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

3   **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:**

129 observing a positive relationship with obesity duration [15,17 23]. The largest of these

130 studies (n=61,821) [21] observed that for each 2-year increment in obesity duration, the risk

131 of type 2 diabetes increased by 14%, though, as observed in other studies [19,22], estimates

132 were attenuated upon adjustment for current weight (representing obesity severity).

194 and 46 years in the 1970 cohort (n=8 581). Measurements of systolic (SBP) and diastolic

195 blood pressure (DBP) were obtained as well as blood cardiometabolic biomarkers (glycated

196 haemoglobin (HbA1c) and high-density lipoprotein cholesterol (HDL-C)). More information

197 about the measurement protocols can be found in S1 Text.

Statistical analysis

199 TN and WJ determined which analyses to perform and include in the present paper in

200 January 2019 after discussing options with all co-authors. The analysis plan was revised in

201 May (modelling obesity duration as a categorical variable rather than a continuous variable)

202 and October 2019 (removing LDL-cholesterol as an outcome due to high amount of missing

203 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

264 unadjusted for covariates. A subsequent model included adjustments for sex, cohort, birth

265 weight (kg), ethnicity (white vs non-white), social class in childhood

266 reported when the child was 10-

267 Classes schema- see S2 Text for more details)and age at follow-up. A final model also
     included an adjustment for

298   Analyses were performed in Stata version 15 (Stata Corp, College Station, TX) and R

299   version 3.5.3 (R Core Team 2019).

300   This study is reported as per the Strengthening the Reporting of Observational Studies in

301   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:**

340 **There was also a** linear trend between obesity duration and risk for elevated HbA1c, with

341 those obese <5 years having a 2.1 (95% CI: 1.8, 2.4) times higher risk of elevated HbA1c of

342 compared to never obese, which more than doubled in those obese for 20-30 years (relative

343 risk 4.6; 95% CI: 3.9, 5.5, *p(trend)*<0.001) (Fig 2, right panel). However, upon adjustment for

344 obesity severity, this graded relationship was attenuated (*p(trend)*=0.006).

345 SBP and DBP

346 There was a positive relationship between ever being obese between 10-40 years and both

347 systolic and diastolic blood pressure. For example, ever obese was associated with a 6.1%
     (95% CI: 5.6, 6.6)

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

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

454   prevalence of abdominal obesity has increased more in females than in males [56].

455   Furthermore, the prevalence of visceral obesity associated with metabolic syndrome is two

456   to ten times higher in women throughout the world [57 59]. It may be therefore, that

457   compared to males, females are more exposed to this metabolically-volatile adipose tissue

458   and thus at increased risk of its deleterious outcomes.

459   **Strengths**

460   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

489   analyses limited to the NCDS and BCS cohorts only and replacing the NSHD blood pressure

490   variables with those collected at 43 years, produced similar estimates (S7-S10 Tables).

Associations observed in this study

References

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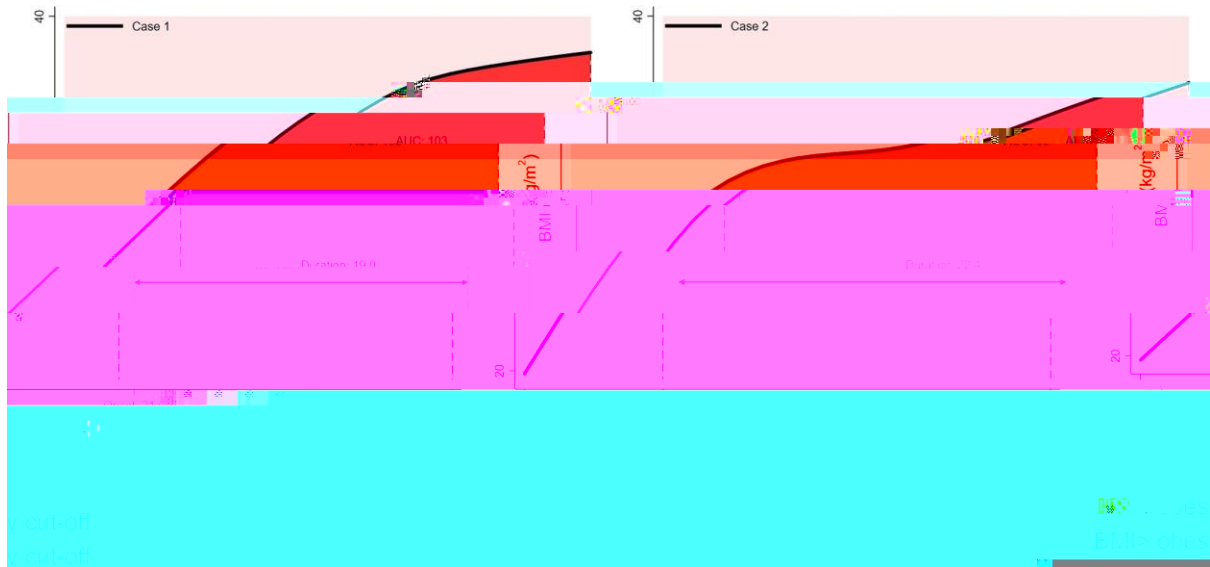
Fig 2: Association between ever obese and categories of obesity duration (vs never obese) and HbA1c (left panel) and risk for elevated HbA1c (right panel)

Fig 3: Association between ever obese and categories of obesity duration (vs never obese) and SBP, DBP and HDL-C
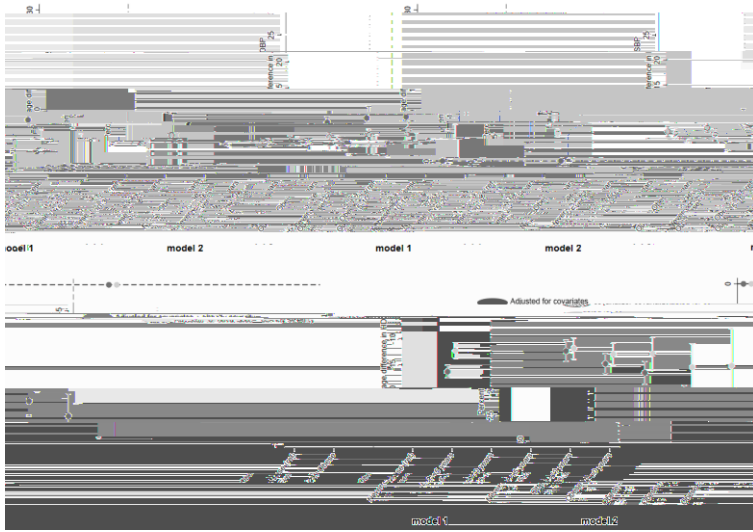
Fig 4: Association between ever obese and categories of obesity duration (vs never obese) and risk for hypertension and low HDL-cholesterol