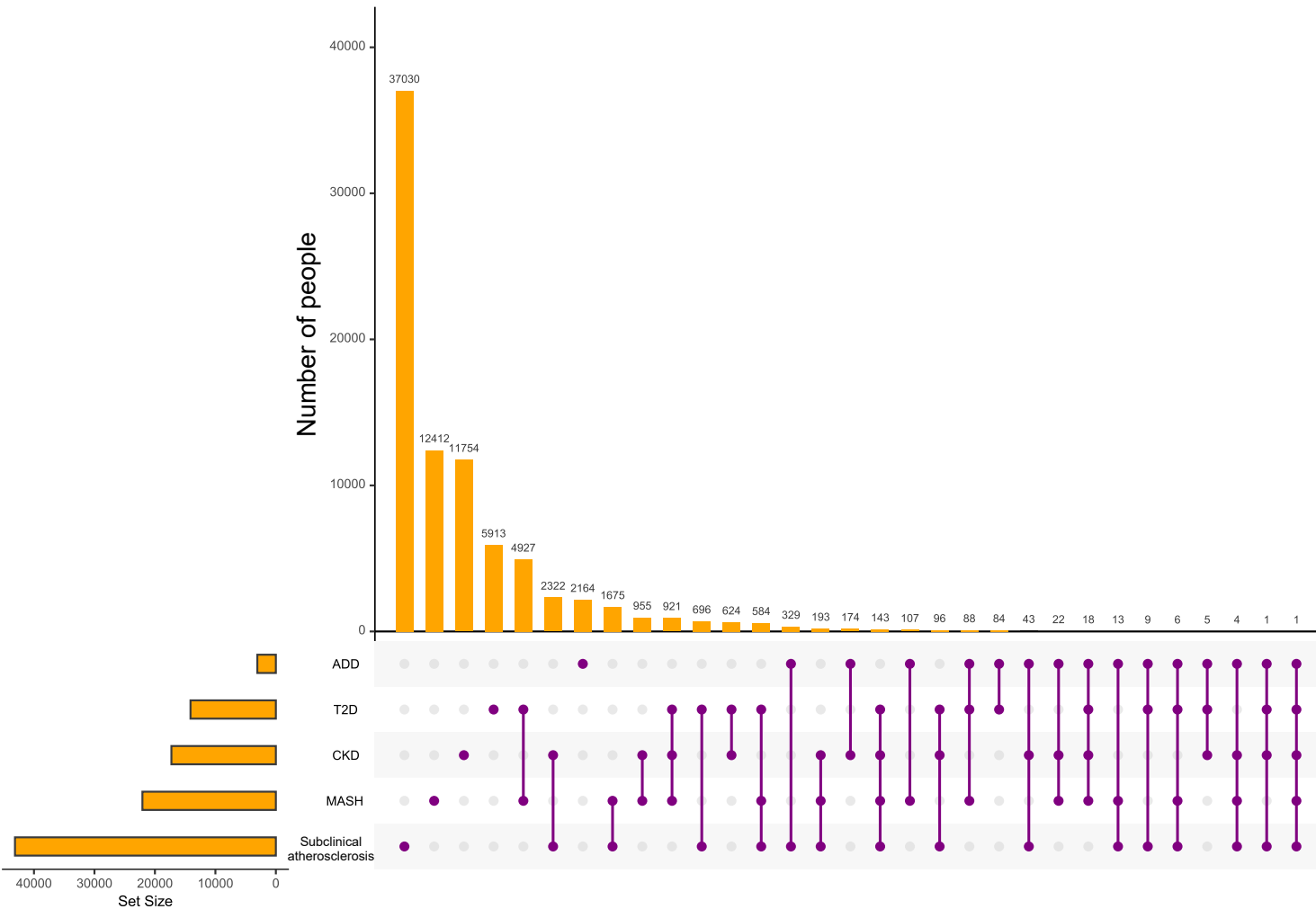
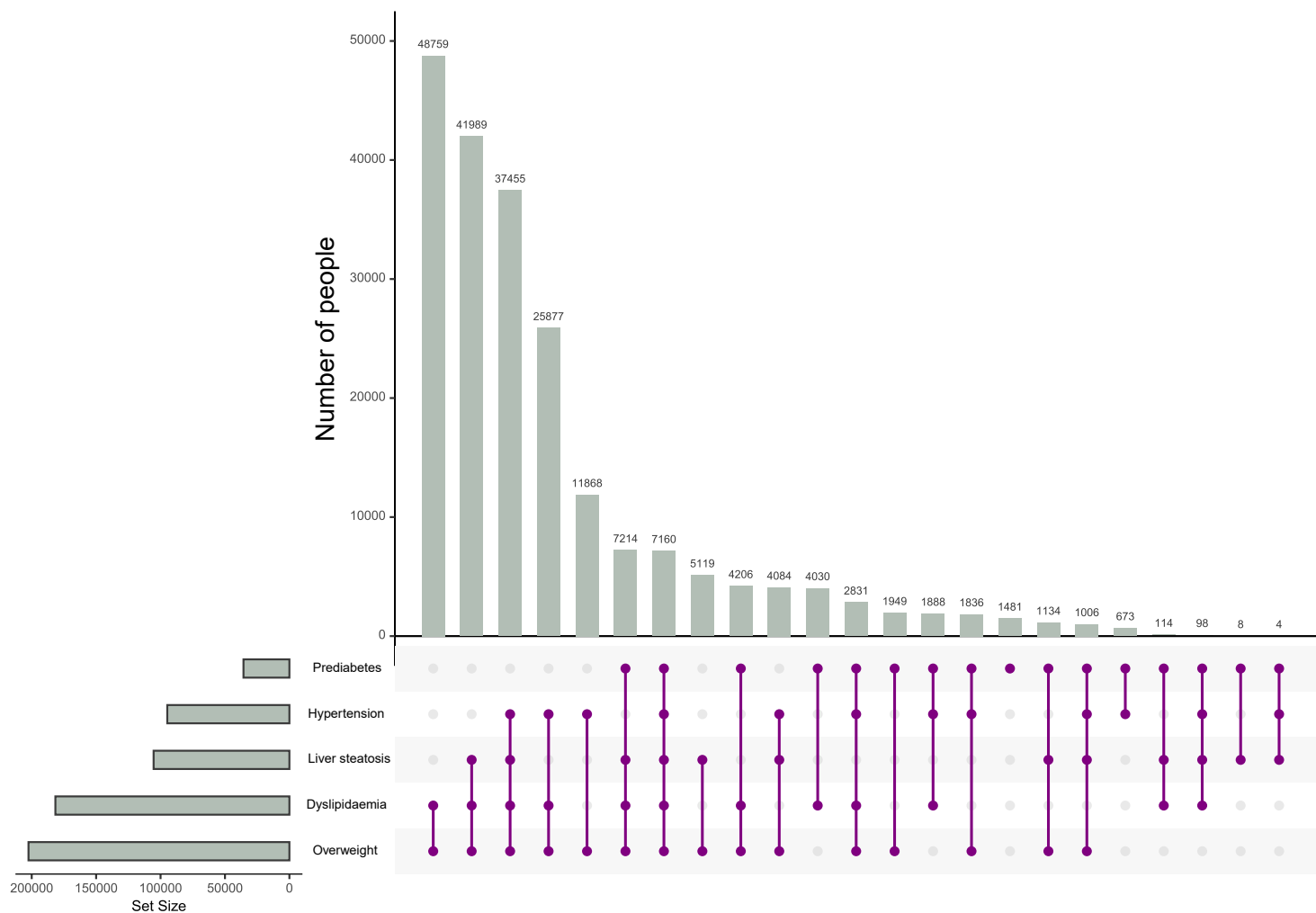


Supplementary figure 1

UpSet plot showing disease distribution in individuals with SMD stage 1 (upper) or stage 2 (lower) among Europeans from the UK Biobank.

The defining criteria for stages 1 and 2 are described in the legend to Figure 5. Individuals who met the criteria for both stages were excluded from stage 1.

The horizontal bars show the total number of individuals with each condition in stages 1 and 2. The presence of only one condition (single circles) and every possible combination (circles connected by vertical lines) are represented by the bottom plots for each stage, and their occurrence is shown by the vertical bars.



Supplementary tables

Supplementary Table 1 How to diagnose asymptomatic diastolic dysfunction and HFpEF¹⁻⁸

	Diagnostic criteria
Asymptomatic diastolic dysfunction	
Echocardiography	Preserved LV function (LVEF $\geq 50\%$) Absence of significant valve disease, and: <u>Resting echocardiography</u> At least three of the following criteria -E/e' average >14 -TR velocity >2.8 m/s -LA volume index >34 mL/m² -Septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s
HFpEF	
Clinical symptoms and signs	Dyspnoea and congestion. See guidelines for additional symptoms and signs. ³
Natriuretic peptides*	BNP: Sinus rhythm ≥ 10 pmol/L (35 pg/mL) Atrial fibrillation ≥ 31 pmol/L (105 pg/mL) NT-proBNP: Sinus rhythm ≥ 15 pmol/L (125 pg/mL) Atrial fibrillation ≥ 43 pmol/L (365 pg/mL)
Echocardiography**	<u>Resting echocardiography:</u> LVEF $\geq 50\%$ Concentric LV hypertrophy or concentric LV remodelling Increased LV mass index or relative mass index: LV mass index ≥ 95 g/m² for women or 115 g/m² for men Relative wall thickness >0.42 Increased LA pressure is diagnosed if at least 2 of the following criteria are met (except when E/A ratio is 0.8 and peak E velocity is ≤ 0.5 cm/s, when LA pressure is considered low): -average E/e' > 14 -LA volume index > 34 mL/m² -TR jet > 2.8 m/s <u>Exercise echocardiography</u> (when resting echocardiography criteria for increased left atrial pressure are not met but clinical suspicion of HFpEF): -average E/e' >14 or septal E/e' ratio > 15 with exercise -peak TR velocity > 3.4 m/s with exercise
Invasive hemodynamic testing (right heart catheterization) – gold standard	<u>Resting invasive haemodynamic test:</u> - PCWP ≥ 15 mmHg - LVEDP ≥ 16 mmHg <u>Exercise haemodynamic test</u> - PCWP ≥ 25 mmHg - LVEDP ≥ 20 mmHg
Multiparameter risk scores***	H₂FPEF HFA-PEFF

*The BNP and NT-proBNP thresholds apply for the diagnosis of chronic heart failure. Higher cutoffs apply for the diagnosis of acute decompensated heart failure.⁶

BNP and NT-proBNP levels in individuals with HFpEF may be lower if they are living with obesity, and cut-offs about 50% lower have therefore been proposed for these people.³ More than 30% of individuals with HFpEF have normal natriuretic peptide values especially if ≥ 1 of the following conditions apply: obesity, young age, normal kidney function. False-positive results are also common; conditions that can cause elevated BNP or NT-proBNP in the absence of heart failure include older age, female sex, atrial fibrillation, valve disease, CKD, acute coronary syndromes, myocarditis, cardiac surgery, cardioversion, anaemia, lung disease, critical illness.

More stringent criteria defined as major criteria in the HFA-PEFF Score are:

- BNP: sinus rhythm >24 mmol/L (80 pg/mL); atrial fibrillation >72 mmol/L (240 pg/mL)
- NT-proBNP: sinus rhythm >26 mmol/L (220 pg/mL); atrial fibrillation >79 mmol/L (660 pg/mL).

**Although the presence of concentric left ventricular hypertrophy or remodelling is supportive, the absence of LV hypertrophy/remodelling does not exclude the diagnosis of HFpEF.

The lower cutoff average E/e' ratio at rest >9 has been proposed.⁴ However, while more sensitive it has low specificity for the presence of HFpEF by invasive hemodynamic testing.

***H₂FPEF score: Heavy (BMI >30 kg/m²), Hypertensive (use of ≥ 2 antihypertensive medications), atrial Fibrillation (paroxysmal or persistent), Pulmonary hypertension (Doppler echocardiographic estimated pulmonary artery systolic pressure >35 mm Hg), Elderly (age >60 years), Filling pressure (Doppler echocardiographic E/e' >9).

HFA-PEFF score: Heart Failure Association of ESC diagnostic algorithm, P (Pretest assessment), E (Echocardiographic and natriuretic peptide score), F1 (Functional testing in case of uncertainty), F2 (Final aetiology).

Abbreviations: E/e', ratio of the peak early mitral inflow velocity (E) over the early diastolic mitral annular velocity (e'). LA, left atrial; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; TR, tricuspid regurgitation.

Supplementary Table 2 Measurements for the identification of visceral adiposity

Measurement	Advantages	Disadvantages
BMI (weight/height ²)	Simple, quick, and inexpensive.	Does not identify excess adiposity or fat distribution and function.
Waist circumference (WC) ^a	Simple, quick and inexpensive; better predictor than BMI of metabolic risk.	Does not discriminate between subcutaneous and visceral adiposity.
Waist to hip ratio ^a	Simple and inexpensive.	Not a good predictor of body fat percentage; sex and ethnic differences.
Waist to height ratio ^a	Simple and inexpensive; predictive value of early risk; single cut-off value; no sex and ethnic differences.	
Dual X-ray absorptiometry (DEXA)	Accurate detection of whole-body fat mass with the possibility for regional analysis.	Costly; mainly available in hospital setting; involves low exposure to radiation.
Imaging techniques: computed tomography (CT) and magnetic resonance imaging	Accurate, quantitative, reliable assessment equivalent to visceral fat volume measurement; determination of intra-abdominal adipose tissue.	Costly; available only in hospital setting; involves radiation in case of CT.
Visceral Adiposity Index (VAI): calculated using BMI, WC, triglycerides and HDL cholesterol.	Accurate, reliable, low-cost, and widely available indicator of visceral adiposity; inverse association with insulin sensitivity; independently associates with SMD risk.	Less applicable and useful in severe obesity; needs validation in non-white populations.

^aUse in combination with BMI to assess the risk of obesity-related mortality

References

1. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. *J Am Coll Cardiol*. 2023;**81**:1810-1834. doi:10.1016/j.jacc.2023.01.049
2. Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, *et al*. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;**81**:1835-1878. doi:10.1016/j.jacc.2023.03.393
3. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, *et al*. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail*. Published online March 1, 2021:S1071-9164(21)00050-6. doi:10.1016/j.cardfail.2021.01.022
4. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal*. 2021;**42**:3599-3726. doi:10.1093/eurheartj/ehab368
5. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, *et al*. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;**17**:1321-1360. doi:10.1093/ehjci/jew082
6. Mueller C, McDonald K, De Boer RA, Maisel A, Cleland JGF, Kozhuharov N, *et al*. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *European J of Heart Fail*. 2019;**21**:715-731. doi:10.1002/ehjhf.1494
7. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, *et al*. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J*. 2019;**40**:3297-3317. doi:10.1093/eurheartj/ehz641
8. Desai AS, Lam CSP, McMurray JJV, Redfield MM. How to Manage Heart Failure With Preserved Ejection Fraction: Practical Guidance for Clinicians. *JACC Heart Fail*. 2023;**11**:619-636. doi:10.1016/j.jchf.2023.03.011