Genetic Risk Scores for Complex Disease Traits in Youth

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BACKGROUND: For most disease-related traits the magnitude of the contribution of genetic factors in adolescents remains unclear.

METHODS: Twenty continuous traits related to anthropometry, cardiovascular and renal function, metabolism, and inflammation were selected from the ongoing prospective Tracking Adolescents' Individual Lives Survey cohort in the Netherlands with measurements of up to 5 waves from age 11 to 22 years (n=1354, 47.6% males) and all traits available at the third wave (mean age [SD]=16.22 [0.66]). For each trait, unweighted and weighted genetic risk scores (GRSs) were generated based on significantly associated single nucleotide polymorphisms identified from literature. The variance explained by the GRSs in adolescents were estimated by linear regression after adjustment for covariates.

RESULTS: Except for ALT (alanine transaminase), all GRSs were significantly associated with their traits. The trait variance explained by the GRSs was highest for lipoprotein[a] (39.59%) and varied between 0.09% (ALT) and 18.49% (LDL [low-density lipoprotein]) for the other traits. For most traits, the variances explained in adolescents were comparable with or slightly smaller than those in adults. Significant increases of trait levels (except ALT) and increased risks for overweight/obesity (odds ratio, 6.41 [95% CI, 2.95–15.56]) and hypertension (odds ratio, 2.86 [95% CI, 1.39–6.17]) were found in individuals in the top GRS decile compared with those at the bottom decile.

CONCLUSIONS: Variances explained by adult-based GRSs for disease-related traits in adolescents, although still relatively modest, were comparable with or slightly smaller than in adults offering promise for improved risk prediction at early ages.

Key Words: adolescent ⚫ blood pressure ⚫ body mass index ⚫ genetic predisposition to disease ⚫ genetic variation

Recently, an increasing number of genetic variants—mostly single nucleotide polymorphisms (SNPs)—have been identified to be associated with human traits through meta-analyses of genome-wide association studies (meta-GWASs). To evaluate the overall contribution of these identified genetic variants, genetic risk scores (GRSs) were constructed for many disease-related traits and were found to often explain a significant portion of the trait variation. As more SNPs continue to be discovered, such GRSs provide possibilities to predict complex disease risk at the individual level and have potential application in disease prevention.

For example, many studies on blood pressure and body mass index (BMI) have shown that increased levels in youth track into adulthood and are associated with immediate and long-term health risks. Applying GRSs at an early age to identify individuals at high genetic risk for hypertension and obesity might, therefore, aid in early prevention. As most SNPs were identified from meta-GWAS in adults, the question whether these adult-based GRSs can be applied in youth needs to be answered. A
longitudinal twin study on blood pressure showed that novel genetic effects emerged between ages 14 and 18 years and explained a significant part of the variation in blood pressure. Another study found that 5 loci had different effects on BMI during adolescence and young adulthood (16–25 years) compared with middle-age adults. These results support age-dependent genetic effects and suggest that GRSs derived from adults may not have the same effect in youth. Thus, there is the need to investigate to what extent adult-based GRSs can predict disease-related traits in youth.

However, so far only a few traits and diseases were explored, and the contributions of GRSs in adolescents for other traits remain unclear. Furthermore, as the list of identified genetic markers has recently expanded dramatically, the effect of updated GRSs using the latest GWAS findings requires evaluation in adolescents. Therefore, the aim of the current study was to assess and evaluate the variance explained by adult-based GRSs on a wide variety of disease-related traits in adolescents from the Netherlands. We used 20 continuous traits from the Tracking Adolescents’ Individual Lives Survey (TRAILS) cohort, related to anthropometry, cardiovascular and renal function, metabolism and inflammation. For each trait, we generated GRSs based on significantly associated SNPs identified from literature. Then we assessed how much of the phenotypic variance could be explained by these GRSs in adolescents and compared it with the phenotypic variance explained in adult populations. We also compared the trait levels and risks of hypertension and obesity between individuals in each of the upper 9 deciles with those in the bottom decile of the GRSs distribution. Furthermore, we replicated findings of some major traits such as BMI and blood pressure in the TRAILS clinical cohort.

METHODS

The research was conducted in TRAILS, an ongoing prospective population-based cohort which assesses physical and psychosocial health from preadolescence to adulthood in the Netherlands. Because of the personal nature of the data, the data set is not online available. Requests to access the data may be submitted by means of a publication plan form for external users, which is available at https://www.trails.nl/en/hoofdmenu/data/data-use.

The traits of interest and the literature from which SNPs were identified are presented in Table 1. All SNPs and their effect sizes for constructing GRS can be found in Table I through XXI in the Data Supplement. Full descriptions of trait and SNP selection, participants and traits measurements, genotyping and imputation, and statistical analyses are available in the Supplementary Methods.

All procedures were approved by the Dutch Central Committee on Research Involving Human Subjects. Written informed consent, including specific consent to undertake genetic analyses, was obtained from participants and their parents or custodians.

RESULTS

Participants and Traits Description

Table 2 shows the descriptive statistics of age and the quantitative traits we selected in the TRAILS cohort at the third wave (for all waves see Table XXII in the Data Supplement). A total of 1354 participants whose GWAS data were available were included in the analyses, 644 (47.6%) of whom being males. The mean ages (in years) of the 5 waves (T1–T5) were 11.1, 13.5, 16.2, 19.2, and 22.4, respectively. In total 20 traits, related to anthropometry, cardiovascular and renal function, metabolism and inflammation were selected.

SNPs Selection

Figure 1 shows the process and results of SNP selection for the 20 traits of interest. We selected 17 articles as sources of SNPs for the 20 traits, of which 13 used GWAS data, 2 used exome-centric chips, and 2 used a combination of GWAS and gene-centric data. From these articles, we identified 8183 SNP-phenotype associations. For 35 associations, SNPs were missing in the TRAILS genotyped or imputed data, but we could successfully find proxies for 10 of them. Eighty-one associations were removed because SNPs were in linkage disequilibrium (LD) with another selected SNP. Finally, 8077 SNP-phenotype combinations were included for
constructing GRSs of the 20 traits (Figure 1; Table I through XXI in the Data Supplement).

**GRS Analysis**

Table 3 shows the results of weighted GRS analysis at the third wave (for results of unweighted genetic risk score [uGRS] see Table XXIII in the Data Supplement, for all waves see Table XXIV in the Data Supplement). The number of SNPs included in the GRSs ranged from 4 (for ALT [alanine transaminase]) to 3290 (for height). Except for the GRSs for ALT, all GRSs were significantly associated with their traits and explained a significant part of the phenotypic variance. The variance explained by the GRSs for the traits varied greatly: the weighted GRS incorporating 49 SNPs for Lp(a) (lipoprotein[a]) explained 39.59% of its variance, while the weighted genetic risk score (wGRS) for ALT only explained 0.10% and was not significant. Apart from Lp(a), GRSs for height, HDL (high-density lipoprotein), LDL (low-density lipoprotein), and total cholesterol had relatively large contributions to their traits (above 10%). For blood pressure, the variance explained by the wGRS is 2.15% for systolic blood pressure (SBP) and 4.48% for diastolic blood pressure. For anthropometric traits that had repeated measurements (Figure 2, Table XXIV in the Data Supplement), we found increases in variance explained by the GRSs for height with older age (eg, from 9.34% at 14 years of age to 12.03% at the age of 16 for the uGRS), but the differences were not significant. The variances explained remained similar for BMI from 11 to 22 years (between 5.79% and 6.55% for wGRS) and for waist-to-hip ratio (BMI adjusted) from 16 to 22 years (between 1.38% and 1.95% for wGRS).

The variance explained by GRSs increased when using the wGRSs compared with the uGRSs for most traits (Table XXIII and Figure I in the Data Supplement), with the biggest increase for LDL. The uGRS for LDL explained 8.88% of the variance compared with 18.49% by the wGRS, an increase of almost 10%. For the traits that needed correction...
for the TRAILS result, wGRSs using corrected effect sizes explained slightly less variance (range: 0.01%–0.43%) than wGRSs using uncorrected effect sizes from the literature as expected (Table XXV in the Data Supplement).

For 17 traits, variances explained in adolescents were compared with variance explained in adults that were extracted from literature (Figure 3, Table 3, and Table XXVI in the Data Supplement). Generally, variances explained in adolescents were similar or slightly less than those in adults, with the biggest difference for CRP (C-reactive protein). The variance explained for CRP was 3.69% in adolescents compared with 11% in adults.

For all traits except ALT, significant increases of trait levels were found in individuals at the top wGRS decile compared with those at the bottom decile (Table 3). For instance, individuals at the top decile of the wGRS for SBP had on average a 6.30 mm Hg higher SBP (95% CI, 3.54–9.07 mm Hg) than those at the bottom decile. For most traits levels of trait increased along with increases in the GRS decile (Figure II in the Data Supplement). Furthermore, over 6-fold higher risk of overweight/obesity (odds ratio, 6.41 [95% CI, 2.95–15.56]) and around 3-fold higher risk of hypertension (odds ratio, 2.86 [95% CI, 1.39–6.17]) were observed between top and bottom deciles of the GRS (Figure 4).

Replication in TRAILS Clinical Cohort

From TRAILS clinical cohort, 341 participants (69.2% males) with available DNA were included in replication.
analyses for height, BMI, waist-to-hip ratio (BMI adjusted), heart rate, SBP, diastolic blood pressure, glycated hemoglobin; %. Generally, GRSs also explained significant proportions of phenotypic variance in TRAILS clinical cohort (Table XXVII in the Data Supplement).

Additional Analyses for BMI and Blood Pressure

Fifteen SNPs were identified in meta-GWAS of childhood BMI and 2 SNPs for SBP in children or adolescents.32,33 For childhood BMI, 6 SNPs showed significant associations with BMI at 11 years in TRAILS (P<0.05), and 14 SNPs had directionally consistent effects with those reported by meta-GWASs (Table XXVIII in the Data Supplement). For childhood SBP, the 2 SNPs were not significantly associated with SBP in TRAILS, but they had the same direction of effect as those in the meta-GWAS (Table XXVIII in the Data Supplement). Comparing with the uGRSs only including SNPs identified in adults, the uGRSs combining SNPs identified in adults and in children/adolescents explained slightly more variance of SBP and BMI at 11 years and 14 years (eg, SBP, R^2=1.69% compared with 1.67%; Table XXIX in the Data Supplement).

DISCUSSION

In this study, we investigated in 1354 Dutch adolescents how much of the variance of 20 complex disease traits could be explained by adult-based GRSs. Our results showed that almost all adult-based GRSs were significantly associated with their respective traits in adolescents. The trait variance explained by the GRSs varied...
from 0.09% to 39.59%, with weighted GRSs generally explaining a larger proportion of variance than the unweighted GRSs. For most traits, the variance explained in adolescents was comparable with or slightly less than in adults. Significant increases of trait levels (except AL T) and increased risks for overweight/obesity and hypertension were found in individuals in the top wGRS decile compared with those at the bottom decile.

Among metabolism traits, the variance explained by GRSs varied greatly, which may be caused by the differences in trait heritabilities and genetic architecture. For example, the wGRS for AL T explained 0.01% of variance which was not significant, while the wGRS for Lp(a) explained nearly 40%. The small variance explained for AL T is likely due to moderate heritability (22%–40% estimated from twin-family studies) and the GRS including only 4 SNPs as many AL T-associated SNPs may not yet have been identified due to insufficient power of the discovery GWAS.34,35 For some other liver enzymes, such as ALP (alkaline phosphatase) and GGT (γ-glutamyl transferase), more SNPs were identified in the original GWAS, but these traits were not measured in TRAILS.22 On the contrary, Lp(a) is highly heritable (≈90%), with 48 identified SNPs located in the LPA gene region and only one SNP in another gene (APOE), indicating that this trait is not (very) polygenic in its architecture.29,36,37 For lipid traits (HDL, LDL, total cholesterol, and triglycerides), we selected SNPs from both genome-wide and exome-centric association studies including some rare variants (minor allele frequency <1%). We found that the GRSs excluding rare variants explained slightly less variance of the lipid traits than the GRSs including rare variants, which indicates that even these rare variants with low imputation quality in TRAILS contribute to lipid trait variance (Table XXX and XXXI in the Data Supplement). For repeatedly measured traits, no significant change was found between different waves. This is probably due to insufficient power of our sample or relatively stable influences of genetic factors during this age period (11–22 years).

The associations between adult-based GRSs and their respective traits in adolescents suggest that many of SNPs identified in adults also have effects in adolescents. Similar findings were reported before for GRSs based on blood pressure and BMI loci.10,12 Another study found a genetic correlation of 0.73 between childhood and adult BMI as calculated by LD score regression, indicating large but not perfect genetic overlap between childhood and adult BMI.32 These results indicate the potential of applying adult-based GRSs to disease-related traits for prediction at an early age. Besides, additional analyses for BMI and blood pressure suggested that combining SNPs identified in adults and in children/adolescents can increase the predictive ability of GRS. If more SNPs will be identified in future GWASs of children or adolescents, GRSs of these traits will likely explain...
more variance of their traits. In addition, Evangelou et al.\textsuperscript{19} discovered that the gGRS for blood pressure was associated with increased risk of cardiovascular events during adulthood. Our study showed that the adult-based GRSs for blood pressure and BMI could also predict hypertension and overweight/obesity, respectively, during adolescence. Therefore, GRSs for blood pressure and BMI may have the potential to guide preventative measures for hypertension and obesity in youth. For example, lifestyle interventions such as diet and physical activity could be targeted in individuals who are identified at high genetic risk already in early life.

Furthermore, we found that the effects of adult-based GRSs are similar or slightly smaller in adolescents compared with adults. The similarities of effects between adolescents and adults suggest that for some traits the influence of genetic factors may remain relatively stable from adolescence to adulthood. One reason for the small differences of effects between adolescents and adults may be age-dependent genetic effects (different genes may play a role or the magnitude of effects of the same genes on the phenotypes may change over time). For instance, variance explained for SBP was less in adolescents than in adults (2.15\% versus 5.70\%).\textsuperscript{19} Other studies on blood pressure confirmed that not all individual SNPs identified in adults were significantly associated with BP in adolescents and that adult-based GRSs explained less variance in adolescents.\textsuperscript{12,33} Another reason may be lack of stability of phenotypes for some traits. Levels of some traits during adolescence may be quite different from levels in adulthood as adolescence is a period of rapid anthropometric change. The growth rate

Figure 3. The comparison between variances explained in adolescents and in adults. At the red dashed line, the variances explained in adolescents and adults are the same.

Seventeen traits are shown: height, body mass index (BMI), waist-to-hip ratio ([BMI adjusted] WHR adjBMI), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), estimated glomerular filtration rate (eGFR), glycated hemoglobin (HbA1c), ALT (alanine transaminase), fasting glucose (FG), fasting insulin (FI), HDL (high-density lipoprotein), LDL (low-density lipoprotein), total cholesterol (TC), triglycerides (TG), Lp(a) (lipoprotein[a]), CRP (C-reactive protein). For some traits, our results were not completely comparable with those from literature as different methods compared with ours were used for some traits to estimate variance explained in adults. In the literature, the method that included all single nucleotide polymorphisms (SNPs) into a linear regression model, adjusted for covariates and calculated the adjusted R\textsuperscript{2} was used for WHRadjBMI, SBP, DBP, HbA1c, FI, HDL, LDL, TC, and TG. The formula (\text{\left[2\times MAF(1−MAF)b^2/v\right]} was used for eGFR and CRP. In addition, for some traits not exactly the same SNPs as ours were included to evaluate variance explained in adults. Some traits included a few more SNPs than ours (SBP, DBP, eGFR, HbA1c, FI), while some traits included a few less (WHRadjBMI, HR, HDL, LDL, TC, TG, Lp[a]). See Table XXVI in the Data Supplement for more details.
varies between individuals as indicated by the less than perfect tracking (eg, the correlation between height at 11 and 22 years old was only 0.414) indicating that during adolescence individuals may be at different stages of development (Table XXXII in the Data Supplement). Finally, we observed a much smaller explained variance for CRP in adolescents compared to adults. However, the original meta-GWAS in adults applied the formula $2 \times \text{MAF}(1-\text{MAF})b^2/\text{var}$ to estimate variance explained rather than performing an out-of-sample prediction in an independent validation cohort, which may have caused an overestimate of their explained CRP variance in adults.30 For some traits, our results were not completely comparable with those from literature, as they used different methods or included not exactly the same SNPs as we did to estimate variance explained in adults (Table XXVI in the Data Supplement). Nonetheless, the comparisons indicate that for most traits genetic markers identified in GWASs of adults may explain similar or slightly less variance in adolescents than in adults.

One statistical issue is that in spite of testing GRSs for 20 different traits, we have chosen not to apply a multiple testing correction in our study, because our aim was to replicate significant results from previous studies. We simply provided exact $P$ values of GRSs for all traits in Table 3. However, it is important to point out that the GRSs for most traits would remain significant even if we used a corrected significance threshold of 0.0025 for 20 independent tests. Therefore, the interpretation of the results would not change if we would have adjusted for multiple testing.

A limitation of our study is that we included only known genome-wide significant SNPs in our GRSs, instead of using approaches which include all available SNPs like a polygenic risk score or LDpred. Polygenic risk score is similar to GRS but includes larger number of independent SNPs by using more lenient significance thresholds.38 LDpred includes all SNPs below a certain significance threshold and accounts for LD among SNPs to reduce loss of information.39 Conducting polygenic risk score or LDpred requires GWAS summary statistics that were not available for all 20 traits we investigated, so we chose to use the GRS approach, which only needs a list of significant SNPs as published in the literature. As such, our results are conservative; polygenic scores generated by polygenic risk score or LDpred are likely to explain more variance. In addition, we selected only SNPs identified from European ancestry and applied GRSs in adolescents of the same ancestry. Our results may not be applicable to adolescents from other ethnicities.

Despite these limitations, our research contributes to the understanding of genetic influence on 20 traits during a specific life period. To our knowledge, we are the first to evaluate the variance explained by adult-based GRSs for a wide range of disease-related traits in one homogeneous adolescent cohort. Even with a relatively small
sample size, we detected associations between adult-based GRSs and 19 traits in adolescents. In addition, as we had repeated measurements for some traits such as height, BMI, and waist-to-hip ratio, we could observe the contributions of known SNPs to these traits at different ages during the critical time period from childhood to early adulthood. Further, we calculated GRSs using the latest GWAS findings, so we could evaluate the value of applying updated adult-based GRSs in adolescence. With the help of larger GWAS studies, more GWASs in children or adolescents and improved approaches for calculating genetic predictors, genetic risk prediction is likely to further gain accuracy. As genetic predictors can be calculated for many diseases simultaneously from birth onwards, genetic risk prediction provides opportunities to identify high-risk strata for many diseases at an early age, which is especially important for diseases with known effective interventions.

In conclusion, we demonstrated that almost all adult-based GRSs for 20 continuous disease trait were significantly associated with their respective traits in adolescents. Overall, these adult-based GRSs explained a small to moderate part of phenotypic variance in adolescents and their effects appeared comparable or with slightly smaller than in adults. Larger GWAS studies and improved approaches to calculating genetic predictors in combination with efforts to integrate genetic, environmental, clinical, and molecular risk factors may offer promise for improvement of disease prevention.

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Disclosures
None.

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