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ORIGINAL RESEARCH ARTICLE

A diabetes-associated genetic variant is associated with diastolic dysfunction and cardiovascular disease

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Abstract

Aims Although the epidemiological association between Type 2 diabetes and congestive heart failure (CHF) as well as cardiovascular disease (CVD) is well established, associations between diabetes-related single-nucleotide polymorphisms (SNPs), CHF, and CVD have been surprisingly inconclusive. Our aim is to examine if 43 diabetes-related SNPs were associated with prevalent diastolic dysfunction assessed by echocardiography and incident CVD and/or CHF.

Methods and results We genotyped 43 SNPs that previously reported genome-wide significant associations with Type 2 diabetes, in 1444 subjects from the population-based Malmö Preventive Project-Re-examination Study (MPP-RES) (mean age 68 years; 29% women, 36% prevalent diabetes) (discovery cohort) and in 996 subjects from the VARA cohort (mean age 51 years, 52% women, 7% prevalent diabetes) (replication cohort). Multivariable logistic regression was assessed. Genetic variants that reached significant association with diastolic dysfunction in both cohorts were then analysed for association with incident CVD/CHF in a larger sample of the MPP-RES cohort (3,407 cases and 11,776 controls, median follow up >30 years) using Cox regression analysis. A common variant at the *HNF1B* [major allele (T) coded, also the risk allele for diabetes] was the only SNP associated with increased risk of prevalent diastolic dysfunction in both the discovery [MPP-RES; odds ratio (OR) 1.21, P = 0.024), and the replication cohort (VARA; OR 1.38, P = 0.042]. Cox regression analysis showed that carriers of the T-allele of *rs757210* had an increased risk of future CVD (HR 1.05, P = 0.042). No significant association was seen for incident CHF.

Conclusions The diabetes susceptibility locus *HNF1B* is associated with prevalent diastolic dysfunction in two independent Swedish cohorts as well as incident cardiovascular disease.

Keywords Congestive heart failure; Cardiovascular disease; Diabetes; Diastolic dysfunction; HNF1B; rs757210; single nucleotide polymorphism

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Introduction

Diastolic dysfunction is considered the earliest manifestation of diabetes-induced left ventricular dysfunction[1] and is in itself a risk factor for incident congestive heart failure (CHF) and cardiac death.[2]

Diastolic dysfunction is common in the general population and, especially in patients with diabetes, diastolic dysfunction is associated with increased all-cause mortality, even in its milder forms.[3–5] Compared with normoglycemic subjects, both the incidence and the prevalence of CHF is significantly higher in diabetes patients, and it also carries a worse prognosis,[6,7] but the underlying mechanisms remain incompletely understood.[1,8]

Although the epidemiological association between diabetes and CHF is well established,[9] associations between

diabetes-related single-nucleotide polymorphisms (SNPs), with CHF and cardiovascular disease (CVD) have been surprisingly inconclusive,[10] and the effect on CVD risk has been lower than expected.[11]

The structural and functional harmful effects on the cardiovascular system induced by glucometabolic disturbances represent a continuum, present before actual diabetes manifests.[12,13] Therefore, another, and maybe more physiologically appealing, approach is to examine the associations between diabetes-related SNPs with signs of functional but subclinical heart disease (e.g. diastolic dysfunction) as measured by echocardiographic examinations (UCG) and thereafter investigate their association with development of CVD and CHF.

Hence, our aim in this observational study was to investigate SNPs with documented association with diabetes and their further association with one of the earliest signs of left ventricular dysfunction (i.e. diastolic dysfunction) in two independent Swedish population UCG cohorts: the population-based Malmö Preventive Project-Re-examination Study UCG (MPP-RES UCG) and the VARA UCG. The SNPs associated with diastolic dysfunction were then analysed regarding prediction of incident CVD and CHF in the whole Malmö Preventive Project-Re-examination Study (MPP-RES).

Methods

Study samples

The Malmö Preventive Project Re-examination cohort and the Malmö Preventive Project Re-examination cohort echocardiographic cohort

Between 1974 and 1992, birth cohorts (men born in 1921, 1926–42, 1944, 1946, and 1948-49; women born in 1926, 1928, 1930–36, 1938, 1941–42, and 1949) of inhabitants residing in Malmö, Sweden, were invited to participate in a large cohort study The Malmö Preventive Project (MPP) with a total of 33 346 participants (67% men, attendance rate 71%, mean age 46 ± 7 years). Between 2002 and 2006, a re-examination of 18 240 surviving MPP participants, the MPP-RES was conducted (63% men, 72% attendance rate, mean age 69 ± 6 years). All participants filled a self-administered questionnaire on lifestyle and medical history. Height and weight were measured in light indoor clothing, waist circumference was measured, and body mass index (BMI) was calculated (kg/m^2). Blood pressure (BP) and pulse rate were measured twice in the supine position after 10 min of rest, and blood samples were drawn after an overnight fast.

Out of the 18 240 participants, 15 215 were successfully genotyped for HNF1B *rs757210* and had valid measurements of all covariates (age, sex, and BMI) (*Figure 1*). In a subsample of 1792 participants, UCG recordings were carried out. These subjects were randomly selected from groups defined by glucometabolic status: normal fasting plasma glucose (FPG) (≤6.0 mmol/L); impaired FPG; new-onset Type 2 diabetes mellitus; and prevalent diabetes mellitus. Subjects with glucometabolic disturbances were oversampled to ensure sufficient numbers of subjects studied from each group. A full description of this study population has been presented elsewhere.[14] Of these, 1444 had valid measurements of all UCG measurements and covariates (systolic BP and diastolic BP, prevalent diabetes and information of antihypertensive medication) and were successfully genotyped for HNF1B *rs757210*. The number of successfully genotyped subjects for the other 42 diabetes-associated SNPs at 42 different genes is shown in *Table 4*. See *Figure 1* for a flowchart describing the MPP-RES and MPP-RES UCG cohorts.

The VARA echocardiographic cohort—replication cohort

Within the framework of the Skaraborg Project, this study includes data from a representative population in Vara, a small community in a rural area in Southwestern of Sweden. Residents in Vara were randomly selected from the population census register stratified by sex and 5 years age groups between 30 and 74 years. Individuals below age 50 were oversampled three times as compared with those who were older. Participation was based on three criteria: (i) a study visit to the nurse for a physical examination, (ii) blood sampling, and (iii) filling the questionnaires. Between 2001 and 2003, 1811 unrelated participants were accordingly included (attendance rate 82%). These participants were then consecutively invited to a separate visit for an UCG examination. In total, 1058 subjects were successfully examined (51% female), and the presence or absence of diastolic dysfunction could be determined for 1044 participants. After excluding subjects with unsuccessful genotyping, 996 participants were included in this study. A full description of this study population has been presented elsewhere.[15]

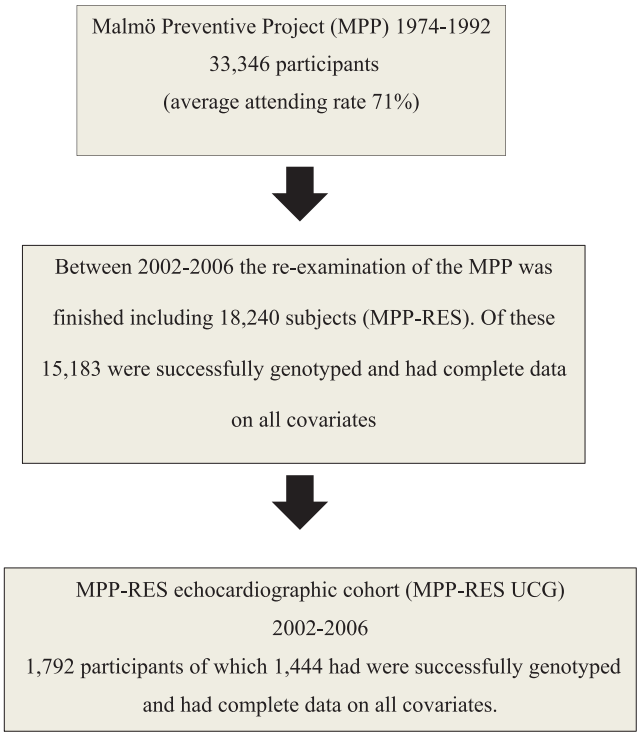
Ethical consent

All participants in this study signed a written informed consent form. The study was approved by The Ethics Committee at Lund University, Sweden (MPP-RES and MPP-RES UCG cohorts) and at the University of Gothenburg, Sweden (VARA UCG).

Echocardiography

In MMP-RES, two experienced sonographers carried out all echocardiograms using an Acuson Sequoia, Mountain View, CA, USA (3V2c transducer) or Sonos 5500 Philips, Andover, MA, USA (S3 transducer). The two sonographers analysed images independently from a random subsample of subject to test inter-observer and intra-observer variability, which was 13.0% and 10.5% for intraventricular end-diastolic septum diameter and 4.1% and 3.3% for left ventricular end-diastolic

Figure 1 Flowchart describing the study-population.



diameter. Both sonographers were experienced and blinded to clinical data.

In VARA UCG, all UCG examinations were performed by the same cardiologist using a General Electrics VingMed S5 System, operating with a 3.5 MHz-probe, and data were stored in the EchoPac System. In Vara, all UCG examinations were conducted by the same cardiologist; no tests for inter-observer variability were undertaken.

Internal left and right ventricular dimensions were evaluated from parasternal long axis view according to the recommendations of the European Association of Echocardiography. Measurements of wall thickness were obtained in two-dimensional end-diastolic parasternal long axis view during a single heart cycle if recordings were homogeneous, otherwise a mean of three to five measurement of different heart cycles was used. Pulsed-wave tissue Doppler imaging was performed in apical views according to clinical standards, and diastolic function was graded using the following grading scheme: normal or Grade I mild or Grade II (impaired relaxation pattern), moderate or Grade III (pseudo-normal left ventricular filling), and severe (restrictive filling) or Grade IV.[16] Grades II, III, and IV were grouped together because of the relatively small number of subjects in the groups III and IV and referred to as *diastolic dysfunction*. Additional analyses that compared normal diastolic function with mild diastolic dysfunction (Grade II) as well as normal function compared with moderate and severe diastolic dysfunction (Grade III + IV) were also performed. All analyses were performed offline using Xcelera software (Philips, Amsterdam, the Netherlands).

Laboratory assays

All FPG analyses were performed by the Department of Clinical Chemistry, Malmö University Hospital applying a national standardization and quality control system (Beckman Coulter LX20, Beckman Coulter Inc, Brea, USA).

Genotyping

In the study, 18 240 MPP-RES participants were genotyped with reference to a panel of containing 43 SNPs from genome-wide association studies for Type 2 diabetes and glycemic traits. Genotyping was performed with the use of matrix-assisted laser desorption–ionization time-of-flight mass spectrometry on the Mass Array iPLEX (Sequenom, San Diego, CA, USA). Replication genotyping for *HNF1B rs757210* in 996 VARA UCG participants was performed using the allelic discrimination assay-by-design method on ABI 7900 (Applied Biosystem). All SNPs had a call rate of >95% and fulfilled the Hardy–Weinberg equilibrium ($P > 0.05$).

Definition of endpoints

Because the genome is fixed and not altered over time, we chose to examine the incidence of CVD and CHF starting from the baseline examination of MPP (conducted between 1974 and 1992) even though the genotyping was performed at MPP-RES (between 2002 and 2006) examination, to increase

the number of incident cases of CVD and CHF. Thus, all the study participants were followed from the baseline examination of MPP until the first hospitalization attributable to CHF, CVD, death, emigration from Sweden or 31 December 2014, whichever came first. We applied linkage of the unique 10-digit personal identification number with the Swedish National Hospital Discharge Register, and the Swedish National Cause of Death Register. The occurrence of the first hospitalization because of CHF episode was ascertained from Swedish National Hospital Discharge Register using diagnosis codes 428 for the 9th Revision (ICD-9), and I50 or I11.0 for the 10th Revision (ICD-10) if CHF was listed as a primary diagnosis. A cardiovascular event was defined as fatal or non-fatal myocardial infarction (ICD-9 code 410, and ICD10 code I21), death due to chronic ischemic heart disease (ICD-9 code 411, 412, 414 and ICD-10 codes I24, I25.1-I25.9) or fatal or non-fatal ischemic stroke (ICD-9 codes 430, 431, 434, 436, and ICD-10 codes I60, I61, I63, I64), whichever came first. The end points were retrieved by data linkage with the Swedish National Hospital Discharge and Swedish Cause of Death Registers (only myocardial infarction and ischemic heart disease) as well as to a local stroke register of Malmö. High case–validity in these registers has previously been described for both CHF and CVD.[17,18]

Other definitions

Antihypertensive drug treatment was defined as use of one or more of the following: β-receptor blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, thiazides, mineralocorticoid receptor antagonists, and loop diuretics. Prevalent hypertension was defined as the presence of either one or more of the following at inclusion: systolic BP $>$ 140 mmHg and/or diastolic BP $>$ 90 mmHg and/or antihypertensive treatment and/or treatment by the time of the third visit. Diabetes was defined as previously known diabetes mellitus Type 1 or 2, whereas new-onset diabetes mellitus Type 2 was defined by either two separate measurements of FPG $\geq$ 7.0 mmol/L or one single measurement $\geq$11.1 mmol/L.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). In the MPP-RES UCG and VARA UCG cohorts, prevalent diastolic dysfunction was modelled as the dependent variable in logistic regression with the 43 genotypes as independent variables using additive models with the diabetes risk alleles coded. All modelling was performed in models adjusted for age and sex (Model 1) and for age, sex, systolic, and diastolic BP, hypertensive treatment and diabetes status (Model 2). A Cox regression model was applied to study the effect of *rs757210* (major allele TT coded) on incident CVD and CHF, adjusting for age, gender and BMI at baseline examination, entering time variable defined as follow-up time between baseline screening and the date of incident CVD and incident CHF in the entire MPP-RES cohort. A two-tailed significance level of $P < 0.05$ was considered statistically significant. All calculations were done in SPSS 23.0 (SPSS Inc, Illinois, US).

Results

Baseline characteristics for the entire populations (MPP-RES UCG, VARA UCG, and MPP) are presented in *Table 1*. Subgroup characteristics (subjects without, and subjects with diastolic dysfunction in the MPP-RES UCG, and the VARA UCG) are presented in *Table 2*.

In the MPP RES UCG, subjects with diastolic dysfunction were older ($P < 0.0001$), more likely to be female (P = 0.006), and had more cases of prevalent hypertension (P = 0.016) and diabetes (P = 0.032) compared with subjects without diastolic dysfunction (*Table 2*). In the VARA UCG, subjects with diastolic dysfunction were older ($P <0.001$), more likely to be female (P = 0.014), had higher systolic BP ($P < 0.001$), diastolic BP ($P > 0.001$), BMI ($P < 0.001$), and had more cases of prevalent hypertension ($P < 0.001$) and diabetes ($P <$ 0.001) (*Table 2*). Genotype frequencies of *rs757210* are presented in *Table 3*.

Diabetes associated single-nucleotide polymorphisms and their relation to diastolic dysfunction

All 43 Type 2 diabetes-associated SNPs were coded for their formerly shown diabetes risk alleles and tested for associations with prevalent diastolic dysfunction in the MPP-RES UCG, which was the discovery cohort (*Table 4*). In the fully adjusted logistic regression analysis (Model 2) of the MPP-RES UCG cohort, common variants in three genes were positively associated ($P < 0.05$) with risk of prevalent diastolic dysfunction, ADAMTS9 [Odds ratio (OR), 1.22, P = 0.041], HNF1B (OR, 1.21, P = 0.024), TSPAN8 (OR, 1.26, P = 0.018), and common variants in three genes were negatively associated with prevalent diastolic dysfunction, HNF1A (OR, 0.78; P = 0.012), TCF7L2 (OR, 0.82, P = 0.024), NOTCH2 (OR, 0.72, P = 0.020). When these six SNPs were tested in the replication cohort (VARA UCG), only one SNP reached nominal significant association ($P < 0.05$) with diastolic dysfunction in the fully adjusted logistic regression analysis; HNF1B *rs757210* (OR, 1.38, P = 0.042) (*Table 4*). Although the HNF1B *rs757210* was significantly associated with all types of prevalent diastolic dysfunction, there was a tendency for a stronger association with more severe degrees of diastolic dysfunction as described in *Table 5*.

Table 1 Baseline characteristics of the study population in the Malmö Preventive Project-Re-examination echocardiographic study, VARA echocardiography, and the Malmö Preventive Project-Re-examination

Characteristic	MPP-RES UCG	VARA UCG	MPP-RES
N	1444	996	15 215
Sex (% women)	28.3	52.1	37.9
Age (years)	67.4 (±5.7)	50.6 (±12)	46.7 (±6.2)
Systolic BP (mmHg)	147.3 (±20.3)	124.5 (±17.0)	131.0 (±15.8)
Diastolic BP (mmHg)	84.6 (±10.6)	71.2 (±10.0)	85.2 (±9.3)
Body mass index (kg/m^2)	28.3 (±4.2)	27.0 (±4.5)	24.4 (±3.4)
Antihypertensive treatment (%)	49.0	12.1	4.9
Hypertension (%)	58.2	18.3	27.4
Prevalent diabetes	36.7	7.2	2.5

Data are expressed as mean (±SD) or percent (%).
BP, blood pressure; MPP-RES, Malmö Preventive Project-Re-examination; UCG echocardiography.

HNF1B rs757210 and association to incident cardiovascular disease and congestive heart failure

In the entire MPP-RES, of the 15 215 subjects who were successfully genotyped for *rs757210* and had valid measurements of all covariates, 32 subjects with prevalent CVD at baseline MPP examination were excluded, leaving 15 183 subjects entered in the Cox regression analysis for incident CVD. The median follow-up from the baseline MPP examination time to first CVD event was 31 years (interquartile range 8). There were 3407 cases of CVD events and 11 776 controls. Carriers of the major T-allele had increased risk of incident CVD with a hazard ratio of 1.05 [95% confidence interval HR 1.051 (1.002–1.102), $P = 0.042$].

The median follow-up from the baseline MPP examination time to first CHF event was 32 years (interquartile range 6). There were no cases with prevalent CHF at MPP baseline examination. During follow-up, 976 cases of incident CHF were registered. Being carrier of the major T-allele had no association with incident CHF (HR 0.98, 95% CI; 0.90–1.07, $P = 0.647$).

Discussion

Key findings

To the best of our knowledge, this study is the first to investigate diabetes predisposing genetic variants and their association with diastolic dysfunction. Our main finding was the association of the HNF1B *rs757210* locus with increased risk of prevalent diastolic dysfunction in two independent population cohorts. In addition, HNF1B *rs757210* predicted increased risk of incident CVD but not with incident CHF.

Physiological relevance of HNF1B

Hepatocyte nuclear factor 1β is a homeodomain-containing transcription factor and was initially discovered as a monogenic diabetes gene and is also commonly associated with renal cysts, which led to the description of the renal cysts and diabetes syndrome.[19,20] Since then, many additional clinical features associated with mutations in HNF1B have become evident,[21] such as pancreatic hypoplasia, genital tract malformations, abnormal liver function, hypomagnesaemia, hyperuricemia, and early-onset gout,[21] HNF1B-associated disease is, therefore, considered to be a multisystem disorder.

The *rs757210* is an intronic SNP with a minor allele frequency of 0.36. In addition to its association with diabetes,[22] it is also associated with prostate cancer[23] and ovarian cancer.[24] Our review of the present literature has not found any studies linking HNF1B to cardiac function or to CVD. Our finding of HNF1B and increased risk of prevalent diastolic dysfunction was independent of its predisposition to diabetes and may therefore represent a novel link between diabetes and cardiac dysfunction.

Table 2 Characteristics (subjects without, and subjects with diastolic dysfunction in the Malmö Preventive Project-Re-examination echocardiography and the VARA echocardiography)

Characteristic	MPP-RES UCG			VARA UCG		
	DD −	DD +	*P*-value	DD −	DD +	*P*-value
N	465	979		863	133	
Sex (% women)	23.7	30.4	0.006	53.7	42.1	0.014
Age (years)	65.2 (±5.7)	68.4 (±5.4)	<0.001	48.5(±11)	64.1(±7.8)	<0.001
Systolic BP (mmHg)	147.2 (±20.0)	147.4 (±20.4)	0.894	121(±15.2)	141.3(±18.0)	<0.001
Diastolic BP (mmHg)	85.2 (±10.1)	84.3 (±10.8)	0.108	70.3(±9.1)	77.2(±12.8)	<0.001
Body mass index (kg/m^2)	28.1 (±4.2)	28.3 (4.2)	0.454	26.7(±4.3)	29.3(±4.8)	<0.001
AHT (%)	46.2	47.4	0.680	8.6	35.3	<0.001
Hypertension (%)	74,8	80.6	0.016	12.7	54.1	<0.001
Prevalent diabetes	34.4	37.8	0.032	4.6	24.1	<0.001

AHT, antihypertensive treatment; BP, blood pressure; DD, diastolic dysfunction; MPP-RES, Malmö Preventive Project-Re-examination; UCG, echocardiography.

Table 3 Genotype frequencies of rs757210

Genotype frequencies	MPP-RES UCG		VARA UCG		MPP-RES	
	Frequency (*n*)	Percent (%)	Frequency (n)	Percent (%)	Frequency (*n*)	Percent (%)
TT	412	28.5	183	18.4	4532	29.8
CT	738	51.1	464	46.6	7530	49.5
CC	294	20.4	349	35.0	3159	20.8
Total	1444	100	996	100	15 221	100

Genotype frequencies of *rs757210* in MPP-RES-UCG and MPP-RES. Major allele represented by T, minor allele represented by C.
MPP-RES, Malmö Preventive Project-Re-examination; UCG, echocardiography.

Table 4 Diabetes-associated single-nucleotide polymorphisms' association with prevalent diastolic dysfunction in the Malmö Preventive Project-Re-examination echocardiography study and VARA echocardiography cohort

SNP	*n*	OR[a]	95% CI Lower	95% CI Upper	*P*-value
ADRA2A_RS10885122	1491	1.03	0.82	1.31	0.78
FAM148B_RS11071657	1492	1.05	0.89	1.24	0.55
CRY2_RS11605924	1491	1.09	0.93	1.27	0.30
ZFAND_RS11634397	1493	1.09	0.92	1.28	0.34
CHCHD9_RS13292136	1490	1.09	0.81	1.45	0.58
HMGA2_RS1531343	1494	0.96	0.71	1.29	0.78
CENTD2_RS1552224	1493	1.04	0.84	1.29	0.73
FADS1_RS174550	1490	0.99	0.83	1.18	0.93
DGKB_RS2191349	1451	0.92	0.78	1.09	0.33
PROX1_RS340874	1484	1.04	0.89	1.22	0.62
IRS1_RS4675095	1494	0.88	0.60	1.30	0.52
G6PC2_RS560887	1492	0.96	0.80	1.14	0.63
GCKR_RS780094	1490	0.88	0.75	1.03	0.11
MADD_RS7944584	1487	0.86	0.71	1.03	0.10
HNF1A_RS7957197	1486	0.77	0.63	0.94	0.01
HNF1A_RS7957197[b]	910	1.10	0.72	1.68	0.65
PRC1_RS8042680	1489	1.04	0.87	1.25	0.65
TP53INP1_RS896854	1491	0.89	0.76	1.05	0.18
KLF14_RS972283	1475	0.86	0.73	1.01	0.06
BCL11A_rs243021	1471	0.95	0.81	1.11	0.54
ZBED3_rs4457053	1469	0.91	0.76	1.09	0.30
GCK_rs4607517	1482	0.87	0.70	1.08	0.22
IGF2BP2rs4402960	1444	0.91	0.77	1.09	0.30
CDKAN2Ars1811661	1405	1.09	0.87	1.36	0.46
HHEX_rs1111875	1466	0.99	0.84	1.18	0.95
FTO_rs9939609	1475	1.06	0.90	1.24	0.48
KCNJ11rs5912	1472	1.03	0.87	1.21	0.75
PPARGrs_1801282	1477	1.11	0.88	1.39	0.39
WFS1rs10010131	1473	0.89	0.76	1.04	0.15
JAZF1rs864745	1473	1.16	0.99	1.36	0.07
SLC30A8_rs13266634	1478	1.04	0.88	1.23	0.66
CDKAL1rs7754840	1446	1.05	0.88	1.25	0.59
TCF7L2_rs7903146	1467	0.81	0.68	0.97	0.02
TCF7L2_rs7903146[b]	974	0.94	0.65	1.36	0.74
ADAMTS9_rs4607103	1460	1.22	1.01	1.48	0.04
ADAMTS9_rs4607103 [b]	990	0.87	0.59	1.27	0.47
ADCY5_rs2877716	1239	0.99	0.81	1.22	0.94
CAMK1D_rs1277979	1451	0.92	0.75	1.13	0.44
GIPR_rs10423928	1326	0.87	0.71	1.07	0.19
HNF1B_TCF2_rs757210	1444	1.21	1.03	1.43	0.02
HNF1B_TCF2_rs757210 [b]	996	1.38	1.01	1.88	0.04
KCNQ1_rs231362	1200	0.95	0.79	1.14	0.57
MTNR1B_rs183963	1308	0.86	0.72	1.03	0.11
NOTCH2_rs1923931	1283	0.73	0.55	0.95	0.02
NOTCH2_rs1923931	866	1.23	0.74	2.07	0.42
THADA_rs7578597	1295	0.96	0.71	1.28	0.76
TSPAN8_rs7961581	1291	1.26	1.04	1.54	0.02
TSPAN8_rs7961581 [b]	990	0.86	0.61	1.20	0.37
DCD_rs1153188	1293	1.16	0.95	1.41	0.15

(*Continues*)

Table 4 (continued)

CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphisms.
[a]MPP-RES UCG, adjusted for sex, age, SBP, DBP, AHT, diabetes.
[b]VARA UCG, also analysed in VARA UCG.

Diastolic dysfunction and diabetes

Subclinical diastolic dysfunction is widespread in the diabetic population with a prevalence ranging from 25% to 78%.[3–5,25] In the MPP-RES UCG cohort, the prevalence of any degree of diastolic dysfunction was 68% regardless of diabetes status. However, the cohort was originally designed to study patients with glucometabolic disturbances (37% of subjects had diabetes), which can explain the higher occurrence of diastolic dysfunction in the MPP-RES UCG cohort[14] compared with the VARA UCG cohort where only 7.2% of the population had prevalent diabetes (*Tables 1 and 2*).

Genetic susceptibility for diabetes and association with cardiovascular disease

A large meta-analysis using Mendelian randomization previously supported a causal relationship between diabetes and coronary heart disease by showing that increased genetic risk of diabetes leads to increased risk of coronary heart disease.[26] In the CARDIOGRAM cohort, 44 genetic variants associated with diabetes were analysed; 10 SNPs were found significantly associated with coronary artery disease (CAD). It was, however, surprising that the effects on CAD risk by the diabetes-related SNPs reported in this study appeared to be by far lower than what would be expected based on the effects of risk alleles on diabetes.[11] One possible explanation to these findings might be that diabetes related SNPs impact on future CAD is mediated and driven by early subclinical signs of heart disease (e.g. diastolic dysfunction) and atherosclerosis.

Table 5 HNF1B rs757210 association with grades of diastolic dysfunction

DD grade	MPP-RES UCG				VARA UCG			
	n	OR[a]	95% CI	*P*-value	*n*	OR[a]	95% CI	*P*-value
I	561	1.0 (referent)			863	1.0 (referent)		
II	736	1.21	1.01–1.45	0.036	133	1.38	1.01–1.88	0.042
III + IV	337	1.27	1.02–1.58	0.033	0	NA	NA	NA

DD, diastolic dysfunction: I normal, II impaired relaxation, III pseudonormaliz, IV restrictive; MPP-RES, Malmö Preventive Project-Re-examination echocardiography; NA, no subjects with DD Grade III + IV in the VARA UCG cohort; OR, odds ratio; UCG, echocardiography.
[a]adjusted for sex, age, systolic blood pressure, diastolic blood pressure, antihypertensive treatment and diabetes status.

Qi *et al*.[10] combined 36 genetic variants predisposing to diabetes and showed that this genetic predisposition score was associated with increased risk of CVD in patients with diabetes. However, this finding was significantly weakened after adjusting for HbA1c, suggesting that the genetic predisposition might actually reflect the degree of hyperglycemia.

In a study from the European Prospective Investigation in to Cancer and Nutrition Norfolk study, 38 common genetic variants associated with diabetes were analysed and found to be associated with CAD.[27] Similar to the above-mentioned study, most of the associations was attenuated when adjusting for incident and prevalent diabetes. However, one of the 38 SNPs, *CDKAN2A/B rs564398,* remained significantly associated with incident coronary disease even after adjusting for incident and prevalent diabetes and may represent a glucose–insulin independent link between coronary heart disease and diabetes, which warrants further studies in line with our findings.

In a recent study following 6501 subjects over 17 years, genetic predisposition to diabetes was associated with all-cause mortality after adjusting for BMI, social, and lifestyle factors and traditional clinical risk factors.[28] Based on their findings, they suggested that lifestyle intervention, for example, weight control, may be especially important for lowering mortality risk in individuals with a high genetic predisposition for diabetes. This line of reasoning may be applicable to our findings, where a genetic predisposition to diastolic dysfunction in an individual, may warrant lifestyle and/or pharmaceutical intervention.

Interestingly, in a cross-sectional study, the same research group analysed genetic predisposition to diabetes and association with subclinical atherosclerosis including coronary artery or abdominal aortic calcium score, common and internal carotid artery intima-media thickness, and ankle-brachial index but were unable to find any association.[29] This parallels our study, as it is reasonable to suggest that subclinical diastolic dysfunction is to the diabetic heart, what subclinical atherosclerosis is to the diabetic vessels. However, in our study, although the analyses of associations between UCG findings and genetic variants were cross-sectional and thus not eligible for any conclusions regarding causality, we found an association between genetic predisposition to diabetes and subclinical cardiac dysfunction. This warrants further studies because diastolic dysfunction can progress to clinical heart failure and is the very hallmark of heart failure with preserved ejection fraction for which there is no convincing treatment.[30,31]

Study limitations

An important strength of the current study is the use of two well-characterized prospective community-based large UCG cohorts. Our discovery cohort and replication cohort differ in many baseline characteristics that are central in the assessment of diastolic dysfunction such as age, prevalence of hypertension and diabetes which may have influenced the results. However, we tried to adjust for these differences in the multivariable logistic regression analysis. The cross-sectional nature of the study prevents any conclusions concerning causality of the findings regarding HNF1B *rs757210* and prevalent diastolic dysfunction.

Clinical implications

Diabetes is an independent risk factor for heart failure and its earliest manifestation of left ventricular dysfunction is diastolic dysfunction, which progresses to clinical heart failure[30] and is in itself associated with increased mortality.[2] Studies suggest that this myocardial decline begins even in the prediabetic stage.[12,13] Common genetic pathways between diabetes and CVD can possibly not only identify patients with high risk of developing cardiovascular complications and benefitting from heightened clinical vigilance but also provide future drug targets.

Conclusions

Our findings suggest a possible common genetic susceptibility to diabetes and diastolic dysfunction through HNF1B *rs757210*, which is also associated with increased incidence of cardiovascular disease.

Conflict of interest

None declared.

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Authors' contributions

JM, PMN, ML, UL, LB, LR, BD, VL and MM contributed to study concept and design. JM, ML, BD, UL and MM acquired data. JM, AJ, ML, BD and MM analysed and interpreted data. JM, PMN, BD and MM drafted the manuscript. JM, AJ, PMN, ML, UL, LR, LB, BD, VL and MM critically revised the manuscript for important intellectual content. JM, AJ, PMN, ML, LB, LR, UL, BD, VL, MM contributed to statistical analysis. UL, LR and MM obtained funding. PMN provided administrative, technical, or material support. JM, BD, UL, LR and MM supervised the study. JM, UL, BD, LR and MM are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval and consent to participate

The study was approved by The Ethics committee at Lund University, Sweden (MPP-RES and MPP-RES UCG cohorts) and at the University of Gothenburg, Sweden (VARA UCG).

Consent for publication

All participants in this study signed a written informed consent form.

Availability of data and material

Data will be available upon request.

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