Duration of obesity exposure between ages 10-40 years and its relationship with cardiometabolic disease risk factors: a cohort study

Running title: Obesity duration and cardiometabolic disease risk factors

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Abstract:

Background: Individuals with obesity do not represent a homogeneous group in terms of cardio-metabolic risk. Using three nationally representative British birth cohorts, we investigated whether the duration of obesity was related to heterogeneity in cardiometabolic risk.

Methods and Findings: We used harmonised body mass index and cardiometabolic disease risk factor data from 20 746 participants (49.1% male and 97.2% White British) enrolled in three British birth cohort studies: the 1946 National Survey of Health and

Why Was This Study Done?

People with obesity (body mass index>30kg/m^2) do not all share the same risk for development of cardiometabolic disease risk factors.

The duration a person has spent with obesity over their life course could be one factor contributing to the variation observed in cardiometabolic risk.

However, previous studies have been unable to adequately separate the effects of obesity duration (how long a person has been obese) and obesity severity (the magnitude of a

What Did the Researchers Do and Find?

We derived body mass index trajectories between 10 and 40 years of age in 20 746 participants

94 **Introduction:**

observing a positive relationship with obesity duration [15,17 23]. The largest of these studies (n=61,821) [21] observed that for each 2-year increment in obesity duration, the risk of type 2 diabetes increased by 14%, though, as observed in other studies [19,22], estimates were attenuated upon adjustment for current weight (representing obesity severity).

and 46 years in the 1970 cohort (n=8 581). Measurements of systolic (SBP) and diastolic blood pressure (DBP) were obtained as well as blood cardiometabolic biomarkers (glycated haemoglobin (HbA1c) and high-density lipoprotein cholesterol (HDL-C)). More information about the measurement protocols can be found in S1 Text.

Statistical analysis

TN and WJ determined which analyses to perform and include in the present paper in January 2019 after discussing options with all co-authors. The analysis plan was revised in May (modelling obesity duration as a categorical variable rather than a continuous variable) and October 2019 (removing LDL-cholesterol as an outcome due to high amount of missing data) when further exposure and outcome data were obtained and explored. Further

229 the presence of obesity at any timepoint was identified, representing any BMI z-score which
230 exceeded the obesity threshold. Secondly, the number of times obese was calculated as
231 the -score crossed upwards through the obesity
232 threshold. Thirdly, age first obese was derived, representing the age, in years, when BMI z-
233 score first crossed upwards through the obesity threshold. Total duration of obesity was
234 calculated as the length of time, in years, that -score exceeded the obesity

unadjusted for covariates. A subsequent model included adjustments for sex, cohort, birth weight (kg), ethnicity (white vs non-white), social class in childhood reported when the child was 10-Classes schema- see S2 Text for more details)and age at follow-up. A final model also included an adjustment for

Analyses were performed in Stata version 15 (Stata Corp, College Station, TX) and R version 3.5.3 (R Core Team 2019).

This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (S1 Checklist).

Code availability

The statistical code for the analyses in this paper has been placed in GitHub, the open-access online repository (repository URL: https://github.com/tomnorris1988/Obesity-duration-and-cardiometabolic-outcomes).

306 **RESULTS:**

There was also a linear trend between obesity duration and risk for elevated HbA1c, with those obese <5 years having a 2.1 (95% CI: 1.8, 2.4) times higher risk of elevated HbA1c of compared to never obese, which more than doubled in those obese for 20-30 years (relative risk 4.6; 95% CI: 3.9, 5.5, *p(trend)*<0.001) (Fig 2, right panel). However, upon adjustment for obesity severity, this graded relationship was attenuated (*p(trend)*=0.006).

SBP and DBP

There was a positive relationship between ever being obese between 10-40 years and both systolic and diastolic blood pressure. For example, ever obese was associated with a 6.1% (95% CI: 5.6, 6.6)

independent association of obesity duration with HDL-C is lacking. To our knowledge only one other study has investigated this and observed an association in females only, though the strength of evidence was modest (p=0.05) [14].

In addition to the cited empirical studies, there is also a plausible biological mechanism supporting the observed association between obesity duration and HbA1c (reflecting impaired glucose metabolism). Obesity is characterised by enlarged fat stores, which results in enhanced lipolysis and an increase in circulating free fatty acids. This state leads to peripheral and hepatic insulin resistance [48,49], resulting in a compensatory insulin hypersecretion by the pancrea -cells in order to preserve normoglycemia[50]. Prolonged -cell exhaustion [51], culminating in a reduced insulin response and an inability to maintain normoglycemia [52]. In addition, prolonged obesity may represent a state in which subcutaneous adipose stores have been exhausted, with the consequence being a deposition of adipose tissue around the visceral organs (e.g. liver and pancreas),

prevalence of abdominal obesity has increased more in females than in males [56]. Furthermore, the prevalence of visceral obesity associated with metabolic syndrome is two to ten times higher in women throughout the world [57 59]. It may be therefore, that compared to males, females are more exposed to this metabolically-volatile adipose tissue and thus at increased risk of its deleterious outcomes.

Strengths

The key strength of our study is the derivation, using over 130 000 serial BMI observations across the life course, of individualised obesity parameters which enabled us to distinguish

analyses limited to the NCDS and BCS cohorts only and replacing the NSHD blood pressure variables with those collected at 43 years, produced similar estimates (S7-S10 Tables).

Associations observed in this study

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cohort, age at follow-up, ethnicity, birth weight, childhood social class and obesity severity): using blood pressure at 43 years in NSHD

S10 Table: Association between ever obese and c

Table 1 Descriptive statistics for life course obesity parameters and cardiometabolic disease risk factors at the biomedical sweep of those in target study sample (n=20 746)

		NSHD 1946 (n=2968)	*1958 NCDS (n=9302)*	*1970 BCS (n=8476)*
Sex				
Males	n (%)	1459 (49.2)	4630 (49.8)	4106 (48.4)
Females	n (%)	1509 (50.8)	4672 (50.2)	4370 (51.6)

Age at follow up (years)	mean (SD)	-	53.5 (0.2)	-	45.2 (0.4)	-	47.3 (0.7)
BMI at follow-up (kg/m^2)	median (IQR)	1.3	26.6 (24.2; 29.9)	1.3	26.6 (24.0; 29.9)	13.4	27.6 (24.6; 31.5)
Obese at follow-up (BMI>30kg/m^2)	n (%)	1.3	707 (24.1)	1.3	2239 (24.4)	13.4	2424 (33.0)
Systolic blood pressure (mmHg)*	mean (SD)	1.9	136.0 (20.1)	0.5	126.5 (16.5)	11.5	124.6 (15.2)
Diastolic blood pressure (mmHg)*	mean (SD)	1.9	84.4 (12.2)	0.5	78.8 (10.8)	11.5	

Figure legends:

Fig 1: Example obesity traits (onset, duration and severity (area-under-the curve and above obesity cut-off)) derived from the BMI-z-score trajectories of two random participants

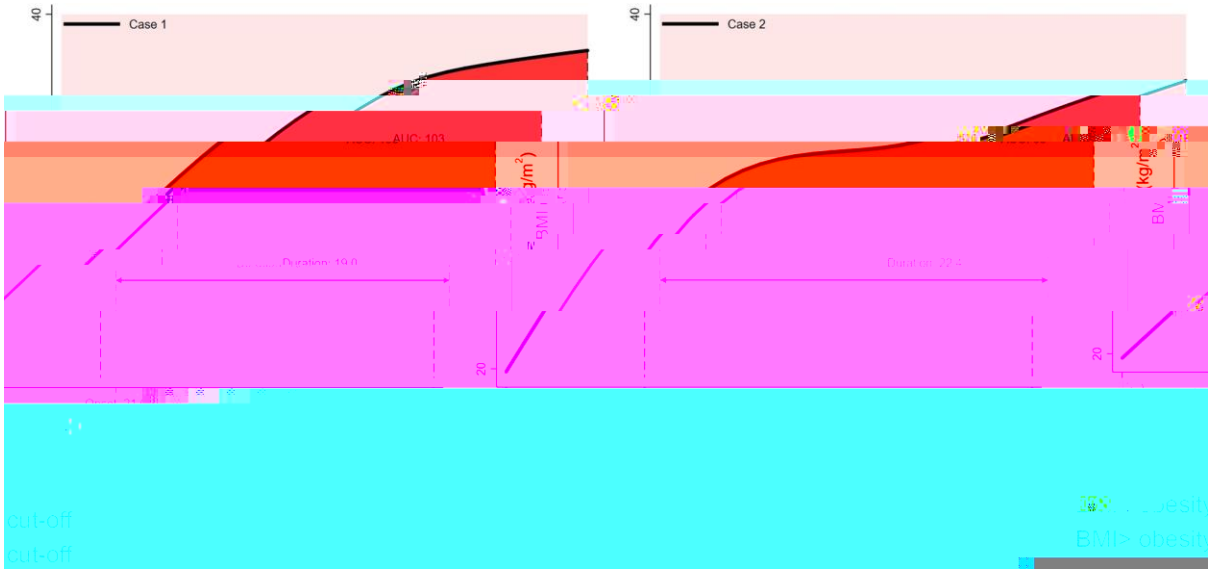

Fig 2: Association between ever obese and categories of obesity duration (vs never obese) and HbA1c (left panel) and risk for elevated HbA1c (right panel)

Fig 3: Association between ever obese and categories of obesity duration (vs never obese) and SBP, DBP and HDL-C

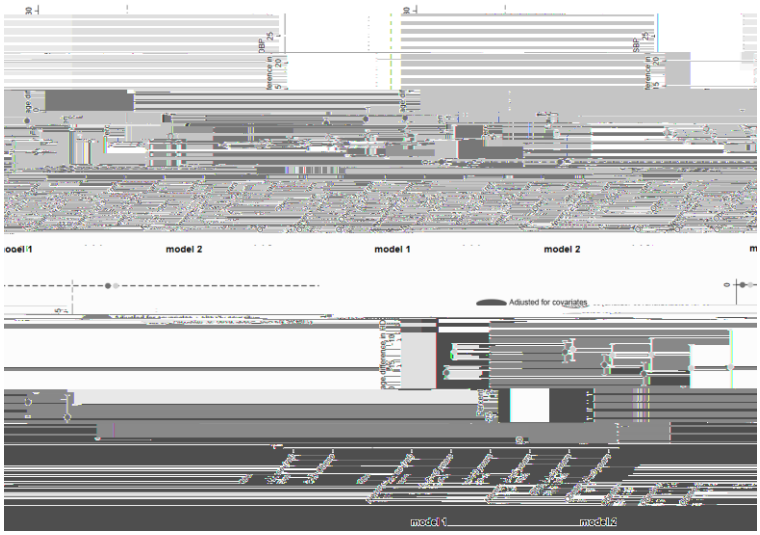

Fig 4: Association between ever obese and categories of obesity duration (vs never obese) and risk for hypertension and low HDL-cholesterol