

Lifetime obesity trends are associated with subclinical myocardial injury: The Trøndelag health study

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Abstract. Lyngbakken MN, de Lemos JA, Hveem K, Røsjø H, Omland T. Lifetime obesity trends are associated with subclinical myocardial injury: The Trøndelag health study. *J Intern Med.* 2021;00:00-00. <https://doi.org/10.1111/joim.13391>

Background. Obesity is associated with subclinical myocardial injury as quantified by concentrations of cardiac troponin T, but whether lifetime excess weight history is associated with increased concentrations of cardiac troponin I (cTnI) and how indices of abdominal adiposity and glycemc dysregulation affect these associations remain unclear.

Methods. We analyzed cTnI with a high-sensitivity assay in 9739 participants in the Trøndelag Health (HUNT) Study at study visit 4 (2017–2019). BMI was assessed at study Visit 1 (1984–1986), 2 (1995–1997), 3 (2006–2008), and 4.

Results. Median age at visit 4 was 68.7 years and 59% were women. Concentrations of cTnI were detectable in 84.1% of study participants, with a

median of 2.5 (1.5–4.5 ng/L). We identified three clusters of BMI trajectories from visit 1 to 4, (1) stable normal weight, (2) stable overweight, and (3) stable obesity. Participants in clusters 2 and 3 were at increased risk of elevated concentrations of cTnI at visit 4 (odds ratio 1.27, 95% CI 1.09–1.47, and odds ratio 1.70, 95% CI 1.33–2.17, *p* for trend <0.001). Participants in cluster 3 had 22.0 (95% CI 14.1–29.9%) higher concentrations of cTnI compared to participants in cluster 1 (*p* for trend <0.001). Dysregulated glucose metabolism and abdominal obesity did not influence our results.

Conclusions. Individuals with stable overweight or obesity are at increased risk of subclinical myocardial injury, independently of glycemc dysregulation and abdominal adiposity. Our data support a direct detrimental effect of long-standing obesity on cardiovascular health.

Keywords: epidemiology, troponin, obesity, cardiovascular risk factors

Introduction

Obesity is an independent risk factor for cardiovascular (CV) disease and a growing worldwide health issue [1]. Cardiac troponins strongly predict unfavorable CV outcomes and reflect subclinical myocardial injury in presumably healthy individuals from the general population [2]. Higher body mass index (BMI), and particularly severe obesity (BMI \geq 35 kg/m²), independently associates with cardiac troponin T (cTnT) in community dwellers

[3]. Longitudinal obesity exposure is additionally associated with increased concentrations of cTnT [4]. Obesity is closely associated with the risk of diabetes mellitus, and increased concentrations of glycated hemoglobin (HbA1c) are associated with increased concentrations of cTnT [5]. Less is known about the associations of longitudinal trends in obesity with concentrations of cardiac troponin I (cTnI). Prior investigations have also failed to take into account the impact of glycemc dysregulation and body fat distribution on cardiac troponin

concentrations, as both these variables may confound the association of obesity with subclinical myocardial injury [6]. Most studies on obesity and subclinical myocardial injury have focused mainly on cross-sectional associations and shorter follow-up time with a limited longitudinal assessment of BMI. Moreover, as BMI is an incomplete characterization of obesity, especially with regard to different metabolic phenotypes and body composition, there is a need to assess also additional indices of obesity when characterizing the association between obesity and subclinical CV disease. Excessive visceral adipose tissue is associated with increased CV risk, and more strongly so than BMI [7]. Accordingly, using a large cohort of community dwellers with several assessments of BMI over a time span of 35 years, we investigated the impact of longitudinal obesity exposure on the risk of subclinical myocardial injury and how these associations would compare to those of the most recent assessment of BMI. We further assessed the influence of body composition, degree of glycemia, and prevalent diabetes mellitus on the association between obesity and subclinical myocardial injury.

Methods

Study overview

The Trøndelag Health (HUNT) Study is the largest population-based cohort in Norway, with more than 150,000 participants from Trøndelag County. Four study visits have so far been conducted; HUNT 1 ($n = 77,212$, 1984–1986), HUNT 2 ($n = 65,237$, 1995–1997), HUNT 3 ($n = 50,807$, 2006–2008), and HUNT 4 ($n = 56,078$, 2017–2019) [8]. Of the initial 77,212 participants from HUNT 1, 18,896 participants (24.5%) have attended all subsequent study visits. The HUNT Study was approved by the Regional Committee for Medical Research Ethics (REC 2012/859 and REC 2016/801) and the Norwegian Data Inspectorate Board and all participants provided informed written consent.

Participants

The present analysis includes 9739 participants with valid measurement of BMI at all four HUNT study visits and measurement of cTnI at HUNT 4. Participants with a BMI < 18.5 kg/m² at any study visit ($n = 213$), or history of angina pectoris ($n = 617$), myocardial infarction ($n = 630$), heart failure ($n = 251$), atrial fibrillation ($n = 771$), or stroke ($n = 465$) at HUNT 4 were excluded from the analy-

ses. Information on demographics and medical history were acquired from questionnaires completed at study baseline. Higher education was defined as more than 12 years of formal education equaling college or university level. Clinical examination including waist and hip circumference and blood pressure was performed at study baseline.

Body composition measurements

Body composition was analyzed by bioelectrical impedance at HUNT 4 using the InBody 770 Body Composition Analyzer (InBody Co., Ltd., Seoul, Korea). Study participants stand barefoot on feet electrodes with their arms holding hand electrodes, and low- and high-frequency alternating currents are sent through the body. The impedance of the current is measured from different body compartments, and is used to determine various body composition measurements, including intracellular and extracellular water (totaling total body water), body fat mass, soft lean mass, fat-free mass, skeletal muscle mass, percent body fat, visceral fat level, and area. Body height and weight were measured during the same session, and BMI was calculated as body weight (in kilograms) divided by squared body height (in meters). We calculated body surface area according to the Mosteller formula [9].

Blood sampling procedures and biochemical assays

cTnI was measured with a high-sensitivity assay from Abbott Diagnostics (ARCHITECT STAT High Sensitive Troponin) from fresh, nonfasting serum samples collected at HUNT 4. All samples were collected by trained nurses, centrifuged at room temperature and serum aspirated. The samples were kept at 4°C and shipped to the Department of Medical Biochemistry, Nord-Trøndelag Hospital Trust, Levanger, Norway, for cTnI analysis within 24 h. The limit of quantification (LoQ) for this assay is reported to be 3.5 ng/L and the limit of detection (LoD) 1.2 ng/L [10]. Concentrations below the LoD were assigned a value of 0.6 ng/L. The assay coefficient of variation is 20% at 1.3 ng/L, 10% at 4.7 ng/L, and 4% at 26.2 ng/L [11]. Precision profile for cTnI with coefficients of variation in the high and low concentrations ranges from our laboratory is presented in Figure S1. For both high and low concentrations of cTnI, we observed a coefficient of variation $< 8\%$ for all laboratory runs. Glomerular filtration rate was estimated (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation [12]. C-reactive protein (CRP), total

cholesterol, and HDL cholesterol were measured from fresh, nonfasting serum samples and HbA1c from fresh, nonfasting whole blood samples on the Architect ci8200 (Abbott Diagnostics).

Statistical methods

Baseline data are reported as absolute numbers (proportion) or median (interquartile range [IQR]) unless otherwise stated. Continuous variables were analyzed using the Mann–Whitney *U* test, and categorical variables with the Fisher exact test. We used latent class analysis to identify clusters of study participants with similar BMI trajectories. Latent class analysis is a method for the analysis of clustering among observations of qualitative and categorical variables. The central principle is to fit a model where the quantitative variables can be explained by a single unobserved “latent” categorical variable. We assumed that specific groups existed according to BMI measurements at study visit 1 through 4, and we fitted a model that clustered study participants into such unobserved groups based on the historical BMI information. We used the *gsem* command (generalized structural equation modeling) to fit the latent class model, and used the predictions of the posterior probabilities to designate cluster membership. We derived latent class clusters using maximum-likelihood estimation over 20 iterations to identify the most common BMI trajectories for 2-, 3-, 4- and 5-class models. The optimal number of clusters was determined using the Bayesian information criterion, and we aimed to classify at least 5% of study participants to each cluster. Models were compared with the Lo–Mendell–Rubin likelihood ratio test. The quality of classification was assessed by entropy statistics (range 0–1, higher values indicating better model classification). We analyzed concentrations of cTnI according to sex-specific cut-offs at 4 ng/L for women and 6 ng/L for men [13], as well as a continuous outcome. We further assessed concentrations of cTnI according to the sex-specific 99th percentiles at 16 ng/L for women and 34 ng/L for men [14]. Continuous concentrations of cTnI were transformed with a natural logarithm prior to regression analyses due to right skewed distribution. Logistic regression was used to assess the associations of BMI trajectories with cTnI as a dichotomized outcome, and linear regression was used to assess the associations with cTnI as a continuous outcome. Due to biomarker transformation with a natural logarithm, coefficients from the linear regression models were interpreted

as proportional differences [15]. All models were adjusted for sex, age, and a priori selected variables influencing CV risk (eGFR, total and HDL cholesterol, CRP, higher education, heart rate, treatment for hypertension, systolic blood pressure, diabetes mellitus, smoking status, visceral fat area, HbA1c). We additionally adjusted for statin therapy, as statin therapy may attenuate concentrations of cTn [16], and body surface area, as body surface area associates with left ventricular mass and concentrations of cardiac troponin [17]. To further account for the impact of glycemic dysregulation and abdominal adiposity, we performed interaction analysis according to prevalent diabetes mellitus. Participants with missing covariate data were excluded from the multivariable regression analyses. Statistical significance was assumed at $p < 0.05$. The analyses were performed with STATA 16 (StataCorp LP, College Station, TX).

Results

The median age at HUNT 4 was 68.7 (range 52.6–101) years and 59% were women. Concentrations of cTnI were detectable in 84.1% of study participants, with median 2.5 ng/L (IQR, 1.5–4.5 ng/L). The distributions of BMI at HUNT 1 to HUNT 4 are illustrated in Figure 1. Based on the indices of model fit classification and the aim to classify at least 5% of study participants to each cluster of BMI trajectories, a 3-class model provided the best fit (Table S1). The entropy was good for all models (>0.80). The BMI trajectories of the three clusters are illustrated in Figure 2, and were phenotypically (1) stable normal weight (47.8% of study participants), (2) stable overweight (42.3%), and (3) stable obesity (9.9%). Compared to the 3-class model, the 4- and 5-class models merely subclassified the most obese participants and are illustrated in Figures S2 and S3.

Baseline characteristics at study visit 4 according to BMI trajectories are outlined in Table 1. Compared to cluster 1 (stable normal weight), participants in cluster 3 (stable obesity) were older with higher systolic blood pressure and more frequently diabetes mellitus. They were less frequently current smokers, had less frequently higher education, and demonstrated a more unfavorable body composition with increased body fat mass, body fat percentage, and more central adiposity. Concentrations of cTnI were higher, and the proportion of participants with detectable concentrations of cTnI was accordingly higher (Figure 3).

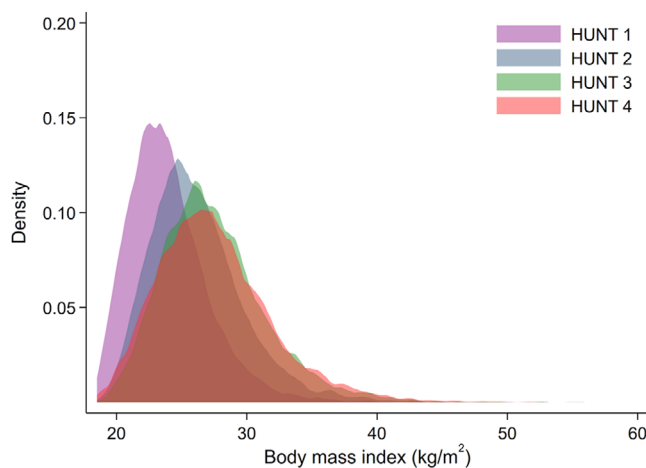


Fig 1 Distributions of body mass index from HUNT 1 to HUNT 4.

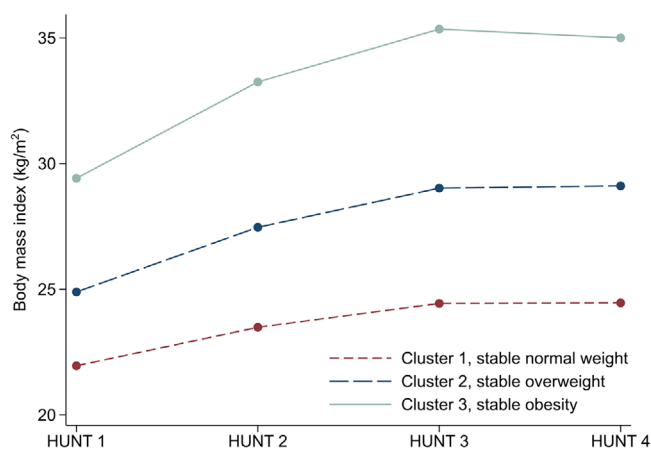


Fig 2 Body mass index trajectories from HUNT 1 to HUNT 4.

Associations of BMI trajectories with cardiac troponin I

Study participants in clusters 2 and 3 were at increased risk of elevated concentrations of cTnI (p for trend <0.001), and participants in cluster 3 had the highest risk (odds ratio 1.70, 95% CI 1.33–2.17, Table 2). The associations with cTnI concentrations above the sex-specific 99th percentile were weaker and not significant for participants in cluster 3 (odds ratio 1.71, 95% CI 0.92–3.15, Table S2). There was a linear increase in concentrations of cTnI with clusters of BMI trajectories (p for trend <0.001), and participants in cluster 3 had 22.0% (95% CI 14.1–29.9) higher concentrations of cTnI compared to participants in cluster 1 (Table 2). The complete results of the regression models are described in Tables S3 and S4. Adjustments for age, renal function, hypertension, and body surface area most strongly influenced the associations between BMI trajectories and concentrations

of cTnI (Table S5). Contrary to the models clustering study participants as stable normal weight, stable overweight, and stable obesity, there was no apparent increased risk of elevated concentrations of cTnI in participants who were overweight and obese at study visit 4 (p for trend = 0.12). Overweight and obese participants at study visit 4 had higher concentrations of cTnI compared to normal weight subjects (p for trend = 0.007, Table 3). BMI and body weight at study visit 4 exhibited comparable associations with subclinical myocardial injury, and more strongly so than body fat mass and visceral fat area (Table S6). The associations of longitudinal stable overweight and stable obesity with concentrations of cTnI were stronger than those of cross-sectionally classified overweight and obesity, for both elevated concentrations of cTnI (p for comparison between adjusted models = 0.012) and continuous concentrations of cTnI (p for

Table 1. Baseline characteristics at HUNT 4 according to BMI trajectories

	Cluster 1, stable normal weight		Cluster 2, stable overweight		Cluster 3, stable obesity		<i>p</i> for trend
	<i>N</i>	Value	<i>n</i>	Value	<i>n</i>	Value	
Male sex, <i>n</i> (%)	4655	1658 (35.6%)	4117	1946 (47.3%) ^b	967	344 (35.6%)	<0.001
Age, years	4655	67.6 (61.7–74.1)	4117	69.5 (63.1–75.6) ^b	967	69.7 (63.5–75.8) ^b	<0.001
Body mass index, kg/m ²							
HUNT 1	4655	21.9 (20.7–23.1)	4117	24.8 (23.6–26.2) ^b	967	29.2 (27.3–31.2) ^b	<0.001
HUNT 2	4655	23.6 (22.3–24.7)	4117	27.4 (26.3–28.7) ^b	967	32.7 (31.2–34.7) ^b	<0.001
HUNT 3	4655	24.6 (23.1–25.8)	4117	28.9 (27.6–30.3) ^b	967	34.8 (33.2–37.1) ^b	<0.001
HUNT 4	4655	24.5 (22.8–26.1)	4117	29.0 (27.4–30.8) ^b	967	34.9 (32.3–37.5) ^b	<0.001
Current smoking, <i>n</i> (%)	4569	474 (10.4%)	4005	287 (7.2%) ^b	937	70 (7.5%) ^a	<0.001
Higher education, <i>n</i> (%)	4563	1277 (28.0%)	4006	944 (23.6%) ^b	933	159 (17.0%) ^b	<0.001
Diabetes mellitus, <i>n</i> (%)	4538	173 (3.8%)	3945	388 (9.8%) ^b	932	226 (24.2%) ^b	<0.001
Antihypertensive therapy, <i>n</i> (%)	4655	1179 (25.3%)	4117	1794 (43.6%) ^b	967	597 (61.7%) ^b	<0.001
Statin therapy, <i>n</i> (%)	4655	812 (17.4%)	4117	1010 (24.5%) ^b	967	304 (31.4%) ^b	<0.001
Waist-to-hip ratio	4421	0.93 (0.89–0.97)	3869	1.00 (0.95–1.04) ^b	891	1.04 (0.98–1.10) ^b	<0.001
Heart rate, bpm	4451	70 (63–78)	3917	71 (64–80) ^b	923	74 (66–83) ^b	<0.001
Systolic blood pressure, mm Hg	4641	133 (121–146)	4103	136 (125–148) ^b	965	138 (126–150) ^b	<0.001
Diastolic blood pressure, mm Hg	4641	74 (67–80)	4103	74 (68–81) ^b	965	73 (66–80)	<0.001
Fat free mass, kg	4282	46.5 (41.9–55.8)	3740	53.2 (45.6–63.7) ^b	840	53.4 (47.4–65.0) ^b	<0.001
Body fat mass, kg	4282	20.7 (16.6–25.1)	3740	29.3 (24.8–34.4) ^b	840	41.6 (35.3–48.3) ^b	<0.001
Body fat, %	4282	30.5 (24.2–35.8)	3740	36.1 (29.4–41.7) ^b	840	43.7 (37.7–48.7) ^b	<0.001
Visceral fat area, cm ²	4282	100.7 (77.5–129.2)	374	150.3 (120.2–182.0) ^b	840	211.4 (180.3–239.6) ^b	<0.001
Total cholesterol, mg/dl	4655	224 (193–251)	4117	213 (186–244) ^b	967	201 (174–232) ^b	<0.001
HDL cholesterol, mg/dl	4655	58 (50–70)	4117	50 (43–62) ^b	967	50 (43–58) ^b	<0.001
HbA1c, %	4647	5.3 (5.1–5.5)	4102	5.4 (5.2–5.7) ^b	958	5.6 (5.3–6.1) ^b	<0.001
HbA1c < 5.7%, <i>n</i> (%)	4647	4165 (89.6%)	4102	3210 (78.3%) ^b	958	582 (60.8%) ^b	<0.001
HbA1c 5.7–6.4%, <i>n</i> (%)	4647	368 (7.9%)	4102	613 (14.9%) ^b	958	209 (21.8%) ^b	<0.001
HbA1c ≥ 6.5%, <i>n</i> (%)	4647	114 (2.5%)	4102	279 (6.8%) ^b	958	167 (17.4%) ^b	<0.001
eGFR, ml/min/1.73 m ²	4655	84.0 (72.0–92.0)	4117	81.0 (68.0–90.0) ^b	967	80.0 (66.0–91.0) ^b	<0.001
CRP, mg/L	4655	1.1 (0.6–2.3)	4117	1.6 (0.9–3.3) ^b	967	2.3 (1.2–4.7) ^b	<0.001
Detectable cardiac troponin I, <i>n</i> (%)	4655	3717 (79.8%)	4117	3590 (87.2%) ^b	967	880 (91.0%) ^b	<0.001
Cardiac troponin I, ng/L	4655	2.2 (1.3–3.9)	4117	2.8 (1.7–5.0) ^b	967	3.2 (1.9–5.6) ^b	<0.001
Elevated cardiac troponin I, <i>n</i> (%)	4655	852 (18.3%)	4117	1045 (25.4%) ^b	967	305 (31.5%) ^b	<0.001
Cardiac troponin I above sex-specific 99th percentile, <i>n</i> (%)	4655	112 (2.4%)	4117	129 (3.1%)	967	35 (3.6%)	0.034

p compared to Cluster 1:^a<0.01^b<0.001. To convert cholesterol concentrations from mg/dl to mmol/L, multiply by 0.02586. Detectable cardiac troponin I, above or at limit of detection (1.2 ng/L). Elevated cardiac troponin I, ≥4 ng/L for women and ≥6 ng/L for men. Sex-specific 99th percentile of cardiac troponin I, ≥16 ng/L for women and ≥34 ng/L for men.

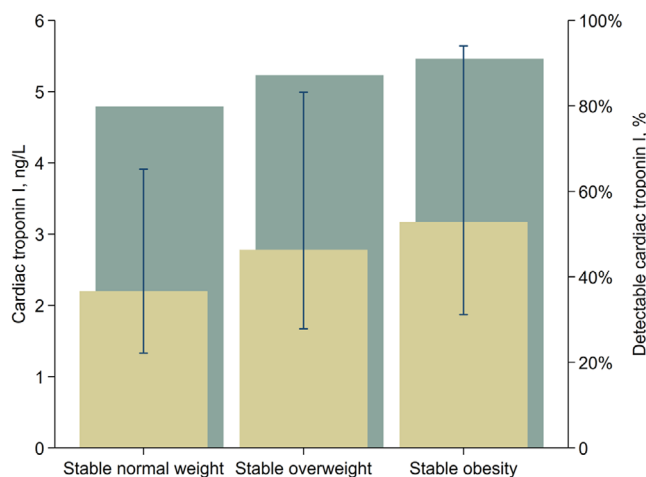


Fig 3 Median concentrations of cardiac troponin I (khaki) and proportion of subjects with detectable cardiac troponin I (teal). Whiskers (navy) represent interquartile range of median concentrations of cardiac troponin I.

Table 2. Association of BMI trajectories with cardiac troponin I at HUNT 4

	Model 1	Model 2	Model 3
Odds ratio (95% CI) of elevated cardiac troponin I			
Cluster 2, stable overweight	1.52 (1.37–1.68)	1.34 (1.20–1.50)	1.27 (1.09–1.47)
Cluster 3, stable obesity	2.06 (1.76–2.40)	1.95 (1.65–2.30)	1.70 (1.33–2.17)
<i>p</i> for trend	<0.001	<0.001	<0.001
Association (95% CI) with continuous cardiac troponin I			
Cluster 2, stable overweight	25.3 (21.1–29.4) %	11.7 (8.1–15.3) %	8.6 (4.1–13.1) %
Cluster 3, stable obesity	38.5 (31.7–45.3) %	30.5 (24.6–36.4) %	22.0 (14.1–29.9) %
<i>p</i> for trend	<0.001	<0.001	<0.001

Cluster 1 (stable normal weight) as reference group. Model 1, unadjusted. Model 2, adjusted for age and sex. Model 3, adjusted for model 2, eGFR, total and HDL cholesterol, CRP, higher education, heart rate, treatment for hypertension, systolic blood pressure, diabetes mellitus, smoking status, statin therapy, visceral fat area, HbA1c, and body surface area.

comparison between adjusted models = 0.015, Table 3). We examined possible interactions by prevalent diabetes mellitus on the association of BMI trajectories with concentrations of cTnI, and found no significant interactions on these associations (all *p* for interaction > 0.05, Table S7).

Discussion

In a substantially sized population-based cohort with follow-up for almost four decades, we identified three distinct trajectories of BMI characterized as stable normal weight, stable overweight, and stable obesity. Participants exhibiting lifetime stable obesity were at especially high risk of increased concentrations of cTnI, a highly sensitive index of subclinical myocardial injury. The risk of subclinical myocardial injury was stronger in the models for lifetime obesity exposure compared to models taking into account only most recent obesity

assessment. Prevalent diabetes mellitus, indices of dysregulated glucose metabolism, and abdominal obesity did not attenuate our results.

Obesity and subclinical myocardial injury

Prevalent obesity is associated with a variety of CV conditions, above all heart failure and coronary artery disease, but also stroke, peripheral artery disease, and sudden cardiac death [18]. Despite a wide variety of phenotypes in individuals with BMI ≥ 30 kg/m² who are considered obese, obesity is independently associated with hypertension, diabetes mellitus, inflammation, and dyslipidemia [19]. A large proportion of the CV risk associated with obesity may be explained by such co-morbid conditions, but despite thorough statistical adjustments, obesity remains a major independent risk factor for coronary artery disease and heart failure [20]. Concentrations of circulating cardiac troponin

Table 3. Association of BMI groups at HUNT 4 with cardiac troponin I at HUNT 4

	Model 1	Model 2	Model 3
Body mass index	Odds ratio (95% CI) of elevated cardiac troponin I		
25.0 to 29.9	1.10 (0.98–1.23)	1.25 (1.10–1.41)	1.12 (0.94–1.34)
≥30.0	1.19 (1.05–1.36)	1.55 (1.35–1.79)	1.22 (0.95–1.56)
<i>p</i> for trend	0.008	<0.001	0.12
	Association (95% CI) with continuous cardiac troponin I		
25.0 to 29.9	10.3 (5.7–14.9%)	8.6 (4.6–12.6%)	5.9 (0.5–11.4%)
≥30.0	12.7 (7.4–18.1%)	19.5 (14.9–24.1%)	10.6 (3.0–18.3%)
<i>p</i> for trend	<0.001	<0.001	0.007

BMI 18.5 to 24.9 as reference group. Model 1, unadjusted. Model 2, adjusted for age and sex. Model 3, adjusted for model 2, eGFR, total and HDL cholesterol, CRP, higher education, heart rate, treatment for hypertension, systolic blood pressure, diabetes mellitus, smoking status, statin therapy, visceral fat area, HbA1c, and body surface area. *p* comparison, comparison with BMI trajectory model from Table 2.

are similarly associated with incidence of most CV conditions, but most strongly with heart failure [21, 22] and CV mortality [2]. For cTnT, the prognostic information appears complementary to that of obesity, and obese individuals with high cTnT concentrations are at particularly high risk of developing heart failure [3]. Especially pertaining to the development of heart failure, long-lasting obesity is associated with increased risk regardless of metabolic status [23]. These results are in line with the current investigation, as obesity exposure over a period of 35 years conferred independent risk of subclinical myocardial injury. This risk was significantly stronger than that conveyed by obesity phenotypes assessed cross-sectionally at study visit 4, further emphasizing the malignant cardiac effects of long-standing obesity.

Despite similar diagnostic properties of cTnI and cTnT for acute coronary syndromes, there are significant differences in the biological [24] and prognostic properties between the two cardiac troponin isoforms, as well as determinants of protein concentrations [25, 26]. With regard to prognosis, recent data from Generation Scotland Scottish Family Health Study demonstrate stronger associations of cTnI with CV outcomes, but only cTnT was associated with non-CV outcomes [27]. Both cTnI and cTnT associate with left ventricular hypertrophy and left ventricular systolic dysfunction, but cTnI appears superior in predicting significant left ventricular hypertrophy in community dwellers [25]. BMI is differentially associated with cTnI and cTnT [26], supporting the notion that these biological differences also pertain to the associations of obesity with subclinical myocardial injury.

Visceral adiposity, dysglycemia, and subclinical myocardial injury

BMI is an incomplete characterization of obesity, especially with regard to different metabolic phenotypes and body composition, and previous investigations have failed to take into account the possible impact of glucose dysregulation and visceral adiposity on subclinical myocardial injury [6]. Increased concentrations of HbA1c are associated with increased concentrations of cTnT [5], which could potentially obscure the associations of obesity with subclinical myocardial injury [6]. Similarly, BMI is a nonspecific indicator of excessive body weight relative to body height, largely disregarding the impact of body fat distribution on CV risk [28]. In the current investigation, we have

mitigated such shortcomings by detailed characterization and adjustment for body fat distribution, and indices of glycemic dysregulation, and adjustment for HbA1c did not attenuate the associations with cumulative obesity exposure.

Increased visceral fat has for long been known to associate with risk of CV disease and cancer, even when adjusting for obesity per se [29]. Visceral fat deposits correlate with epicardial fat, which in turn cause abnormalities in cardiac function and structure, leading to left ventricular hypertrophy, diastolic dysfunction, and ultimately overt heart failure [30]. Individuals with impaired glucose tolerance and type 2 diabetes mellitus exhibit increased myocardial fat content [31] and this accumulation of epicardial fat may partially explain the association of both prediabetes and diabetes with subclinical myocardial injury [32]. We demonstrate that indices of abdominal adiposity did not affect the associations of BMI trajectories with subclinical myocardial injury. Individuals with morbid obesity have increased left ventricular mass [33] and drastic weight loss after bariatric surgery attenuates both left ventricular mass [34] and diastolic dysfunction [35]. Weight loss alleviates subclinical myocardial injury in individuals with severe obesity [36, 37], and parallel increases in BMI and left ventricular mass most likely explains a significant proportion of the observed association of obesity with subclinical myocardial injury. Adjustment for body surface area, a proxy for left ventricular mass, did however not attenuate the associations between long-standing and subclinical myocardial injury.

Strengths and limitations

The current study has its strengths and limitations. The analyses are based on a considerable sample from a contemporary population cohort with prospective measurement of cTnI, as opposed to most comparable population studies with retrospective biomarker analysis. The cTnI assay used is one of the most sensitive currently available, but the analytical precision is lower in the low normal range. The absolute values of cTnI in the current study were predominantly below the LoQ of the assay, and may due to US Food and Drug Administration (FDA) legislation not have been reported should they have originated from a US clinical laboratory. However, a recent opinion has called for the FDA to permit laboratory reporting between the LoD and the LoQ [38], which is common practice in Norway and elsewhere outside the United

States. The study participants were followed from their late 20s and for approximately 35 years, and this is among the longest follow-up times for any cohort study of individuals recruited from the general population, with an assessment of BMI at several time points. Due to this study design, our results may be subject to some degree of selection bias. Further, recall bias will always be challenging in observational studies based on questionnaires. The main predictor variable of the current investigation was however BMI, an objective measure not prone to such bias. Body composition was quantified by bioelectrical impedance and not by dual-energy X-ray absorptiometry, which is considered the gold standard for body composition assessment. Both methods are, however, considered valid for body composition investigations with comparable sensitivity [39, 40]. The lack of myocardial imaging is a major study limitation, as this would have added mechanistic insight to the associations between obesity and subclinical myocardial injury. Longitudinal biomarker measurement would also have strengthened the study. In contrast to BMI, the remaining risk factors in our statistical models were only assessed at study visit 4, barring us from time-varying model adjustment. As the study population is predominantly northern European Caucasian, our results may not be generalizable to other ethnicities.

Conclusions

Individuals with stable overweight or obesity are at increased risk of subclinical myocardial injury, independently of glycemic dysregulation and abdominal adiposity. Our data support a direct detrimental effect of long-standing obesity on CV health.

Acknowledgments

The Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health.

Author contributions

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Conflict of interest

JAL has received grants from Abbott Diagnostics and Roche Diagnostics not related to the current work, and consulting fees from Ortho Clinical Diagnostics, Siemen's Health Care Diagnostics, and Quidel not related to the current work. TO has received funding from Abbott Diagnostics related to the current work, nonfinancial support from Novartis, Abbott Diagnostics, Roche Diagnostics, and SomaLogic not related to the current work, and honoraria from Siemens Healthineers, Roche Diagnostics, and Abbott Diagnostics not related to the current work. The remaining authors declare that they have no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supporting Information

Table S1: Model fit classifications for the latent class analysis

Table S2: Association of BMI trajectories with cardiac troponin I above the sex-specific 99th percentile at HUNT 4

Table S3: Associations with elevated cardiac troponin I at HUNT 4, all model variables

Table S4: Associations with continuous cardiac troponin I concentrations at HUNT 4, all model variables

Table S5: Impact of individual adjustment variables on associations between BMI trajectories and continuous cardiac troponin I concentrations at HUNT 4

Table S6: Associations of BMI, body weight, body fat mass and visceral fat area at HUNT 4 with cardiac troponin I at HUNT 4

Table S7: Association of BMI trajectories with cardiac troponin I at HUNT 4 according to prevalent diabetes mellitus

Figure S1: Precision profile for cardiac troponin I analyzed in HUNT 4

Figure S2: BMI trajectories from HUNT1 to HUNT 4, 4-class model

Figure S3: BMI trajectories from HUNT1 to HUNT 4, 5-class model

