International Journal of Obesity (2020) 44:1733–1742
https://doi.org/10.1038/s41366-020-0611-x

ARTICLE

Epidemiology and Population Health

Longitudinal association of a body mass index (BMI) genetic risk score with growth and BMI changes across the life course: The Cardiovascular Risk in Young Finns Study

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Received: 23 September 2019 / Revised: 27 March 2020 / Accepted: 20 May 2020 / Published online: 3 June 2020

Abstract

Background The role of genetic risk scores associated with adult body mass index (BMI) on BMI levels across the life course is unclear. We examined if a 97 single nucleotide polymorphism weighted genetic risk score (wGRS97) associated with age-related progression in BMI at different life stages and distinct developmental trajectories of BMI across the early life course.

Methods 2188 Cardiovascular Risk in Young Finns Study participants born pre-1980 who had genotype data and objective measurements of height and weight collected up to 8 times from age 6 to 49 years. Associations were examined using Individual Growth Curve analysis, Latent Class Growth Mixture Modelling, and Poisson modified regression.

Results The wGRS97 associated with BMI from age 6 years with peak effect sizes observed at age 30 years (females: 1.14 kg/m^2; males: 1.09 kg/m^2 higher BMI per standard deviation increase in wGRS97). The association between wGRS97 and BMI became stronger with age in childhood but slowed in adolescence, especially in females, and weakened at age 35–40 years. A higher wGRS97 associated with an increased BMI velocity in childhood and adulthood, but not with BMI change in adulthood. Compared with belonging to a 'normal stable' life-course trajectory group (normal BMI from childhood to adulthood), a one standard deviation higher wGRS97 associated with a 13–127% increased risk of belonging to a less favourable life-course BMI trajectory group.

Conclusions Individuals with genetic susceptibility to higher adult BMI have higher levels and accelerated rates of increase in BMI in childhood/adolescence, and are at increased risk of having a less favourable life-course BMI trajectory.

Introduction

Body mass index (BMI) tracks, or persists, from childhood to adulthood, suggesting the roots of adult overweight and obesity lie in childhood [1, 2]. Although those overweight or obese in childhood and adolescence have 5–13 times higher odds of being obese in adulthood [3], those able to amend, or resolve, their high-risk childhood BMI status by adulthood

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Supplementary information The online version of this article (https://doi.org/10.1038/s41366-020-0611-x) contains supplementary material, which is available to authorized users.

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are generally able to amend the increased risk that childhood overweight or obesity contributes to subsequent cardiometabolic outcomes [3, 4]. Examination of life-course BMI development using data from multiple time-points spanning childhood to adulthood established the presence of six distinct BMI trajectories that individuals typically follow [4]. The developmental origins of BMI trajectories vary, but data suggest differences in BMI in childhood and rates of BMI change across the life course [5].

Obesity and the developmental trajectories of BMI across the life course are complex multifactorial traits influenced by environmental and genetic factors, with twin and family studies suggesting genetic factors contribute 40–70% of inter-individual variability in BMI [6, 7]. Genome-wide association studies (GWAS) have allowed several genetic variants consistently associated with BMI, fat mass, weight, and risk of obesity to be isolated, with meta-analysis confirming 97 independent loci that influence BMI [8]. To provide better insight into the aetiology of obesity, it is necessary to understand the timing of such genetic influences, particularly how known adult genetic variants influence the variation in BMI growth patterns at different periods in the life course [9].

Studies with genetic data and serial anthropomorphic measurements during narrow periods of the life course [10–15], particularly childhood, support the notion that there may be distinct genetic effects of BMI loci that varies over the life course, and even age-specific expression [13]. However, because few cohort studies have a population sample that encompasses childhood, adolescent and adult life stages, the extent to which these findings can be generalised across the life course and to other life stages, especially transitional periods that are high risk for excess weight gain such as adolescence and young adulthood [16, 17] remains poorly understood [12]. The identification of age- or period-specific genetic effects is crucial to inform effective obesity prevention and management strategies [18]. Therefore, we examined the combined influence of 97 known genetic risk loci (combined into a weighted genetic risk score (wGRS97)) on individual progression of BMI levels in childhood, adolescence, and adulthood. In addition, we examined the association between the wGRS97 and six distinct typical child-to-adult BMI trajectory patterns we previously identified in a large European cohort [4].

Methods

Study cohort

The Cardiovascular Risk in Young Finns (YFS) study is an on-going population-based follow-up of cardiovascular risk factors in a homogenous white population of European ancestry. In 1980, 3596 participants aged 3, 6, 9, 12, 15, and 18 years were examined in five Finnish cities and their rural surroundings. Subsequent follow-ups were conducted every 3 years until 1992, and again in 2001 ($n = 2620$), 2007 ($n = 2159$), and 2011 ($n = 2012$), resulting in up to eight waves of measurements per individual (full details on the study design have been published [19]). Participants included 2188 individuals for whom genotype data and objective measurements of height and weight were available from age 6 to 49 years over the 31 years of follow-up. All participants or their parents gave written informed consent and the study was approved by local ethics committees.

Genotyping and genetic risk score computation

Genotyping was performed using the custom-built Illumina Human 670k BeadChip, and genotypes were called using Illumina's clustering algorithm [20]. Imputation of genotypes was performed using IMPUTE2 [21] and the 1000 genomes phase 1 Integrated Release Version 3 as a reference panel [22]. A weighted genetic risk score (wGRS97) was computed using 97 independent adult BMI-associated SNPs reported by Locke et al. [8]. The wGRS97 was defined as the arithmetic sum of the SNP values x_i (number of effective/BMI-increasing alleles at each locus (0, 1, or 2)) weighted by their corresponding β scores (β_I effect sizes in kg/m^2 per allele):

$$\mathrm{wGRS} = \sum_{\mathrm{i}=1}^{97} \beta_{\mathrm{i}} \mathrm{x}_{\mathrm{i}}.$$

Participants were categorised as 'low', 'mid', or 'high' genetic risk defined as the cohort-specific lower (25th percentile), middle (25th–75th percentile), upper (75th percentile) wGRS97 quartile(s) respectively.

Anthropomorphic measures and assessment of growth

At each wave, unclothed weight was measured to the nearest 0.1 kg using digital scales and standing height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. BMI at each follow-up was calculated as BMI = weight (kg)/(height (m)^2). To identify biologically implausible anthropomorphic measures taken in childhood (3–18 years), sex- and age-adjusted BMI z-scores were computed using the World Health Organisation growth standards. Implausible BMI measurements (>4 standard deviations from the mean for sex- and age-specific BMI Z-score category) were considered outliers and recoded to missing [23, 24]. For measures in adulthood, BMI was recoded to missing for any records where weight > 250 kg or height > 3 m [23] (total of five records).

Life-course BMI trajectory groups

In a previous study, we identified six distinct long-term BMI trajectories from age 6 to 49 years among 2631 YFS participants using Latent Class Growth Mixture Modelling (LCGMM) [4]. The six identified trajectories depicted distinct patterns of growth and change in BMI levels from childhood to mid-adulthood, indicative of normal stable weight status throughout the observed life course for 55.2% participants ('stable normal' group, $n = 1453$), high-BMI improving from young adulthood for 1.6% ('improving' group, $n = 43$), progression to overweight for 33.4% ('progressively overweight' group, $n = 879$), progression to adult obesity in young adulthood (late onset obesity) for 4.2% ('progressively obese' group, $n = 110$), rapid progression to obesity (early onset obesity) for 4.3% ('rapidly overweight/obese group', $n = 113$), and persistent and increasing obesity from an early age for 1.2% ('persistent increasing overweight/obese', $n = 33$). Each participant was assigned to one of these six trajectories in the sample, based on his/her highest Bayesian posterior probabilities across latent classes retrieved from the six classes LCGMM model [4]. Life-course BMI trajectory group membership was available for all 2188 YFS participants included in the present study.

Statistical analyses

Cross-sectional and longitudinal associations between the wGRS97 and BMI from childhood to mid-adulthood (6–49 years) was examined using age-stratified linear regression analysis and Individual Growth Curve (IGC) analyses, a hierarchical/multilevel mixed effect modelling approach that allows between-person differences in intra-individual change to be modelled for continuous longitudinal outcomes [25–27]. IGC analysis was also used to examine the time-averaged and time-dependent associations of the wGRS97 with BMI levels across more restricted developmental periods, by breaking down the study sample into three separate life-stages: childhood (6–12 years), adolescence (12–21 years), and adulthood (21–49 years). Across each considered life stage, IGC models allowed us to test if the wGRS97 associated with increased BMI on average (time-averaged effects), or if it associated with greater rates of change in BMI levels (time-dependent effects). Statistical models were stratified by sex or adjusted for study year when relevant. The detailed IGC model specification is presented in Supplementary methods S1.

Multinomial logistic regression was used to examine the association between the wGRS97 with the six BMI trajectories our group previously identified in the YFS cohort using LCGMM. This allowed to test if having a larger number of risk variants increased the odds of belonging to a more adverse life-course BMI trajectory group [4]. All statistical analyses were conducted in R [28].

Results

Table 1 shows the sex-specific average BMI levels by life stage and the sex-specific average wGRS97 of participants in 'high', 'mid', and 'low' genetic risk groups. The average

Table 1 Sex-specific average BMI levels (kg/m^2) across the life course and by life stages, and wGRS97 scores among 2188 participants in the YFS and by wGRS97 categories.

	Males		Females	
	N (N_{obs})[a]	Mean (SD)	N (N_{obs})[a]	Mean (SD)
BMI levels (kg/m^2)				
Life course (6–49 years)	1004 (5249)	22.11 (5.29)	1184 (6193)	22.70 (5.25)
Life stages				
Childhood (6–12 years)	671 (1360)	17.01 (2.53)[c]	806 (1305)	17.11 (2.66)[c]
Adolescence (12–21 years)	1184 (2140)	20.41 (3.25)	1004 (1916)	20.27 (3.01)
Adulthood (24–49 years)	1004 (2642)	26.26 (4.96)	1184 (3187)	25.06 (5.02)
wGRS97 categories[b]				
High	246 (1929)	23.58 (5.75)	310 (2430)	22.79 (5.5)
Mid	523 (4095)	22.64 (5.17)	562 (4095)	22.11 (5.27)
Low	235 (1843)	22.01 (4.93)	312 (2451)	21.41 (4.85)

Values in parentheses indicate standard deviation, except for, where they indicate the wGRS97 range.

[a]$N(N_{obs})$: N number of participants considered in each analyses or number of participants in each wGRS97 category; N_{obs} number of non-missing BMI observations used in the analyses for each sex within each time period.

[b]The grouping of wGRS97 into high (wGRS97 > 2.43), mid (2.21 < wGRS97 ≥ 2.43), and low genetic risk (wGRS97 < 2.21) score categories was based on whole cohort 25th and 75th percentiles (see "Methods").

[c]For the childhood period, the corresponding average BMI z-scores were 0.05 (0.002) for males and 0.06 (0.004) for females.

Table 2 Time-averaged and time-dependent effects of the combined BMI genetic risk score (wGRS97) on BMI levels (in kg/m2) at different life stages (childhood, adolescence, adulthood, and life course).

	Time-averaged wGRS effect[a]		Time-dependent wGRS effects[b]		Goodness of fit[d] (variance explained)
Life stage	β(se)[c]	p value	β(se)[c]	p value	
Childhood (6–12 years)					
Females ($N = 806$)	0.30 (0.06)	<0.01*	L: 0.12 (0.028) Q: −0.01 (0.005)	<0.01*0.03*	$R^2_{marginal} = 0.239$ $R^2_{conditional} = 0.943$
Males ($N = 671$)	0.17 (0.07)	<0.01*	L: 0.06 (0.03) Q: 0.0008 (0.004)	0.05*0.85	$R^2_{marginal} = 0.211$ $R^2_{conditional} = 0.953$
Adolescence (12–21 years)					
Females ($N = 1184$)	0.20 (0.07)	0.02*	L:0.13 (0.03) Q:−0.009 (0.05)	<0.01*0.09	$R^2_{marginal} = 0.26$ $R^2_{conditional} = 0.91$
Males ($N = 1004$)	0.26 (0.07)	<0.01*	L:0.07 (0.03) Q:−0.005 (0.004)	<0.01*0.13	$R^2_{marginal} = 0.22$ $R^2_{conditional} = 0.95$
Adulthood (24–49 years)					
Females ($N = 1184$)	0.72 (0.13)	<0.01*	L: 0.018 (0.02) Q:−0.0002 (−0.0006)	0.280.73	$R^2_{marginal} = 0.09$ $R^2_{conditional} = 0.94$
Males ($N = 1004$)	0.70 (0.01)	<0.01*	L: 0.018 (0.02) Q:−0.0009 (0.0007)	0.180.20	$R^2_{marginal} = 0.09$ $R^2_{conditional} = 0.91$
Life course (6–49 years)					
Females ($N = 1184$)	0.69 (0.10)	<0.01*	L: 0.02 (0.01) Q: 0.001 (0.0008) C: -0.0002 (1.0×10^{-4}) 4th: -1.0001 (0.8×10^{-4})	<0.01*0.120.130.34	$R^2_{marginal} = 0.45$ $R^2_{conditional} = 0.933$
Males ($N = 1004$)	0.68 (0.11)	0.006*	L:0.012 (0.028) Q:0.005 (0.002) C:1.0×10^{-5} ($4.2 \times 10^{-4)}$ 4th:$-1.3.10^{-5}$ ($4.2 \times 10^{-4)}$	0.05*0.580.920.05*	$R^2_{marginal} = 0.57$ $R^2_{conditional} = 0.952$

For each considered life stage period, regression coefficients are extracted from the best fitting sex-specific conditional IGC model. Time-averaged effects are expressed in kg/m^2 change per 1 standard deviation (SD) increase in the wGRS97, and time-dependent effects are expressed in kg/m^2 change per time unit increase per 1 SD increase in wGRS97 (see footnote). Novel conditional R^2 and marginal R^2 indicate goodness of fit of each final IGC model. Predictors included in final IGC models included polynomial age terms, wGRS97, birth cohort and follow-up year (and their interactions).

BMI body mass index, *L,Q,C* linear/quadratic/cubic rate of change in BMI (in kg/m^2) as a function of age (in years), *SD* standard deviation, *se* standard error.

*Regression coefficients significant at the 0.05 significance level ($p \le 0.05$).

[a,b]For ease of interpretation of the estimates of time-averaged and time-dependent effects of the wGRS97 in each model, all 'age' terms were centred around the youngest age in each considered period prior IGC modelling (i.e., age 6 years for childhood model (age range: 6–12 years), age 12 years for the adolescence model (age range: 12–21 years) and age 21 years for the adult model (age range: 24–49 years)), and around the average age (24.5 years) for the life course model (age range: 6–49 years).

[c]Reported regression coefficients βs are kg/m^2 per 1 SD increase in the wGRS97 (time-averaged effects) and in kg/m^2 per 1 SD increase in wGRS97 per time unit increase (i.e. year, year^2, year^3, or year^4 for the linear, quadratic, cubic, and quartic age terms respectively. These parameters control the acceleration/deceleration of effect).

[d]The novel conditional R^2 and marginal R^2 [34] describes the proportion of variance explained by the fixed effects alone, while the conditional R^2 describes the proportion of variance explained by both the fixed and participant-level random factors.

wGRS97 was 2,32 (1.79–2.79) in males and 2.318 (1.80–2.83) in females followed an approximately normal distribution (Supplementary Fig. S1).

Longitudinal associations between wGRS97 and BMI

The best non-linear fits were achieved using a quadratic age term for the periods of childhood, adolescence and adulthood, and a fourth-order polynomial (quartic age term) for the life-course model that described BMI development as a function of age from childhood to mid-adulthood (i.e. unconditional models yielding the lowest AIC and BIC values) (Table 2). Final models included a continuous first-order autoregressive correlation structure for the error and considered time-averaged and age-related secular trends in BMI between subsequent

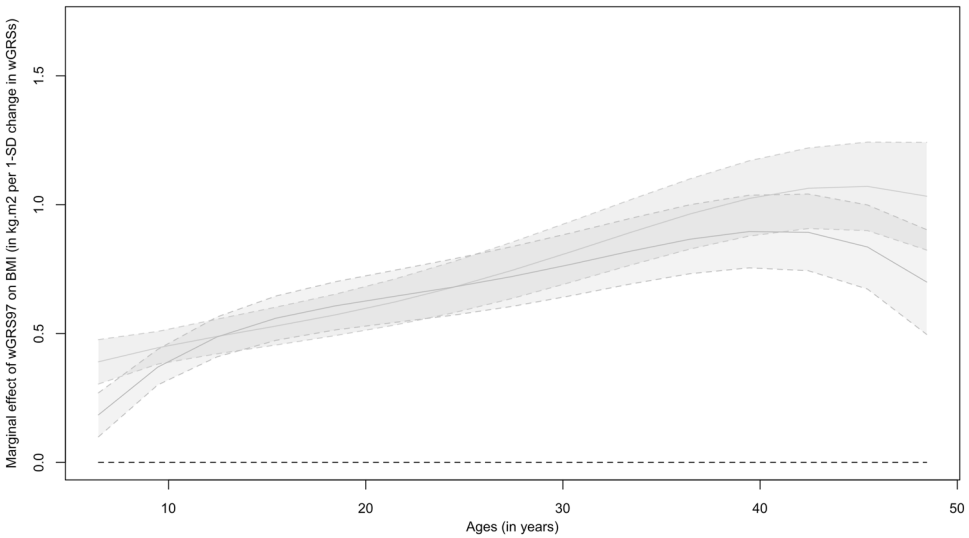

Fig. 1 Sex-specific marginal effects and 95% confidence intervals (shaded) of the wGRS97 on BMI levels as a function of age. Marginal effect expressed as kg/m2 increase in BMI per 1 standard deviation (SD) higher wGRS97. Colour code: pink, females; light blue, males. Marginal effects were derived from the time-averaged wGRS97 effect estimates and the significant higher-order polynomial interaction terms with age (i.e., modification of the linear, quadratic, cubic. and quartic rate of change in BMI) in the final life course IGC models shown in Table 2. The delta method was used for approximating the standard errors of the average marginal effects to derive the 95% confidence intervals. For simplicity, the marginalised wGRS97 effects were computed holding the other parameters at their average values (i.e., hypothetical follow-up year set to 1995, year of birth set to 1968) (Colour figure online).

study years and birth cohort effects (see Supplementary results S1).

Consistent with results from age-stratified regression analyses (Supplementary results S2), time-averaged effect estimates were significant in all considered life stages ($p < 0.01$, Table 2). Time-dependent effects were significant in childhood and adolescence (i.e. $\beta_{\text{wGRS97} \times \text{Age}}$ and $\beta_{\text{wGRS97} \times \text{Age2}}$ parameters p values < 0.05, Table 2). An increase in the wGRS97 was associated with faster BMI growth rates in childhood and adolescence (i.e., p values <0.05 for time-dependent estimates, Table 2). In contrast, the time-dependent wGRS97 effects estimates in adult IGC models were smaller and non-significant for either sex ($p > 0.18$, Table 2). The final childhood and adolescence IGC models explained up to 26% of the variance in BMI levels (R^2_{marginal}, Table 2), but the same combination of variables explained only 9% of variance in BMI in the adult IGC model. The life-course IGC models explained 45% deviance in BMI in females and 55% variance in BMI in males. In this model, some time-dependent wGRS97 effect estimates were significant, but the inclusion of linear, quadratic, cubic, and fourth-order age polynomial terms in the functional form makes the interpretation of interactions (i.e. $\beta_{\text{wGRS97} \times \text{polynomial Age}}$ parameter estimates) difficult. Time-dependent effects were visualised using parameter estimates from the final IGC models to compute and plot the marginal effects of the wGRS97 on BMI levels as a function of age for each sex (Fig. 1). The marginalised wGRS97 estimates showed again that the genetic effect is present and significant at age 6 years for both sexes, but the within-person association with BMI across the life course differed by sex. For males, the magnitude of the association increased rapidly with age within-person in childhood and kept increasing at a slower rate through adolescence (Fig. 1). For females, the effect was stronger than males at age 6 years and gradually increased in childhood and adolescence becoming more pronounced, on average, in young adulthood (from ~22 years of age). The peak genetic effect was reached at 35–40 years for both sexes (Fig. 1), and was stronger for females. Results suggested a stabilisation, and even slight decrease in males, of the wGRS97 effect on BMI after 40 years.

Although average BMI levels were ~2 kg/m^2 higher in the 'high' compared with 'low' wGRS97 group from age 6 years, the smoothed averaged life-course BMI trajectories of these two wGRS97 groups did not diverge noticeably at any point in the life course (Fig. 2).

Associations between wGRS97 and latent life-course BMI trajectory groups

wGRS97 tended to increase incrementally across more adverse life-course trajectory groups (Table 3), however, the average wGRS97 of participants attributed to the 'high-BMI improving' group (participants whose BMI levels improved greatly from obese levels after age 25 years) was comparable to those in the 'rapidly obese' and 'persisting/worsening high obesity' groups. Compared with the

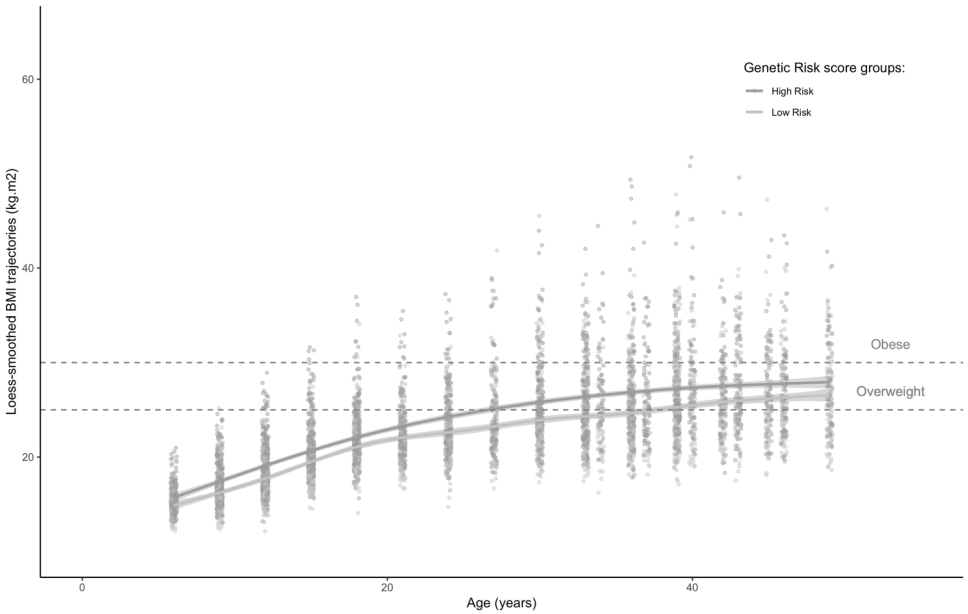

Fig. 2 Smoothed averaged BMI trajectory in the 'High genetic risk group' (75th wGRS97 percentile) and 'Low genetic risk' group (25th wGRS97 percentile), with adult overweight and obese cut-offs. The difference in the averaged BMI between the two genetic risk score groups is about 2 kg/m^2.

Table 3 Mean and standardised wGRS97, relative risk (RR) and 95% confidence intervals (CI) across distinct life course BMI trajectory groups.

	Mean wGRS (SD)[c]	Mean z-score wGRSz(SD)[c]	$N_{participants}$	RR	
				wGRSz (95% CI)[a]	Sex (95% CI)[b]
Normal stable	2.30 (0.16)	−0.1 (1)	1197	Ref	Ref
Progressively overweight	2.32 (0.16)	0.01 (0.97)	726	1.13 (1.09–1.16)*	2.15 (2.01–2.30)*
High-BMI improving	2.39 (0.15)	0.41 (0.95)	34	1.72 (1.51–1.95)*	1.79 (1.41–2.29)*
Progressively obese	2.36 (0.14)	0.22 (0.88)	106	1.39 (1.30–1.51)*	1.08 (0.93–1.21)
Rapidly obese	2.41 (0.17)	0.56 (1.06)	92	2.01 (1.87–2.17)*	2.16 (1.85–2.52)*
Persisting/worsening high obesity	2.43 (0.15)	0.68 (0.93)	33	2.27 (2.01–2.62)*	0.95 (0.73–1.23)

("Normal stable" group, $N = 1197$) for a 1 SD increase in the wGRS.

*Indicates significant RR coefficients at the $a = 0.05$ level (p values obtained from two-tailed p values (Wald z-test) where all highly significant (p values $< 1.0 \times 10^{-12}$).

[a]For wGRSz, the estimates represent the relative risk ratios for belonging to each BMI trajectory class vs. the reference class.

[b]The reference category for sex was female, so the reported estimates are the difference of relative risk ratio in Males for being in each BMI trajectory class against the reference trajectory class (stable normal).

[c]Mean standardised deviation score wRGSz (SD) in reference class ("normal stable" group, $N = 1197$ participants) was 2.30 (0.16). Student t tests revealed no sex differences in average wGRSz within each trajectory groups, so group-average wGRSz in the table are for trajectory groups that include both males and females.

'normal stable' (reference) group, a 1 SD higher wGRS97 associated with incrementally increased risk for belonging to more adverse BMI trajectory classes (Table 3). To help with interpretation, model parameters were used to derive and plot predicted probabilities of belonging to each of the six life-course BMI trajectory groups as a function of change in the standardised wGRS97z (Fig. 3). The probability of belonging to the 'normal stable' (reference) group decreased markedly as wGRS increased, but always remained higher among females (bottom panel, Fig. 3). Higher deviations from average wGRS were associated with the highest probabilities of belonging to the most adverse trajectory classes (i.e., 'rapidly obese', 'progressively obese', and 'persisting/worsening high obesity'). However, the probability of belonging to the 'progressively overweight' group followed a curved shape, increasing between lower than average to average wGRS97 scores, but decreasing as the scores became more extreme (third panel from top, Fig. 3). This is consistent with our observation that average adult BMI levels of participants classified as 'low' genetic risk were above the overweight cut-off (≥25 kg/m^2, Fig. 2).

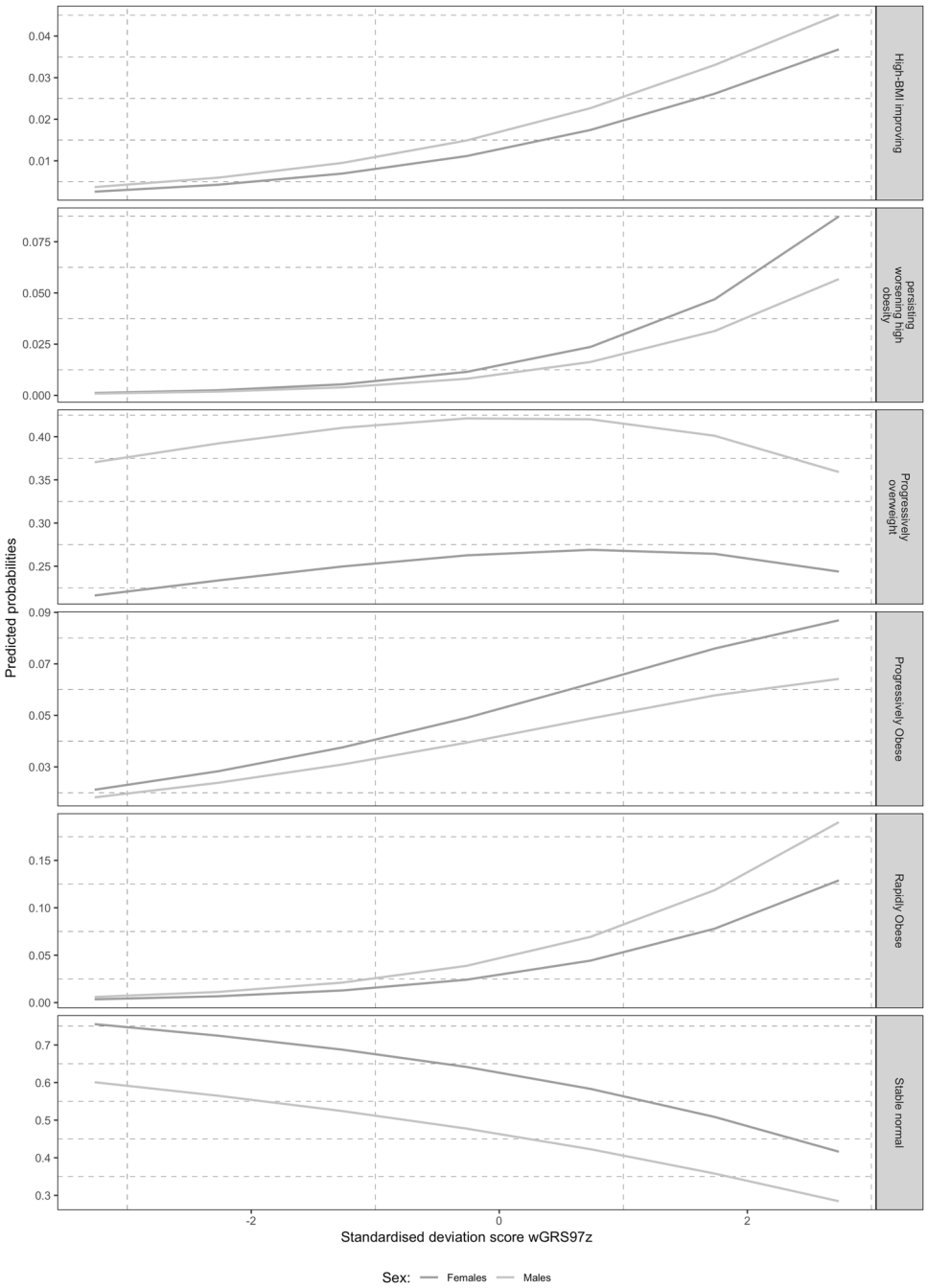

Fig. 3 Predicted probabilities of belonging to each identified life-course BMI trajectory as a function of the standardised deviation genetic risk score (wGRS97z). The plot is derived using parameter estimates from the sex- and wGRSz-score-adjusted multinomial regression model over a simulated grid of predictors, and shows how a 1 SD increase in the wGRS modifies the chance of belonging to a more or less healthy BMI life-course profile.

Discussion

This is the first study to investigate the combined effect of obesity-predisposing genetic variants on child-to-adult BMI trajectories. We found that a multigenic susceptibility for higher adult BMI could be tracked from young childhood, acting both on the BMI levels at age 6 years and the rates of change in BMI across childhood and adolescence. In line with a previous individual SNPs study that found most obesity-associated polymorphisms had a larger impact on BMI during childhood [29], we also found the genetic variants that influence adult BMI become increasingly important across childhood and the adolescent years, promoting faster BMI gain during these developmental stages. Moreover, our findings show that an individual with a higher number of risk alleles is at increased risk of belonging to a less favourable growth trajectory characterised by high-BMI values from childhood to adulthood. Our data are consistent with the hypothesis that the genetic determinants of adult susceptibility to obesity develops across the life course [10–12], and previous studies [9, 30, 31] with data from more restricted periods of the life

course. Our results also suggest sex differences in the apparent timing of effects of the wGRS97 on BMI, not previously reported.

The combined genetic effect on BMI was highest in young adulthood, but stabilised or decreased slightly in males as they aged (>40 years). This suggests that past this age, the multigenic effect on BMI plateaus or becomes weaker, with exogenous factors such as diet, smoking, and physical activity potentially becoming increasingly important determinants of inter-individual variations in adult BMI levels. This finding is consistent with individual SNP associations studies [10–12] that reported a larger effect size on BMI in early life than in adults for eight adult-associated SNPs included in our combined genetic risk score (FTO, MC4R, TMEM18, TNN13K, SEC16B, GNDPA2, QPCTL, BNDF). These variants, known to control factors that regulate biological mechanisms such as glycaemic homoeostasis and metabolism, are thought to be more sensitive to genetic alteration in early life, whereas environmental elements might play a larger role at older ages [10–12]. Our results also concord with findings that the collective effect of adult-associated BMI variants on body weight increases during childhood and plateaus in late adolescence and young adulthood [9, 13], although these studies did not have any anthropomorphic measures past age 25 years.

Our final IGC adulthood model explained <10% variance in BMI, suggesting that wGRS97 is not a strong determinant of inter-individual variability in adult BMI. It is likely that factors other than genetic play an important role in between-person differences in adult BMI. In addition, the lack of age-dependent interactions in this model suggests the wGRS97 does not predict change/increases in BMI levels within-person after age 24 years, suggesting the cumulative score does not explain inter-individual variation in weight gain across the adult period. This lack of association between the wGRS97 and adult BMI change from age 24 to 49 years could also reflect developmental stage-specific effects of genetic obesity mechanisms or the relatively greater influence of accumulated environmental factors [10–12].

Although participants in more adverse life-course trajectory groups tended to have larger numbers of risk-increasing variants, obese adults whose BMI levels reduced greatly after age 25 years (e.g., 'high-BMI improving' group) had a multigenic risk allele load comparable with those in the two most adverse BMI trajectory groups. While further research should focus on characterising these 'high-BMI improvers', this finding suggests that the mechanism by which this small group managed to overcome obesity or greatly improve their BMI levels in adulthood is most likely related to exogenous factors such as lifestyle changes or intervention.

While our combined genetic risk score was associated with increased average BMI levels and greater rates of BMI change in childhood and adolescence, it explained a relatively small proportion of the deviance in BMI levels in these life periods (~23–26%), suggesting other variants might be more important at these ages. It is also possible the variants included in the wGRS97, identified in adult populations, did not substantially alter BMI levels at these stages of the life-course (delayed cumulative effect theory [13]), or that they failed to play a measurable effect on BMI because other endogenous or exogenous factors that only manifest later in life were yet to occur [10–12]. This highlights the importance of identifying age-specific effects of genetic variants, which may help shed light on the life-course aetiology of obesity and gene function. Especially, conducting GWAS in growing children and adolescent populations might help identify loci that have early life effects [14, 32], providing an opportunity for new insights into childhood obesity. From a clinical perspective, future studies should investigate whether the wGRS97 provides added predictive utility over paediatric BMI measures in screening for later obesity.

We acknowledge our use of a composite risk score prevents inference on the possible differential contribution of individual SNPs. Moreover, as our study sample was born pre-1980 younger generations have matured in a comparatively more obesogenic environment and may experience differential contribution of genetic influence on BMI, BMI increases, and weight gain across the life course. We did not investigate other predictors of between-person change in within-person BMI over time. The effects of genotype on this change is likely impacted by many factors other than age. These include time-varying lifestyle factors of diet and physical activity, in addition to, or in conjunction with, obesity-predisposing alleles. Further studies are needed to determine the time-varying effect of these factors from the effects of genetic variants. Finally, our study did not consider the potential effects of gene–environment interaction. Further studies should determine if the composite risk score (or individual SNPs) modify individual BMI in response to environmental risk factors, or if the combined genetic effects of these variants differs between groups depending on lifestyle. In addition, despite many advantages over single SNP analyses, polygenic risk scores are not suitable to examine if SNP–SNP interactions influence disease outcome. Future genome-wide searches for these interactions might provide insight into the genetic architecture that underlies the development of obesity [33]. Despite these limitations, our study strengthens the current understanding of combined genetic influences of adult-associated obesity-predisposing variants on developmental trajectories of BMI across important life stages for the

development of obesity, as well as across a 30-year period of the life course.

We found a multigenic effect of adult obesity-associated variants on BMI development across the life course, with the effect most pronounced in early adulthood. Our findings support the notion that prevention of adult obesity should begin early in life when the joint effect of genetic variants is still relatively low, and when adopting healthy lifestyle habits might contribute to mitigate the genetic effect to establish children on healthy BMI trajectories. Additional replication in cohorts with anthropomorphic measures taken from infancy and across young childhood are needed to further evaluate the genetic contribution to early weight milestones and BMI growth. This is particularly important in the accepted paradigm for the developmental origins of health and diseases, stating the importance of optimising growth during early life for improving life-long health.

Acknowledgements The YFS has been financially supported by the Academy of Finland: grants 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research; Finnish Cultural Foundation; The Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; Diabetes Research Foundation of Finnish Diabetes Association; and EU Horizon 2020 (grant 755320 for TAXINOMISIS); and European Research Council (grant 742927 for MULTIEPIGEN project); Tampere University Hospital Supporting Foundation. CGM is supported by National Heart Foundation of Australia Future Leader Fellowship (100849).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. Ludwig DS. Childhood obesity-the shape of things to come. N Engl J Med. 2007;357:2325–7.
2. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med. 1997;337:869–73.
3. Juhola J, Magnussen CG, Viikari JS, Kahonen M, Hutri-Kahonen N, Jula A, et al. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the Cardiovascular Risk in Young Finns Study. J Pediatr. 2011;159:584–90.
4. Buscot M-J, Thomson RJ, Juonala M, Sabin MA, Burgner DP, Lehtimäki T, et al. Distinct child-to-adult body mass index trajectories are associated with different levels of adult cardiometabolic risk. Eur Heart J. 2018;39:2263–70.
5. Buscot MJ, Thomson RJ, Juonala M, Sabin MA, Burgner DP, Lehtimaki T, et al. BMI trajectories associated with resolution of elevated youth BMI and incident adult obesity. Pediatrics. 2018;141.
6. Rokholm B, Silventoinen K, Tynelius P, Gamborg M, Sorensen TI, Rasmussen F. Increasing genetic variance of body mass index during the Swedish obesity epidemic. PLoS ONE. 2011;6:e27135.
7. Visscher PM, Brown MA, McCarthy MI, Yang J. Five years of GWAS discovery. Am J Hum Genet. 2012;90:7–24.
8. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015;518:197–206.
9. Munthali RJ, Sahibdeen V, Kagura J, Hendry LM, Norris SA, Ong KK, et al. Genetic risk score for adult body mass index associations with childhood and adolescent weight gain in an African population. Genes Nutr. 2018;13:24.
10. Graff M, Ngwa JS, Workalemahu T, Homuth G, Schipf S, Teumer A, et al. Genome-wide analysis of BMI in adolescents and young adults reveals additional insight into the effects of genetic loci over the life course. Hum Mol Genet. 2013;22:3597–607.
11. Graff M, North KE, Mohlke KL, Lange LA, Luo J, Harris KM, et al. Estimation of genetic effects on BMI during adolescence in an ethnically diverse cohort: The National Longitudinal Study of Adolescent Health. Nutr Diabetes. 2012;2:e47.
12. Graff M, North KE, Richardson AS, Young KL, Mazul AL, Highland HM, et al. BMI loci and longitudinal BMI from adolescence to young adulthood in an ethnically diverse cohort. Int J Obes. 2017;41:759–68.
13. Warrington NM, Howe LD, Paternoster L, Kaakinen M, Herrala S, Huikari V, et al. A genome-wide association study of body mass index across early life and childhood. Int J Epidemiol. 2015;44:700–12.
14. Day FR, Loos RJ. Developments in obesity genetics in the era of genome-wide association studies. J Nutrigenet Nutrigenom. 2011;4:222–38.
15. Song M, Zheng Y, Qi L, Hu FB, Chan AT, Giovannucci EL. Longitudinal analysis of genetic susceptibility and bmi throughout adult life. Diabetes. 2018;67:248–55.
16. Dietz WH. Critical periods in childhood for the development of obesity. Am J Clin Nutr. 1994;59:955–9.
17. Dietz WH. Health consequences of obesity in youth: childhood predictors of adult disease. Pediatrics. 1998;101:518–25.
18. Hardy R, Wills AK, Wong A, Elks CE, Wareham NJ, Loos RJ, et al. Life course variations in the associations between FTO and MC4R gene variants and body size. Hum Mol Genet. 2010;19:545–52.
19. Raitakari OT, Juonala M, Ronnemaa T, Keltikangas-Jarvinen L, Rasanen L, Pietikainen M. Cohort profile: the cardiovascular risk in Young Finns Study. Int J Epidemiol. 2008;37:1220–6.
20. Teo YY, Inouye M, Small KS, Gwilliam R, Deloukas P, Kwiatkowski DP, et al. A genotype calling algorithm for the Illumina BeadArray platform. Bioinformatics. 2007;23:2741–6.
21. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet. 2009;5:e1000529.
22. Consortium TGP. A map of human genome variation from population-scale sequencing. Nature. 2010;467:1061–73.
23. Freedman DS, Lawman HG, Skinner AC, McGuire LC, Allison DB, Ogden CL. Validity of the WHO cutoffs for biologically implausible values of weight, height, and BMI in children and adolescents in NHANES from 1999 through 2012. Am J Clin Nutr. 2015;102:1000–6.
24. Shi J, Korsiak J, Roth DE. New approach for the identification of implausible values and outliers in longitudinal childhood anthropometric data. Ann Epidemiol. 2018;28:204–11.e3.
25. Mirman D. Growth curve analysis and visualization using R. Boca Raton: Chapman and Hall/CRC; 2014.
26. Mirman D, Dixon JA, Magnuson JS. Statistical and computational models of the visual world paradigm: Growth curves and individual differences. J Mem Lang. 2008;59:475–94.

27. Singer JD, Willett JB. Applied longitudinal data analysis: modeling change and event occurence. New York: Oxford University Press; 2003.
28. Team RC. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2013. http://www.R-project.org/.
29. Hohenadel MG, Baier LJ, Piaggi P, Muller YL, Hanson RL, Krakoff J, et al. The impact of genetic variants on BMI increase during childhood versus adulthood. Int J Obes. 2016;40:1301–9.
30. Fulford AJ, Ong KK, Elks CE, Prentice AM, Hennig BJ. Progressive influence of body mass index-associated genetic markers in rural Gambians. J Med Genet. 2015;52:375–80.
31. Warrington NM, Howe LD, Wu YY, Timpson NJ, Tilling K, Pennell CE. et al. Association of a body mass index genetic risk score with growth throughout childhood and adolescence. PLoS ONE. 2013;8:e79547.
32. Felix JF, Bradfield JP, Monnereau C, van der Valk RJ, Stergiakouli E, Chesi A, et al. Genome-wide association analysis identifies three new susceptibility loci for childhood body mass index. Hum Mol Genet. 2016;25:389–403.
33. Seyednasrollah F, Makela J, Pitkanen N, Juonala M, Hutri-Kahonen N, Lehtimaki T, et al. Prediction of adulthood obesity using genetic and childhood clinical risk factors in the Cardiovascular Risk in Young Finns Study. Circ Cardiovasc Genet. 2017;10.
34. Nakagawa S, Schielzeth H. A general and simple method for obtaining R2 from generalized linear mixed-effects models. Methods Ecol Evol. 2013;4:133–42.