg, Germany (16). Subjects aged between 25 and 74 years, residents in the Augsburg region, were recruited in the study, and participants were examined between June 2013 and September 2014 at the KORA study center. A whole-body MRI scan (3 Tesla) was incorporated in the follow-up KORA-MRI FF4 study (17). Subjects were selected for an MRI scan if they met the following inclusion criteria: informed study consent, and qualification of being in the prediabetes, diabetes, or control group. The following exclusion criteria were applied: age > 74 years; participants with a known history of coronary artery disease, myocardial infarction, peripheral artery disease, stroke, and/or unavailable oral glucose test, pregnancy, poor overall health condition or other physical limitations. Subjects with contraindications to MRI scan, such as known gadolinium contrast allergy, cardiac stents, cardiac pacemaker or implantable defibrillator, implanted metal parts, breast-feeding women, subjects with claustrophobia, and subjects with impaired renal function were excluded. From a total of participants with an MRI scan (n = 400) subjects with incomplete information on glucose (n = 2), insulin (n = 3), or HOMA index (n = 30) and incomplete visualization of the right ventricle (n = 28) were excluded. Hence, 337 subjects were included in the analysis (Fig. 1). The KORA-MRI FF4 study was approved by the Institutional Research Ethics Board of the Medical Faculty of Ludwig-Maximilian University Munich and compiled with Helsinki declaration on human research (18). All participants gave written informed consent.

Whole-body MR imaging

Whole-body MRI scans were performed with a 3-Tesla MRI system (Magnetom Skyra, Siemens AG, Healthcare Sector, Erlangen, Germany) (17) using an 18-channel body surface coil and a table-mounted spine matrix coil. The protocol comprised sequences covering the entire body (from neck to below hip) for tissue/organ quantification, as well as for particular organs, for example, brain, carotid

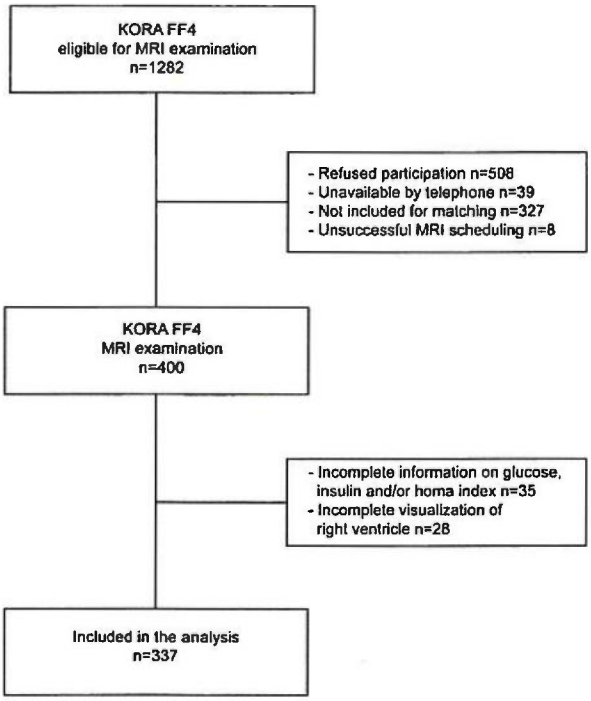

Figure 1
Flowchart of the study.

arteries, or fat compartments. For analysis of the lung, a 2-point DIXON T1 sequence was used in submaximal inspiration breath-hold and an acquisition time of 15s. Slice thickness was 3 mm, coronal acquired, including a field of view (FOV) of 488 mm × 716 mm, a matrix of 256 × 256, a repetition time (TR) of 4.06 ms, and an echo time (TE) of 1.26 ms. For analysis of the heart, the cine-steady-state free precession sequence was acquired in a short-axis view with 10 layers and 25 phases. Slice thickness was 8 mm, including a FOV of 297 mm × 360 mm, a matrix of 240 × 160, a TR of 29.97 ms, a TE of 1.46 ms, and a flip angle of 62°.

MR-image analysis for cardiac volume

RV function was evaluated using commercially available cvi[42] software (version 4.1.5(190)); Circle Cardiovascular Imaging Inc. (Calgary, Alberta, Canada) by two independent readers. After manually segmenting the lumen of the RV in the end-systole and end-diastole in each layer from the cardiac apex to the pulmonary valve (19), the software calculated automatically the corresponding volumes. The difference between the end-systolic and end-diastolic volumes comprises the parameters for stroke volume and ejection fraction, according to defined normal values for cardiovascular magnetic resonance in adults and children values proposed by a recent publication (20).

MR image analysis for lung volume

An algorithm was used for the automatic procession of the MR data lung volumes as described previously in detail (15, 21). The algorithm consisted of the following segmentation steps: correction of intensity inhomogeneities, pre-extraction of a coarse region of interest containing the airways, segmentation of the bilateral lung and trachea regions, trachea extraction, and lung separation (right and left lung), and lung region refinement. Pulmonary blood vessels outside the mediastinal contours were included in the lung region (15). The whole MRI scan set after the automated processing was visually checked by an independent reader, unaware of the clinical information, and high-quality outputs of the framework have been verified (15).

Assessment of serum glucose and insulin

After overnight fasting venous blood was taken from all subjects at the study center. Serum fasting glucose (FG) was sampled, and 75 g of anhydrous glucose (Dextro OGT; Boehringer Mannheim, Mannheim, Germany) was given to participants without a known diagnosis of type 2 diabetes or taking glucose-lowering agents. Serum FG and 2h post-load glucose levels (oral glucose tolerance test; OGTT) were measured using an enzymatic colorimetric method (Dimension Vista 1500, Siemens Healthcare Diagnostics, Eschborn, Germany or Cobas c702, Roche Diagnostics GmbH, Mannheim, Germany). Serum fasting insulin (FI) levels were determined from blood samples using serum FI and 2h post-load insulin values were measured by a solid-phase enzyme-labeled chemiluminescent immunometric assay (Immulite 2000 Xpi, Siemens Healthcare Diagnostics) or by an electrochemiluminescence immunoassay (Cobas e 602, Roche Diagnostics GmbH,). The homeostasis model assessment-insulin resistance index (HOMA-IR) was calculated using the formula: (fasting glucose (mmol/L) × fasting insulin (μU/L)/22.5) (22).

Other risk factors

Information on risk factors was obtained through physical examination, interview, and blood sampling. BMI and body surface area (BSA) were calculated, smoking

status, alcohol use (g/day), and glucose-lowering, antihypertensive, lipid-lowering medication were assessed by questionnaire. Diabetes state was defined according to the WHO criteria as prediabetes (Impaired glucose tolerance, IGT: normal fasting glucose concentration and a 2-h serum OGTT glucose concentration between 140 and 200 mg/dL; and/or an impaired fasting glucose concentration, as defined by fasting glucose levels between 110 and 125 mg/dL, and a normal 2-h serum glucose concentration), and diabetes (2-h serum glucose concentration as determined by OGTT that was >200 mg/dL and/or a fasting glucose level that was >125 mg/dL) (23). Moreover, hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90mmHg, or receiving current antihypertensive treatment. Glycated hemoglobin (HbA1c) was analyzed in hemolyzed whole blood using the cation-exchange high performance liquid chromatographic, photometric VARIANT II TURBO HbA1c Kit-2.0 assay on a VARIANT II TURBO Hemoglobin Testing System (Bio-Rad Laboratories Inc.). Total serum cholesterol and serum creatinine concentrations were analyzed using an enzymatic colorimetric method (Dimension Vista 1500, Siemens Healthcare Diagnostics, or Cobas c702, Roche Diagnostics GmbH). The estimated glomerular filtration rate (eGFR) was calculated based on creatinine/cystatin C or combination according to a standardized formula (24).

Statistical analysis

The distribution of study population characteristics was described by using mean and s.d., median (interquartile ranges (IQRs), or percentages for continuous and categorical variables, respectively. A natural logarithmic transformation was performed to normalize the distribution of insulin and HOMA index. We used a two-step approach to investigate the association between glucose, insulin, and HOMA index with cardiac parameters and lung volumes respectively. First, using linear regression models we investigated the association between fasting glucose, insulin, and HOMA index with cardiac parameters and lung volumes. In model 1, we adjusted for sex and age. Model 2 adjusted for smoking, alcohol use, BMI, systolic and diastolic blood pressure, total cholesterol, and eGFR. Model 3 was additionally adjusted for glycated hemoglobin (HbA1c), antihypertensive medication, lipid-lowering medication, and glucose, or insulin. In model 4 we addressed the potential confounding effect of the right ventricle function into lung function or vice versa and adjusted for right ventricle parameters or lung volumes, respectively. Second, a sensitivity adjustment was performed for all parameter associations in subjects without diabetes. All analyses were performed using Stata (Stata 16.1 Corporation).

Results

Table 1 summarizes the characteristics of the study population. The mean age of the population was 55.7 ± 9.1 years and 43% of subjects were women. Among the subjects, 21.4% were current smokers, and mean alcohol use was 18.3 ± 22.3 g/day. Hypertension was present in 31.2% of subjects and only 5.3% of subjects had a diagnosis of diabetes mellitus. In all subjects, the mean (s.d.) fasting glucose was 5.53 ± 0.69 mmol/L, and median (IQR) fasting insulin was 56 (38–87) pmol/L.

Association between serum insulin and right ventricle

The association between serum insulin, HOMA index, and right ventricle is provided in Table 2. In a model adjusted for sex and age, we found an inverse association between insulin and RV end-diastolic volume (per s.d. increase in insulin level: $\beta = -6.31$, $P = 0.001$), end-systolic volume (per s.d. increase in insulin level: $\beta = -3.90$, $P = 0.002$) and stroke volume (per s.d. increase in insulin level: $\beta = -2.43$, $P = 0.017$), but not with ejection fraction. The association remained significant after further adjustment for other risk factors in model 2 and 3. When additionally adjusting for lung volumes in model 4, the association remained significant for RV end-diastolic volume (per s.d. increase in insulin level: $\beta = -12.85$, $P \leq 0.001$), end-systolic volume (per s.d. increase in insulin level: $\beta = -7.26$, $P < 0.001$) and stroke volume (per s.d. increase in insulin level: $\beta = -5.59$, $P < 0.001$) (Fig. 2 and Table 2). Considering the HOMA index, we found similar association estimates for RV parameters and lung volumes in magnitude and direction to serum insulin (Table 2). Moreover, sensitivity analysis confirmed the results when restricting the analyses on subjects without a history of diabetes (Supplementary Table 1, see section on supplementary materials given at the end of this article). We found no association between glucose with any parameter of the right ventricle function (Table 2).

Association between serum insulin and lung volume

The inverse association was observed between insulin and lung volume in the model adjusted for sex and age

Table 1 Study population characteristics. The subjects were stratified in tertiles (denoted as low, medium and high) of serum fasting insulin. The values represent mean ± S.D., median (interquartile ranges) or frequency along with percentage.

	Fasting insulin, pmol/L				
	All	Low 13.9–43.2	Medium 43.3–72.0	High 72.1–288	*P*
n	337	114	113	110	
Age, years	55.7 ± 9.1	54.2 (±9.3)	55.3 (±8.5)	57.8 (±9.1)	0.003
Women, %	145 (43%)	57 (50%)	49 (43.4%)	39 (35.5%)	0.028
BMI, kg/m²	27.9 ± 4.7	24.4 (±2.8)	27.8 (±3.8)	31.5 (±4.4)	<0.001
Body surface area, m²	1.95 ± 0.21	1.86 (±0.20)	1.94 (±0.21)	2.05 (±0.20)	<0.001
Smoking status					0.861
Never, %	126 (37.4%)	45 (39.5%)	39 (34.5%)	42 (38.2%)	
Past, %	139 (41.3%)	42 (36.8%)	51 (45.1%)	46 (41.8%)	
Current, %	72 (21.4%)	27 (23.7%)	23 (20.4%)	22 (20.0%)	
Alcohol use, g/day	18.3 ± 22.3	18.1 (±23.7)	19.2 (±21.5)	17.7 (±21.7)	0.870
Diabetes status					<0.001
Normal, %	225 (66.8%)	98 (86%)	87 (77%)	40 (36.4%)	
Prediabetes, %	94 (27.9%)	14 (12.3%)	24 (21.2%)	56 (50.9%)	
Diabetes, %	18 (5.3%)	2 (1.8%)	2 (1.8%)	14 (12.7%)	
HbA1c, %	5.4 ± 0.4	5.4 (±0.3)	5.4 (±0.3)	5.6 (±0.5)	<0.001
Fasting glucose, mmol/L	5.53 ± 0.69	5.20 (±0.53)	5.48 (±0.55)	5.94 (±0.76)	<0.001
HOMA index	2.2 (1.4–3.5)	1.2 (0.9;1.4)	2.2 (2;2.6)	4.0 (3.5;5.2)	<0.001
Hypertension, %	105 (31.2%)	19 (16.7%)	32 (28.3%)	54 (49.1%)	<0.001
Systolic blood pressure, mm/Hg	119.9 ± 16.6	113.7 (±14.7)	120.1 (±14.1)	126.2 (±18.6)	<0.001
Diastolic blood pressure, mm/Hg	75.4 ± 9.9	71.1 (±8.1)	76.6 (±9.1)	78.6 (±10.9)	<0.001
Antihypertensive medication, %	77 (22.9%)	16 (14.0%)	21 (18.6%)	40 (36.4%)	<0.001
Total cholesterol, mmol/L	5.63 ± 0.93	5.49 (±0.86)	5.74 (±0.85)	5.68 (±1.05)	0.285
Lipid lowering medication, %	29 (8.6%)	4 (3.5%)	11 (9.7%)	14 (12.7%)	0.014
eGFR, mL/min/1.73 m²	87.1 ± 12.8	88.7 (±12.5)	87.9 (±12.6)	84.8 (±13.1)	0.030
Right ventricle					
End-diastolic volume, mL	166.9 ± 39.7	169.7 (±42.1)	171.4 (±39.3)	159.6 (±36.7)	0.061
End-systolic volume, mL	80.1 ± 26.0	82.3 (±28.7)	82.0 (±25.1)	75.7 (±23.7)	0.123
Stroke volume, mL	87.0 ± 19.5	87.5 (±19.6)	89.4 (±19.1)	83.9 (±19.5)	0.171
Ejection fraction, %	52.7 ± 7.1	52.3 (±7.4)	52.7 (±6.4)	53.1 (±7.6)	0.429
Lung volume, L	3.97 (±1.12)	4.15 (±1.14)	3.98 (±1.13)	3.77 (±1.07)	0.019

P-value for trend.
eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c.

(per S.D. increase in insulin level: $\beta = -0.23$, $P < 0.001$). The association remained significant after further adjustment for risk factors in model 2 and 3. When adjusting for additional right ventricle function parameters in model 4, the association remained significant (per S.D. increase in insulin level: $\beta = -0.18$, $P = 0.017$) (Fig. 2 and Table 3). HOMA index provided similar effect estimates in magnitude and direction to serum insulin for the association with lung volumes. Furthermore, in sensitivity analysis, we found confirmatory results when concentrating the analyses on subjects without a history of diabetes (Supplementary Table 2). No association was found between serum glucose and lung volumes (Table 3).

Discussion

In this population-based cohort study, serum insulin was associated with reduced RV end-diastolic volume, end-systolic volume, stroke volume, but not with ejection fraction. Additionally, serum insulin was associated with reduced lung volumes.

Our findings suggest that serum insulin and insulin sensitivity may play an important role in the early stages of RV impairment and influences pulmonary circulation before diabetes disease onset. A recent KORA study found that in persons with diabetes or prediabetes RV function was reduced compared to healthy controls (7). Similarly, other studies focusing on LV function provided evidence on the role of an increased level of insulin and impaired LV function. In participants of SHIP and KORA studies, insulin was found to be related to a greater arterial stiffness, smaller LV volume, and higher LV thickness, resulting in LV concentric remodeling and lower LV stroke volume (13). Further, a study from FLEMENGHO found out that serum insulin was associated with longitudinal changes of LV (12). An independent association between the degree of insulin

Table 2 Association between serum glucose, serum insulin and HOMA index with right ventricle parameters. The beta estimate given with a 95% CI represents the estimate size between glucose, insulin and HOMA index and lung volume from linear regression model. The model 1 = adjusted for sex and age; model 2 = model 1 + BMI, smoking, alcohol use, systolic blood pressure, diastolic blood pressure, total cholesterol and eGFR; model 3 = model 2 + HbA1c, insulin* or glucose†, antihypertensive medication, lipid lowering medication; model 4 = model 3 + lung volumes.

Per s.d.	Model 1	*P* value	Model 2	*P* value	Model 3	*P* value	Model 4	*P* value
End-diastolic volume								
Glucose	−1.87 (−5.80; 2.06)	0.35	−1.96 (−6.12; 2.21)	0.35	−0.04 (−4.80; 4.71)*	0.98	0.03 (−4.72; 4.78)	0.99
Insulin	−6.31 (−10.01; −2.61)	0.001	−12.19 (−16.89; −7.50)	<0.001	−12.43 (−17.37; −7.50)†	<0.001	−12.85 (−17.81; −7.89)	<0.001
HOMA index	−6.10 (−9.85; −2.34)	0.002	−11.82 (−16.62; −7.02)	<0.001	−12.53 (−17.48; −7.58)	<0.001	−12.89 (−17.86; −7.92)	<0.001
End-systolic volume								
Glucose	−0.21 (−2.76; 2.34)	0.87	0.33 (−2.42; 3.08)	0.81	1.20 (−1.98; 4.38)*	0.45	1.22 (−1.96; 4.41)	0.45
Insulin	−3.90 (−6.30; −1.50)	0.002	−6.56 (−9.70; −3.42)	<0.001	−7.12 (−10.4; −3.83)†	<0.001	−7.26 (−10.57; −3.94)	<0.001
HOMA index	−3.62 (−6.06; −1.19)	0.004	−6.03 (−9.24; −2.81)	<0.001	−6.58 (−9.89; −3.27)	<0.001	−6.69 (−10.02; −3.36)	<0.001
Stroke volume								
Glucose	−1.70 (−3.79; 0.40)	0.11	−2.32 (−4.54; −0.10)	0.040	−1.28 (−3.84; 1.28)*	0.32	−1.23 (−3.78; 1.32)	0.34
Insulin	−2.43 (−4.43; −0.44)	0.017	−5.64 (−8.17; −3.10)	<0.001	−5.32 (−7.98; −2.65)†	<0.001	−5.59 (−8.27; −2.92)	<0.001
HOMA index	−2.50 (−4.52; −0.48)	0.015	−5.81 (−8.39; −3.22)	<0.001	−5.97 (−8.64; −3.30)	<0.001	−6.22 (−8.89; −3.54)	<0.001
Ejection fraction								
Glucose	−0.38 (−1.13; 0.37)	0.32	−0.73 (−1.55; 0.10)	0.08	−0.72 (−1.69; 0.26)*	0.14	−0.71 (−1.68; 0.27)	0.15
Insulin	0.50 (−0.22; 1.22)	0.17	0.38 (−0.58; 1.35)	0.43	0.62 (−0.39; 1.62)†	0.23	0.57 (−0.45; 1.58)	0.27
HOMA index	0.40 (−0.32; 1.13)	0.27	0.18 (−0.81; 1.17)	0.71	0.27 (−0.74; 1.29)	0.59	0.23 (−0.79; 1.24)	0.66

eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c.

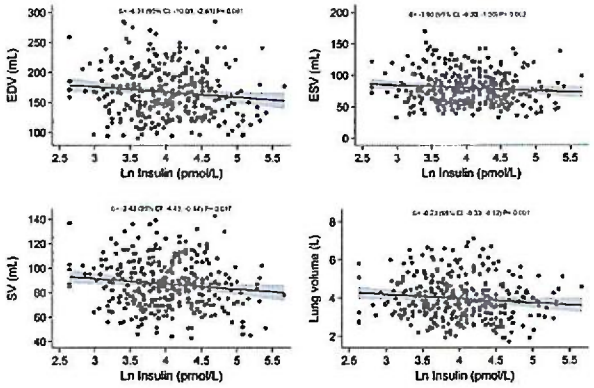

Figure 2

The relationship between serum insulin and right ventricle end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), and lung volumes, scatter plots with regression line and 95% CI.

resistance represented as HOMA index or hyperinsulinemia, and increased LV mass index, LV mass, and volume were observed in the MESA study (Multi-Ethnic Study of Atherosclerosis) (25). Furthermore, in the FRAMINGHAM heart study insulin resistance was associated with lower diastolic function, even before diabetes disease onset (9).

Given that our findings accounted for RV function, they are in line with previous studies involving the left ventricle and extend the evidence on the role of the insulin in the right heart also. The potential underlying pathophysiological mechanism may be a decreased glucose uptake by cardiomyocytes and consequently a lower glycolysis rate in the insulin-resistant state, with increased serum insulin beyond physiological levels (26, 27). Consequently, energy production from free fatty acids oxidation will increase and lipotoxicity may occur, leading to increased oxygen consumption, stress, and reduced cardiac contractility (28). Alternatively, serum insulin levels were associated with a higher presence of intraplaque hemorrhage in existing atherosclerotic plaque (29), a plaque feature responsible for plaque progression in coronary arteries (30), leading to RV coronary ischemia (31). However, the link between the RV function and pulmonary circulation remains poorly understood (14). In this regard, we additionally assessed the role of insulin on lung volumes as a potential volumetric parameter of pulmonary pathology. Our findings build novel evidence on the role of insulin and reduced lung volumes. In this context, pulmonary vasculature seems to be affected by dysregulated levels of insulin. Abnormalities may result from the obliterative remodeling of pulmonary circulation which is characterized by occlusion of the lumen of medium-sized and small arteries in the lungs due to excessive cellular proliferation of vascular wall, and loss of microvasculature and capillaries due to elevation of serum insulin (32). This could be explained by insulin role on vascular endothelial growth factor which may induce further angiogenesis in pulmonary vessels (33), increase pulmonary vascular permeability in early stages of acute lung injury leading to loss of pulmonary volume (34), as well as impair the endothelial function of the pulmonary arteries leading to pulmonary hypertension (PH) (35). PH is a disease that predominantly affects distal pulmonary arteries with pathological changes including vasoconstriction, medial hypertrophy, intimal proliferation, and complex plexiform lesions (14). On this basis, we may hypothesize that through the combined interpretation of findings from RV and lung volumes insulin affects concomitantly RV function and pulmonary vasculature. Dysregulated serum insulin levels may occur even 15 years prior to diabetes disease onset (2), and this long-term effect may be sufficient for silent pathological changes in heart and lungs that at a later stage may be translated as overt PH disease in elderly subjects (36).

To date, there are no studies that assessed the role of insulin in RV and lung volumes as to the main axis of pulmonary circulation in disease-free subjects, and our findings may represent novel evidence in this matter and merit further investigation. Surprisingly, we did not

Table 3 Association between glucose, insulin and HOMA index with lung volume.

	Lung volume							
Per s.d.	Model 1	*P* value	Model 2	*P* value	Model 3	*P* value	Model 4	*P* value
Glucose	−0.10 (−0.20; 0.01)	0.08	−0.04 (−0.15; 0.08)	0.50	0.03 (−0.11; 0.16)*	0.68	0.02 (−0.12; 0.16)	0.77
Insulin	−0.23 (−0.33; −0.12)	<0.001	−0.14 (−0.28; −0.01)	0.035	−0.15 (−0.29; −0.01)†	0.037	−0.18 (−0.32; −0.03)	0.017
HOMA Index	−0.22 (−0.33; −0.12)	<0.001	−0.14 (−0.28; −0.01)	0.040	−0.13 (−0.27; 0.01)	0.06	−0.16 (−0.31; −0.02)	0.027

The beta estimate given with a 95% CI represents the estimate size between glucose, insulin and HOMA index and lung volume from linear regression model. The model 1 = adjusted for sex and age; model 2 = model 1 + BMI, smoking, alcohol use, systolic blood pressure, diastolic blood pressure, total cholesterol and eGFR; model 3 = model 2 + HbA1c, Insulin* or glucose†, antihypertensive medication, lipid lowering medication; model 4 = model 3 + end-diastolic volume, end-systolic volume, stroke volume and ejection fraction.
eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c.

find any role of glucose affecting RV function and lung volumes, despite previous evidence of serum glucose, and cardiovascular complications in general (37).

To our knowledge, our study is the first to assess the relation of serum insulin with RV cardiac function and lung volumes by combining both organs within a single MRI scan examination. The strengths of the study incorporate the implementation of advanced 3T whole-body MRI, which is superior to echocardiography in RV function assessment, in a population-based cohort without known cardiovascular disease. The MRI cardiac assessment and lung volumetric quantification was performed using advanced automatic and semi-automatic processes with a detailed protocol. Additionally, we performed a multi-level adjustment testing to confirm our results. Also, to rule out the possible overfitting issues and effect modification of the blood pressure, we accounted for testing with minimal adjustment. Given that high blood pressure is one of the main criteria for metabolic syndrome diagnosis (38) and a condition that is closely related to higher insulin levels, minimal adjustment model and fully adjusted models provided confirmatory results. However, a few limitations of the study warrant to be mentioned. The cross-sectional analysis limits to conclude causal inference, and our study may be regarded as hypothesis generation. Although we performed sensitivity analysis and excluded participants with known diabetes, a population-based cohort study consists of a rather small number of study participants.

Conclusion

Serum insulin was inversely associated with right ventricle function and lung volumes in subjects from the general population free of cardiovascular disease, suggesting that increased insulin levels may contribute to subclinical cardiopulmonary circulation impairment.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EJE-20-1010.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement
Study concept and design were performed by R V K, F B, C L S, and B M. Acquisition, analysis, or interpretation of data was performed by R V K, R L, F B, C L S, and B M. Drafting of the manuscript was performed by R V K, F B, C L S, and B M. Critical revision of the manuscript for important intellectual content was performed by R V K, R L, S R, C S, E A, C K, W R, A P, S K, F B, C L S, and B M. Statistical analysis was performed by R L. Administrative, technical, or material support was performed by R V K, F B, C L S, and B M. Study supervision B M. All authors read and approved the final manuscript. R L had had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

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