



The Early Growth Genetics (EGG) and EARly Genetics and Lifecourse Epidemiology (EAGLE) consortia: design, results and future prospects

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Received: 20 November 2018 / Accepted: 25 January 2019 / Published online: 18 March 2019
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Abstract

The impact of many unfavorable childhood traits or diseases, such as low birth weight and mental disorders, is not limited to childhood and adolescence, as they are also associated with poor outcomes in adulthood, such as cardiovascular disease. Insight into the genetic etiology of childhood and adolescent traits and disorders may therefore provide new perspectives, not only on how to improve wellbeing during childhood, but also how to prevent later adverse outcomes. To achieve the sample sizes required for genetic research, the Early Growth Genetics (EGG) and EARly Genetics and Lifecourse Epidemiology (EAGLE) consortia were established. The majority of the participating cohorts are longitudinal population-based samples, but other cohorts with data on early childhood phenotypes are also involved. Cohorts often have a broad focus and collect(ed) data on various somatic and psychiatric traits as well as environmental factors. Genetic variants have been successfully identified for multiple traits, for example, birth weight, atopic dermatitis, childhood BMI, allergic sensitization, and pubertal growth. Furthermore, the results have shown that genetic factors also partly underlie the association with adult traits. As sample sizes are still increasing, it is expected that future analyses will identify additional variants. This, in combination with the development of innovative statistical methods, will provide detailed insight on the mechanisms underlying the transition from childhood to adult disorders. Both consortia welcome new collaborations. Policies and contact details are available from the corresponding authors of this manuscript and/or the consortium websites.

Keywords Genetics · Consortium · Childhood traits and disorders · Longitudinal

Background

The full author list for this manuscript, including affiliations, includes all current active members of both consortia and is listed at the end of the paper followed by the membership lists of the EGG and EAGLE consortia as well as the acknowledgments and disclosures of interests.

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In countries with a high-sociodemographic index, the major contributors to burden of disease during childhood and adolescence are non-communicable diseases such as obesity,

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asthma or allergies, and psychiatric disorders. These have a large cumulative impact on individuals, families and society [1]. Moreover, many early-life traits track throughout childhood and adolescence into adulthood. Childhood obesity, for example, is associated with adult obesity and cardiovascular disease [2]. Several childhood psychiatric disorders persist into adolescence and adulthood or precede severe mental illness such as schizophrenia, which usually starts at late adolescence or early adulthood [3, 4]. Low birth weight, as a proxy for a suboptimal intrauterine environment, has been shown to be robustly associated with many later-life non-communicable traits, including cardiovascular, respiratory and psychiatric disorders (see e.g., 5–7). This prompted researchers, including those within the Developmental Origins of Health and Disease (DOHaD) field, to investigate the basis for the early origins of later life differences in health and disease.

Insight into the etiology of childhood and adolescent traits and disorders may provide new perspectives, not only on how to improve wellbeing during childhood, but also how to prevent later adverse outcomes. Individual differences in developmental phenotypes, such as body weight and composition, behavioral problems, language skills, and their stability across ages are partly influenced by genetic factors [8–13]. Identifying the specific genetic variants that influence these traits, and the biological pathways through which they operate, can therefore help to unravel etiological mechanisms. Genetic studies can also define whether the relationships between childhood and adult traits, for example, birth weight and cardiovascular disease, are causally mediated by early life exposures. In addition, genetics can support how specific environmental factors contribute to variation in these traits, i.e., whether there is gene-environment

interaction with the increase in risk depending on an individual's genetic risk.

It is increasingly recognized that large sample sizes are essential in genetic research [14] and studies performed in large international consortia have become the norm. Two such consortia with a particular focus on the genetics of early life phenotypes are the Early Growth Genetics (EGG) consortium (<http://egg-consortium.org/>) and the EARly Genetics and Lifecourse Epidemiology (EAGLE) consortium (<http://www.wikigenes.org/e/art/e/348.html>) (Fig. 1). This paper describes these two consortia as they have shared objectives and the participating cohorts partly overlap. We also highlight the results so far and outline the directions of future research.

Description and aims of the EGG and EAGLE consortia

Both consortia arose in 2009 out of the EU-funded European Network for Genetic And Genomic Epidemiology (ENGAGE). The EGG consortium focuses on the genetic basis of growth-related phenotypes spanning from fetal life into adolescence, including birth weight, childhood obesity and pubertal development. EAGLE was established to investigate the genetic basis of the wide range of further phenotypes collected by these cohorts from fetal life into adolescence, such as those relevant to asthma and eczema, childhood psychopathology, cognition, and neurodevelopment. The collective objectives of EGG and EAGLE are:

1. to characterize the genetic background of traits and diseases in fetal life, childhood and adolescence by facilitating collaboration between pregnancy, birth, childhood

Fig. 1 Logo's

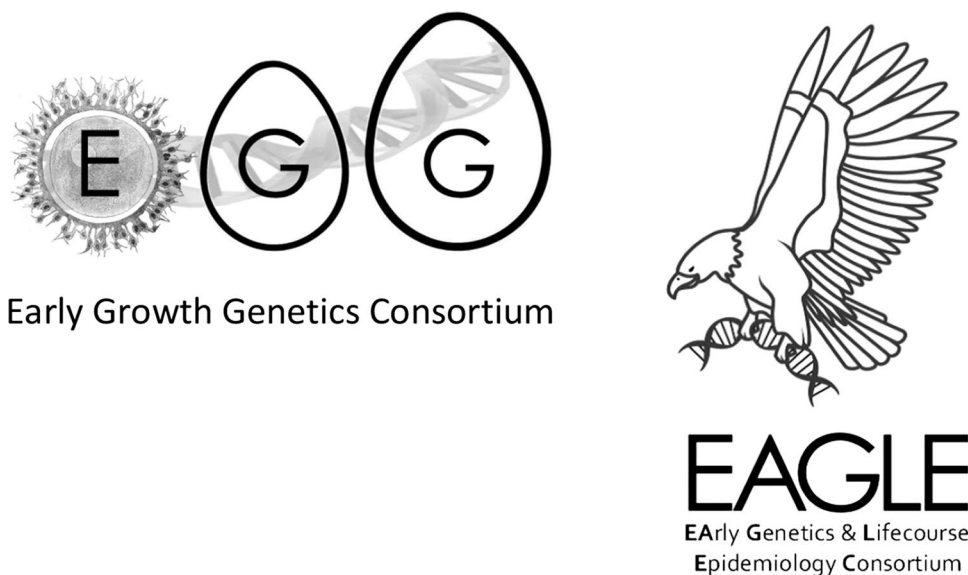


Table 1 Participating cohorts

Short name	Full name cohort	Website	References
ABCD	Amsterdam Born Children and their Development	https://abcd-studie.nl/	20813863
ALSPAC	Avon Longitudinal Study on Parents and Children	www.bristol.ac.uk/alspac/	22507743, 22507742
B58C	1958 British Birth Cohort	www.cls.ioe.ac.uk/page.aspx?&siteid=724&site=Development http://www.ncl.ac.uk/development	16155052, 17255346
BAMSE	Children, Allergy, Milieu, Stockholm, Epidemiology	https://ki.se/en/imm/bamse-project	26505741
BMDCS	Bone Mineral Density in Childhood Study	https://bmdcs.nichd.nih.gov/	17311856
Breathe	BRAIn dvelopment and Air pollution ultrafine particles in school children	https://www.isglobal.org/en-/breathe-brain-development-and-air-pollution-ultrafine-particles-in-school-children	25734425, 27656889
CATSS	Child and Adolescent Twin Study in Sweden	https://ki.se/en/meb/the-child-and-adolescent-twin-study-in-sweden-cats	22506305
CHOP	Children's Hospital of Philadelphia	https://www.caglab.org/	22138692
CHS	Children's Health Study	https://www.healthstudy.usc.edu/	10051249, 10051248, 17307103, 25738666, 28103443, 27115265
CLHNS	Cebu Longitudinal Health and Nutrition Survey	http://www.cpc.unc.edu/projects/cebu	20507864
COPSAC	Copenhagen Prospective Studies on Asthma in Childhood	www.copsac.com	15521375, 24118234, 24241537
DNBC	Danish National Birth Cohort	https://www.ssi.dk/English/RandD/Research%20areas/Epidemiology/DNBC.aspx	
EFSOCH	Exeter Family Study of Childhood Health		16466435
Finnwin12	Finnish Twin Cohort Study	https://wiki.helsinki.fi/display/twineng/Twinstudy	23298696, 17254406, 12537860
Gen3G	Genetics of Glucose regulation in Gestation and Growth Generation R Study	n/a	26842272
GINIplus	German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development	https://www.generationr.nl/ https://www.helmholtz-muenchen.de/epi/research/research-group/s/allergy-epidemiology/projects/giniplus/index.html	28070760, 25527369 20082618
GLAKU	Glycyrrhizin in Licorice	https://blogs.helsinki.fi/depsy-group/research/	19808634, 17076756; 11390327
HBSC	Helsinki Birth Cohort Study	https://thl.fi/en/web/thlfi-en/research-and-experimentwork/projects-and-programmes/helsinki-birth-cohort-study-hbc-idefix	11312225
Health2006	Health2006	https://clinicaltrials.gov/ct2/show/NCT00316667	23615486
INMA	Infancia y Medio Ambiente	http://proyectoinma.org/en_index.html	21471022
Inter99	The Inter99 Study	https://www.regionh.dk/rph/population-based-epidemiology/Pages/The-Inter99-Study.aspx	14663300
LISA	Influence of life-style factors on the development of the immune system and allergies in East and West Germany	https://www.helmholtz-muenchen.de/epi/research/research-group/s/allergy-epidemiology/projects/lisa/index.html	12358337
MAAS	Manchester Asthma and Allergy Study	http://maas.org.uk/	25805205, 15029579, 12688622
MOBA	Norwegian Mother and Child Cohort Study	https://fhi.no/studier/moba/	27063603,
MUSP	Mater University Study of Pregnancy	https://social-science.uq.edu.au/mater-university-queensland-study-pregnancy	25519422
NTR	Netherlands Twin Register	http://www.tweelingenregister.org/	23186620, 23265630

Table 1 (continued)

Short name	Full name cohort	Website	References
NFBC1966 and NFBC1986	Northern Finland Birth Cohort	http://www.oulu.fi/nfbc/	750195; 19060910; 9246691
PIAMA	Preventie en Incidentie van Astma en Mijt Allergie Project Viva	http://piama.iras.uu.nl/ http://dacr.org/viva/	12688626, 23315435 24639442
Qtwain	Queensland Twin Registry	http://www.qimrberghofer.edu.au/qtwain/	DOI: 10.1080/00049530410001734865
Raine	The Western Australian Pregnancy Cohort (Raine) Study	https://www.rainestudy.org.au/	8105165; 23230915; 233016741; 26169918; 28064197; 28662683
SKOT	Småbørns Kost Og Trivsel	https://skot.ku.dk/om-projektet/engilsh/	28947836
STRIP	Special Turku Coronary Risk Factor Intervention Project	http://stripstudy.uu.fi/english.html	18430753
TCHAD	Twin Study of Child and Adolescent Development	https://ki.se/en/meb/twin-study-of-child-and-adolescent-development-tchad	17539366
TDCOB	The Danish Childhood Obesity Biobank	https://clinicaltrials.gov/ct2/show/NCT00928473	23110994
TEDS	Twins Early Development Study	http://teds.ac.uk/	25431468
TRAILS	TRacking Adolescents' Individual Lives Survey	https://www.trails.nl/	18263651
Young Finns	The Cardiovascular Risk in Young Finns Study	http://youngfinnsstudy.utu.fi/	

- and adolescent cohort studies, as well as adult biobanks (such as UK Biobank) with relevant information;
- to define the causal relationships between early life exposures and related early life phenotypes and major sources of morbidity and mortality in later life;
- to develop and improve statistical methods for analyzing complex, high-dimensional and longitudinal phenotypic data;
- to provide training opportunities for junior researchers to develop in the field of genetic epidemiology.

The EGG and EAGLE consortia started as collaborations of population-based pregnancy and birth cohort studies, each of which has collected longitudinal data across a wide range of developmental phenotypes. As the collaboration developed, cohorts that started data collection during childhood and adolescence were also included. Almost all participating studies have genome-wide genotype data available. In addition, early life data collected through self-report and/or record linkage in adult biobanks, such as UK Biobank or the population based cohorts listed in Table 1 that have an adult counterpart, have been brought into the genome-wide association (GWA) meta-analyses for phenotypes such as birth weight. Both consortia welcome new collaborations, and they are keen to add data from longitudinal cohorts that are currently in the process of obtaining genotype data.

Tables 1 and 2 provides a summary of the participating studies and their design, as of April 2018. Table 3 gives further details on the extensive data available, indicating, per cohort, whether data collection has taken place at least once at preschool, school, adolescent and adult age. However, many cohorts have had multiple follow-up rounds within any given period or follow-up data collection is ongoing, through research clinic assessments, questionnaires or record linkage. The majority of the cohorts have around equal numbers of males and females included.

Most cohorts were established with the aim of investigating risk and protective factors for a broad range of developmental phenotypes. They have collected data on physical traits, cognition, emotional and behavioral problems, as well as on lifestyle and environmental factors, such as smoking during pregnancy and physical exercise. Other cohorts were set up with a specific focus, such as asthma research, but many of these have collected ancillary information on a wider range of phenotypes. Table 2 gives an indication as to whether data collection was focused on a specific phenotype. Additional details on many of these studies will be available from cohort websites and publications (see Table 1).

Participating cohorts have obtained DNA from blood samples, saliva or buccal swabs. A variety of different genotyping arrays have been used over the years, but meta-analysis has been facilitated by imputation of directly genotyped data using reference panels such as those generated by 1000

Genomes or the Haplotype Reference Consortium [15, 16]. Moreover, an increasing number of cohorts have, or plan to get, additional ‘omics data including parental genotypes, DNA methylation profiles, RNA expression levels, metabolomics and/or microbiome data.

Results of the genetic studies performed in the EGG and EAGLE consortia

The implementation of GWA meta-analyses for each of the phenotypes of interest to EGG or EAGLE has usually been championed and organized at the level of a working group, formed by a subset of motivated investigators and analysts, who have assumed responsibility for assembling, combining and interpreting the genetic data. The wide range of phenotypes available to study across these consortia has provided fertile ground for many such working groups and has resulted in a large number of peer-reviewed papers across this wide range of phenotypes [17–45]. These are typically GWA meta-analyses, focusing on the effects of individual genetic variants, but increasingly now extend to multivariate, polygenic analyses, that evaluate the joint effects of multiple associated genetic variants and apply this information to address questions of causality.

Amongst the many GWA analyses led by EGG and EAGLE, the traits for which the largest numbers of genetic loci reached genome-wide statistical significance ($p < 10^{-8}$) have been birth weight (65 loci), atopic dermatitis (31), childhood BMI (15), allergic sensitization (10), and pubertal growth (10) [17, 19, 23, 26, 28, 36]. For other phenotypes with a large number of genome wide hits, such as age at menarche (108 loci) or ADHD (16 loci), the association analysis has involved collaborations with other consortia [25, 37]. The summary statistics for many of the genome-wide association studies undertaken by EGG and EAGLE investigators can be found on consortium websites (<http://egg-consortium.org/>; <http://www.wikigenes.org/e/art/e/348.html>) or are available from corresponding authors.

As with adult phenotype GWA studies, the number of association signals recovered by these studies is influenced heavily by sample size ($N = 182,416$ for age at menarche, $N = 153,781$ for birth weight) and, to a lesser extent, by phenotype characteristics (somatic or behavioral traits, continuous or binary outcomes).

In addition to cross-sectional GWA analyses, there have been many examples of projects that have investigated genetic relationships within childhood traits or between childhood traits and related adult phenotypes, often revealing shared genetic factors. For example, genetic overlap was found among related atopic conditions during childhood, and between atopic conditions and auto-immune disorders

[19, 36]; among puberty-related phenotypes, and between puberty-related phenotypes and BMI [23, 24, 37]; between childhood and adult blood pressure [41]; between preschool internalizing symptoms and adult psychiatric disorders [18]; and between childhood and adult anthropometric traits [21, 26, 40, 44]. The development of statistical methods that support the calculation of genetic correlations from summary GWAS results [46] and the easy availability of such data from a growing number of GWA meta-analyses for adult traits have enabled these analyses to be undertaken with adequate statistical power.

Figure 2 shows genetic correlations, calculated exclusively from GWAS data, between birth weight and a range of continuous and disease phenotypes [28], generated using the linkage disequilibrium score regression approach [46] as implemented in the LDHub web utility [47]. For many cardiometabolic and anthropometric traits measured in late adult life, there is evidence of substantial sharing of genetic variation with birth weight. In line with the wider epidemiological data, the genetic correlations between birth weight and adult cardiometabolic traits (including type 2 diabetes, blood pressure, and coronary artery disease) tend to be negative. These data indicate that a substantial proportion of the observed covariance between birth weight and cardiometabolic disease predisposition is likely to be driven by genetic rather than environmental factors. However, the potential for more complex causal relationships (such as those that connect fetal genotype to adult disease via the correlation with maternal genotype and altered maternal environment) also needs to be considered. Full characterization of these complex relationships requires the application of statistical methods that enable partitioning of genetic effects into maternal and fetal components both at the level of individual SNPs [48] and genome-wide [49]. Using the M-GCTA method [49], for example, it has been reported that maternal genotypes contribute more to gestational weight gain in the mother, while offspring genotypes contribute more to birth weight [45].

Another critical advantage of genetic studies is the potential to characterize causal relationships using Mendelian randomization approaches [50]. Tyrrell et al. [42] found evidence of a positive causal effect of maternal BMI and fasting glucose levels on offspring birth weight but inverse effect of maternal systolic blood pressure on offspring birth weight. Despite bringing together the largest number of studies at the time with relevant data, there was insufficient power to dissect how the opposing effects of maternal glucose and systolic blood pressure are reflected in the maternal BMI effect (one reason why we are keen to extend the collaboration to any new cohorts). Crucially, however, appropriate application and interpretation of studies that seek to elucidate the mechanisms underlying associations between maternal and offspring phenotypes require investigators to

Table 2 Study designs

Cohort	Study design	Years of recruitment	Country
ABCD	Population based pregnancy cohort	2003–2004	The Netherlands
ALSPAC	Population based birth cohort	1990–1992	UK
B58C	Population based birth cohort	1958	UK
BAMSE	Population based cohort	1994–1996	Sweden
BMDCS	Multi-center observational cohort	2002–2009	United States
Breathe	Population based cohort	2002–2006	Spain
CATSS	Population based twin birth cohort	1992-ongoing	Sweden
CHOP	Population based cohort	1988-Present	USA
CHS	Community based children cohort	1993–2002	United States
CLHNS	Population based birth cohort	1983–1984	Philippines
COPSAC-2000	Asthma risk birth cohort	From 2000-	Denmark
COPSAC-2010	Population based birth cohort	Ongoing From 2010	
COPSAC-REGISTRY	Severe asthma cases (children)	Ongoing	
DNBC-GOYA	Population based pregnancy cohorts	From 1997	Denmark
DNBC-PTB		Ongoing	
EFSOCH	Community-based pregnancy cohort of parent–offspring trios	2000–2004	United Kingdom
Finntwin12	Population-based twin-family cohort	1983–1987	Finland
Gen3G	Population based birth cohort	2010–2013	Canada
Generation R ^a	Population-based birth cohort	2002–2006	The Netherlands
GINIplus	Population based birth cohort	1995–1998	Germany
GLAKU	Population-based birth cohort	1998	Finland
HBSC	Population-based birth cohort	1934–1944	Finland
Health2006	General population study	2006–2008	Denmark
INMA	Population-based birth cohort	1997–2008	Spain
Inter99	Population-based randomized intervention study	1999–2006	Denmark
LISA	population based birth cohort	1997–1999	Germany
MAAS ^a	Population-based birth cohort	1996/1997	UK
MOBA	Population based birth cohort	1999–2008	Norway
MUSP	Pregnancy general population	1981–1984	Australia
NTR ^a	Birth general twin population	From 86—ongoing	Netherlands
NFBC1966 and NFBC1986	longitudinal birth cohort	1966 and 1986	Finland
PIAMA	Population based birth cohort, enriched for high risk allergy children (allergic mother)	1996–1997	Netherlands
Project Viva ^a	Population based birth cohort	1999–2002	USA
Qtwin	Longitudinal twin study	1980–2004	Australia
Raine	Longitudinal pregnancy cohort study	1989–1991	Australia
SKOT	Observational cohort study, monitoring healthy young children from 9 to 36 months of age.	2006–2007 (SKOT I); 2011–2013 (SKOT II)	Denmark
STRIP	Prospective randomized life-style intervention trial	1990–1992	Finland
TCHAD	Birth general twin population	1985–1987	Sweden
TDCOB	Case–control study	Children and adolescence with obesity: 2007–2013; Population-based sample: 2010–2013	Denmark
TEDS	Population based twin birth cohort	From 1994—Ongoing	UK
TRAILS-pop	Population based	2001/2002	Netherlands
TRAILS-CC	High risk	2004	Netherlands
Young Finns	Population based follow-up from childhood to adulthood	1980	Finland

^aIncludes individuals from non-European descent

Table 3 Data collected

Cohort	N genotyped children ^a	Phenotypes	Age periods data available				
			Pregnancy	Pre-school	School	Adolescence	Adult
ABCD	1192	Broad	x	x	x	x	
ALSPAC	10,000	Broad	x	x	x	x	x
B58C	6491	Broad	x	x	x	x	x
BAMSE	2500	Broad	x	x	x	x	x
BMDCS	1885	Broad		x	x	x	x
Breathe	1667	Broad			x		
CATSS	13,576	Broad, focus on psychiatry	x, information from registers		x	x	x
CHOP	43,320	Broad		x	x	x	
CHS	3986	Broad, focus on respiratory and metabolic health			x	x	
CLHNS	1779	Broad		x	x	x	x
COPSAC-2000	411	Broad	x	x	x	x	x
COPSAC-2010	700	Broad	x	x	x		
COPSAC-REGISTRY	1240	Broad	x	x			
DNBC	1500	Broad	x	x	x	x	
-GOYA	1500						
DNBC-PTB							
EFSOCH	812	Anthropometric and glycemic traits	x	x			Parents only
Finntwin12	1264	Broad	Retrospective	Retrospective	x	x	x
Gen3G	582	Broad, focus on metabolic/adiposity	x	on-going			
Generation R	5731	Broad	x	x	x	x	
GINIplus	835	broad	x	x	x	x	Ongoing
GLAKU	357	Broad	x	x	x	x	x
HBCS	1566	Broad		x	x	x	x
Health2006	2802	Cardiovascular disease, type 2 diabetes, and other lifestyle related diseases					x
INMA	1517	Broad	x	x	x	Ongoing	
Inter99	6184	Cardiovascular disease, type 2 diabetes, other lifestyle related diseases, glucose tolerance					x
LISA	674	Broad	x	x	x	x	Ongoing
MAAS	919	asthma and allergy focused	x	x	x	x	Ongoing
MOBA	17,000	Broad	x	x	x	x	x
MUSP	1200	Broad	x	x	x	x	x
NTR	7750	Broad	x	x	x	x	Ongoing
NFBC1966 NFBC1986	5402	Broad	x	x	x	x	x
	3743						
PIAMA	2113	Broad, focus on respiratory health	x	x	x	x	
Project Viva	1580	Broad	x	x	x	x	
Qtwin	4500	Broad			x	x	x
Raine	1500	Broad	x	x	x	x	Ongoing

Table 3 (continued)

Cohort	N genotyped children ^a	Phenotypes	Age periods data available					
			Pregnancy	Pre-school	School	Adolescence	Adult	
SKOT I	260	Dietary intake, growth, cognitive development, overweight and lifestyle related diseases		x				
SKOT II	112							
STRIP	666	Broad	x	x	x	x	x	
TCHAD	990	Broad			x	x	x	
TDCOB	1771	Overweight and Obesity		x	x	x	x	
TEDS	10,346	Broad		x	x	x	x	
TRAILS-pop	1354	Broad	Retrospective	Retrospective	Retrospective	x	x	
TRAILS-CC	341							
Young Finns	2442	Broad	x	x	x	x	x	

^aSome cohorts also have genotype data on parents

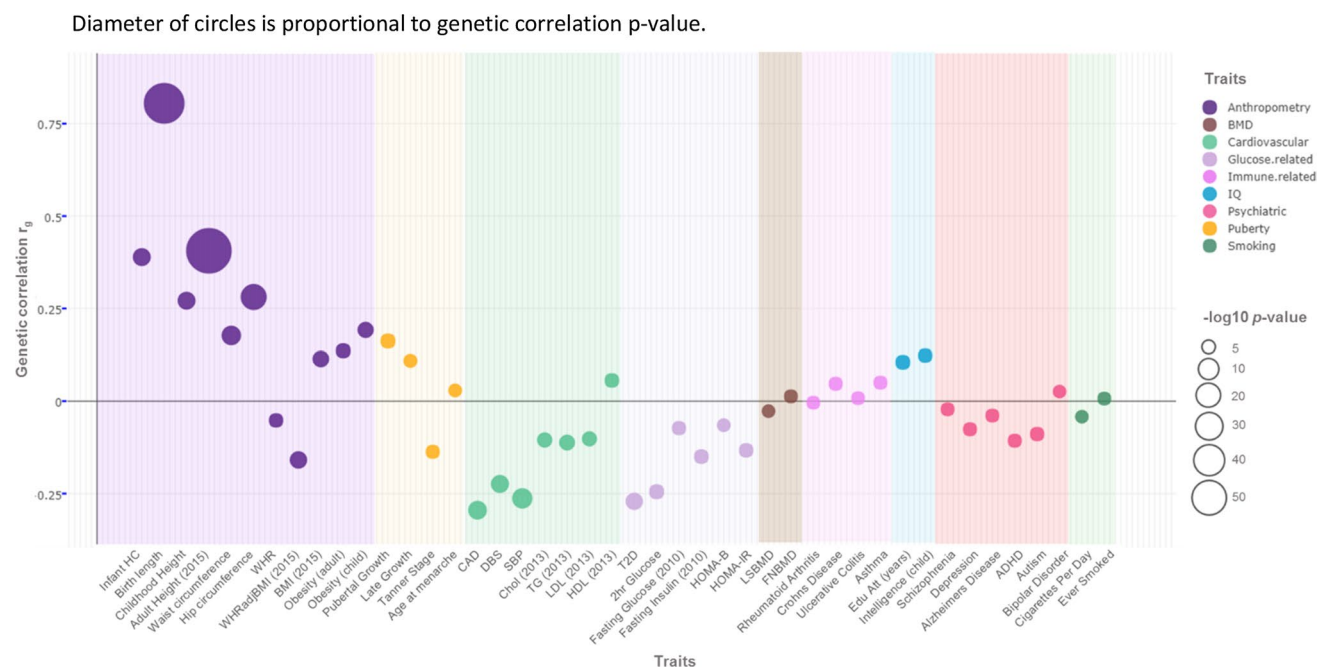


Fig. 2 Genome-wide genetic correlation between birth weight and a range of traits and diseases in later life. Genome-wide genetic correlations between birth weight and traits and diseases evaluated in later life. The figure (adapted from Horikoshi et al. 2016 [28] with permission of the authors) displays the genetic correlations between birth weight and a range of traits and diseases in later life as estimated using LD Score regression. Traits selected were those for which genome-wide association summary statistics were available in suitably large sample sizes, and the analyses were typically performed

on the largest meta-analyses available as of early 2016. The genetic correlation estimates (r_g) are colour coded according to phenotypic area. Allelic direction of effect is aligned to increased birth weight. Size of the circle denotes the significance level for the correlation (per the key). Correlations with a lower significance level are not depicted. Further detail on the methods and studies involved is available in Horikoshi et al. 2016 [28]. Diameter of circles is proportional to genetic correlation p value

consider diverse complicating factors including the correlation between maternal and fetal genetic instruments, and to account for these sources of potential bias in the Mendelian randomization analyses wherever possible [51].

The longitudinal data collected in EGG and EAGLE cohorts provide the means to investigate whether the influence of genetic variants changes over time. This has only recently been explored given the need for large numbers

of studies with repeated measures. We have found that genetic variation in FTO, one of the first BMI increasing genetic variants to be identified in GWAS and one of the variants most strongly associated with mean BMI (in adults) is inversely associated with BMI in infancy only becoming positive in later childhood and adult [38], indicating the value of research that explores gene-by-age interactions. On a genome-wide scale, using meta-regression methods, polygenic risk scores generated from adult schizophrenia data yielded associations with variation in childhood and adolescent psychiatric symptom scores, which strengthened in magnitude with increasing age [52].

Strengths and weaknesses

The aggregation of data in consortia such as EGG and EAGLE provides vastly improved sample sizes and a powerful way to overcome the major weakness of many of the early GWAS, which were, in hindsight, underpowered to detect the generally small genome-wide significant associations. This has brought multiple robust association signals across many traits, and provided a valuable basis for dissecting the, often complex, causal relationships between epidemiologically-correlated traits.

A clear strength of the EGG and EAGLE consortia is the wealth of data available. This encompasses not only repeated measures for physical and behavioral traits, but also copious information on lifestyle and environmental circumstances. Moreover, some of the cohorts have collected data for several decades, and now provide repeated measures well into adulthood. This enables developmental research as well as analyses of the interplay between genes and environment.

To date, one of the limitations has been that the majority of participating cohorts have data based on European-ancestry populations (see Table 2 for exceptions). There is a clear need for equivalent data to be generated in samples from other ethnic groups, so that the genetic contribution to reproducible ethnic differences in the distribution of early life phenotypes can be explored and the implications for adult disease risk quantified.

Since the cohorts are population-based and lack a particular disease-focus, the consortia are not so well-suited to investigate conditions with a low prevalence. They are better-placed to analyze common traits, particularly those that can be measured on continuous scales and analyzed as quantitative measures, such as blood pressure instead of hypertension and ADHD symptom score instead of ADHD diagnosis [32, 34]. Power analyses demonstrate that identification of a genetic variant is, in most circumstances, more powerful for continuous traits than for dichotomous variables based on clinical cut-offs [53].

Future

Considerable progress is to be expected from ongoing increases in sample sizes, especially for traits such as childhood aggression, ADHD-related traits and internalizing symptoms, where the number of identified genetic variants has been limited so far. Access to new data sets can motivate efforts to tackle phenotypes that have not hitherto been subject to detailed genetic analysis.

The results emerging from many of these studies provide a timely reminder that analysis of early life phenotypes often requires researchers to consider the joint impacts of multiple genomes (e.g., those of the fetus and the mother) together with the web of environmental influences as potential contributors to individual variation. They also highlight the need to take into account the changes happening throughout development. This is now possible because of large, rich and complex datasets that support use of novel statistical methods for the analysis of causality or gene-by-age interaction [48, 49, 51, 54]. There have already been several examples of papers performing such analyses and this will only increase with the number of identified genetic variants. In addition, existing gender differences in the associations between early life and adult factors (such as cardiometabolic risk) suggest a need for more thorough analysis of the effects of gender on these early acting mechanisms. The focus to date on the role of maternal and offspring GWAS information indicates a failure to properly consider the contribution of genetic variation in the father that will be remedied as more data from complete trios and pedigrees becomes available.

We are also planning to expand these consortia to accommodate access to the increasing amount of 'omics data now becoming more available. Combining the results from EGG and EAGLE GWA analyses with those from DNA methylation analyses performed by the Pregnancy And Childhood Epigenetics (PACE) consortium [55] and with the pregnancy/child cohorts in the Consortium of METabolomic Studies (COMETS; <https://epi.grants.cancer.gov/comets/>) will shed further light on the biological mechanisms underlying associations of early-life risk factors and childhood, adolescent and adult health outcomes.

The focus on translating this knowledge to clinical and public health settings represents a major motivation. Insight into genetic factors underlying stability in traits such as obesity and psychiatric disorders may aid in providing targeted interventions to the groups at highest need. A more complete understanding of the contributions of genetic and non-genetic factors in the relationships between early life and later life traits may focus attention on the most effective strategies for behavioural or environmental modification.

Acknowledgements cohorts We are grateful to all families and participants who took part in these studies. We also acknowledge and

appreciate the unique efforts of the research teams and practitioners contributing to the collection of this wealth of data. C.M.M. is supported by funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement no. 721567. J.F.F. has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 633595 (DynaHEALTH) and 733206 (LifeCycle). R.M.F. and R.N.B. are supported by Sir Henry Dale Fellowship (Wellcome Trust and Royal Society grant: WT104150). D.L.C. is funded by the American Diabetes Association Grant 1-17-PDF-077. D.O.M.-K. was supported by Dutch Science Organization (ZonMW-VENI Grant 916.14.023). N.M.W. is supported by an Australian National Health and Medical Research Council Early Career Fellowship (APP1104818). T.S.A. was partially funded by the Gene-Diet Interactions in Obesity (GENDINO) project on behalf of GOYA male cohort data management and analyses and acknowledges the same. S.D. was supported by National Institute of Health Research. T.M.F. is supported by the European Research Council grant: 323195 SZ-245 50371-GLUCOSEGENES-FP7-IDEAS-ERC. The Novo Nordisk Foundation Center for Basic Metabolic Research is an independent Research Center at the University of Copenhagen partially funded by an unrestricted donation from the Novo Nordisk Foundation (www.metabol.ku.dk). H.H. is funded by The Children's Hospital of Philadelphia Endowed Chair in Genomic Research. A.T.H. is supported by the Wellcome Trust Senior Investigator Awards (WT098395), National Institute for Health Research (NIHR) Senior Investigator Award (NF-SI-0611-10219). J.Hebebrand received grants from German Research Society, German Ministry of Education and Research. M-F.H. is currently supported by an American Diabetes Association (ADA) Pathway Program Accelerator Early Investigator Award (1-15-ACE-26). S.J. is supported by Helse Vest no. 23929, Bergen Forskningsstiftelse and KG Jebsen Foundation and University of Bergen. J.K. has been supported by the Academy of Finland Research Professor program (grants 265240 & 263278). J.P.K. is funded by a University of Queensland Development Fellowship (UQFEL1718945). H.L. has served as a speaker for Eli-Lilly and Shire and has received research grants from Shire; all outside the submitted work. C.M.L. is supported by the Li Ka Shing Foundation, WT-SSI/John Fell funds and by the NIHR Biomedical Research Centre, Oxford, by Widenlife and NIH (5P50HD028138-27). S.E.M. was funded by an NHMRC Senior Research Fellowship (APP1103623). K.Panoutsopoulou is funded by a career development fellowship (grant 20308) and by the Wellcome Trust (WT098051). C.P. at UCL Institute of Child Health, with support from the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London. I.P. was funded in part by the Wellcome Trust (WT205915), and the European Union's Horizon 2020 research, the European Union FP7-IDEAS-ERC Advanced Grant (GEPIDIAB, ERC-AG – ERC- 294785), and innovation programme (DYNAhealth, H2020-PHC-2014-633595). R.C.R. is supported by CRUK (grant number C18281/A19169). J.G.S. is supported by an NHMRC Practitioner Fellowship Grant (APP1105807). J.T. is funded by the European Regional Development Fund (ERDF), the European Social Fund (ESF), Convergence Programme for Cornwall and the Isles of Scilly and the Diabetes Research and Wellness Foundation Non-Clinical Fellowship. N.V.T. is funded by a pre-doctoral grant from the Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) (2015 FI_B 00636), Generalitat de Catalunya. T.G.M.V. was supported by ZonMW (TOP 40-00812-98-11010). J.F.W. is supported by the MRC Human Genetics Unit quinquennial programme "QTL in Health and Disease". H.Y. is funded by Diabetes UK RD Lawrence fellowship (grant: 17/0005594). M.H.Z. was supported by BBMRI-NL (CP2013-50). E.Z. is supported by the Wellcome Trust (098051). B.F. is supported by Novo Nordisk Foundation (12955) and an Oak Foundation Fellowship. S.S. and M-R.J. have received funding from the European Union's Horizon 2020 research and innovation programme [under grant

agreement No 633595] for the DynaHEALTH action. P.R.N. was supported by the European Research Council (ERC), University of Bergen, KG Jebsen and Helse Vest. G.D.S. works within the MRC Integrative Epidemiology Unit at the University of Bristol (MC_UU_12013/1). D.A.L. was supported by the European Research Council under the European Union's Seventh Framework Programme (FP/2007-2013) / ERC Grant Agreement (Grant number 669545; DevelopObese), US National Institute of Health (grant: R01 DK10324), the UK Medical Research Council (grant: MC_UU_00011/6), Wellcome Trust GWAS grant (WT088806), an NIHR Senior Investigator Award (NF-SI-0611-10196) and the NIHR Biomedical Research Centre at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. L.Paternoster was supported by the UK Medical Research Council Unit grants MC_UU_12013_5. N.J.T. is a Wellcome Trust Investigator (202802/Z/16/Z), is the PI of the Avon Longitudinal Study of Parents and Children (MRC & WT 102215/2/13/2), is supported by the University of Bristol NIHR Biomedical Research Centre (BRC) and works within the CRUK Integrative Cancer Epidemiology Programme (C18281/A19169). V.W.V.J. received an additional grant from the Netherlands Organization for Health Research and Development (NWO, ZonMw-VIDI 016.136.361), a European Research Council Consolidator Grant (ERC-2014-CoG-648916) and funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 633595 (DynaHEALTH) and 733206 (LifeCycle). D.M.E. is funded by the UK Medical Research Council Unit grant MC_UU_12013_4, Australian Research Council Future Fellowship (FT130101709) and a NHMRC Senior Research Fellowship (GNT1137714). S.F.A.G. is funded by the Daniel B. Burke Endowed Chair for Diabetes Research and R01 HD056465. D.I.B. is supported by Spinozapremie (NWO-56-464-14192) and the Royal Netherlands Academy of Science Professor Award (PAH/6635) to DIB. M.I.M. is a Wellcome Senior Investigator and NIHR Senior Investigator supported by the Wellcome (090532, 098381, 203141), NIHR (NF-SI-0617-10090) and the NIHR Biomedical Research Centre, Oxford. The views expressed in this article are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

ABCD The ABCD study has been supported by grants from The Netherlands Organisation for Health Research and Development (ZonMW) and The Netherlands Heart Foundation. Genotyping was funded by the BBMRI-NL Grant CP2013-50.

ALSPAC The UK Medical Research Council and Wellcome (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. A comprehensive list of grants funding is available on the ALSPAC website (<http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf>).

B58C We acknowledge use of phenotype and genotype data from the British 1958 Birth Cohort DNA collection, funded by the Medical Research Council Grant G0000934 and the Wellcome Trust Grant 068545/Z/02. (<http://www.b58cgenome.sgu.ac.uk/>). Genotyping for the B58C-WTCCC subset was funded by the Wellcome Trust Grant 076113/B/04/Z. The B58C-T1DGC genotyping utilized resources provided by the Type 1 Diabetes Genetics Consortium, a collaborative clinical study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Human Genome Research Institute (NHGRI), National Institute of Child Health and Human Development (NICHD), and Juvenile Diabetes Research Foundation International (JDRF) and supported by U01 DK062418. B58C-T1DGC GWAS data were deposited by the Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research (CIMR), University of Cambridge, which is funded by Juvenile Diabetes Research Foundation International, the Wellcome Trust and the National Institute for

Health Research Cambridge Biomedical Research Centre; the CIMR is in receipt of a Wellcome Trust Strategic Award (079895). The B58C-GABRIEL genotyping was supported by a contract from the European Commission Framework Programme 6 (018996) and grants from the French Ministry of Research.

BAMSE BAMSE was supported by The Swedish Heart-Lung Foundation, The Swedish Research Council, Stockholm County Council (ALF), the Strategic Research Programme (SFO) in Epidemiology at Karolinska Institutet, MeDALL (Mechanisms of the Development of ALLergy) a collaborative project conducted within the European Union (Grant agreement No. 261357), The Swedish Research Council Formas, the Swedish Environment Protection Agency and an ERC Grant from the EU (agreement n° 757919, TRIBAL to EM).

BMDCS We are grateful for the support of Dr. Karen Winer, Scientific Director of the Bone Mineral Density in Childhood Study.

Breathe The research leading to these results has received funding from the European Research Council under the ERC Grant Agreement Number 268479—the BREATHE project.

CATSS The Child and Adolescent Twin Study in Sweden study was supported by the Swedish Council for Working Life, funds under the ALF agreement, the Söderström Königska Foundation and the Swedish Research Council (Medicine, Humanities and Social Science; Grant number 2017-02552, and SIMSAM). The research leading to these results has also received funding from the European Union Seventh Framework Programme (FP7/2007–2013) under Grant agreement No. 602768.

CHOP The authors would also like to thank S. Kristinsson, L.A. Hermannsson and A. Krisbjörnsson of Raförninn ehf for extensive software design and contributions.

CHOP was financially supported by an Institute Development Award from the Children's Hospital of Philadelphia, a Research Development Award from the Cotswold Foundation, NIH Grant R01 HD056465 and the Daniel B. Burke Endowed Chair for Diabetes Research (SFAG).

CHS The CHS was supported by the Southern California Environmental Health Sciences Center (Grant P30ES007048); National Institute of Environmental Health Sciences (Grants 5P01ES011627, ES021801, ES023262, P01ES009581, P01ES011627, P01ES022845, R01 ES016535, R03ES014046, P50 CA180905, R01HL061768, R01HL076647, R01HL087680, RC2HL101651 and K99ES027870), the Environmental Protection Agency (Grants RD83544101, R826708, RD831861, and R831845), and the Hastings Foundation.

COPSAC All funding received by COPSAC is listed on www.copsac.com. The Lundbeck Foundation (Grant No. R16-A1694); The Ministry of Health (Grant No. 903516); Danish Council for Strategic Research (Grant No. 0603-00280B) and The Capital Region Research Foundation have provided core support to the COPSAC research center.

DNBC *DNBC-GOYA*: This study is nested within the DNBC which was established with major grants from the Danish National Research Foundation, the Danish Pharmacists' Fund, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation, and the Health Fund of the Danish Health Insurance Societies. The genotyping for DNBC-GOYA was funded by the Wellcome Trust (WT 084762).

DNBC-PTB: This study is nested within the DNBC which was established and is maintained with major grants from the Danish

National Research Foundation, the Danish Pharmacists' Fund, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation, and the Health Fund of the Danish Health Insurance Societies. The generation of GWAS genotype data for the DNBC-PTB samples was carried out within the Gene Environment Association Studies (GENEVA) consortium with funding provided through the National Institutes of Health's Genes, Environment, and Health Initiative (U01HG004423; U01HG004446; U01HG004438).

EFSOCH The Exeter Family Study of Childhood Health (EFSOCH) was supported by South West NHS Research and Development, Exeter NHS Research and Development, the Darlington Trust and the Peninsula National Institute of Health Research (NIHR) Clinical Research Facility at the University of Exeter. The opinions given in this paper do not necessarily represent those of NIHR, the NHS or the Department of Health. Genotyping of the EFSOCH study samples was funded by the Wellcome Trust and Royal Society Grant WT104150.

Finntwin12 Finntwin12 data collection and analyses have been supported by the National Institute of Alcohol Abuse and Alcoholism (Grants AA-12502, AA-00145, and AA-09203 to RJR) and the Academy of Finland (Grants 100499, 205585, 118555, 141054 and 264146 to JK). JK has been supported by the Academy of Finland Research Professor program (Grants 265240 & 263278)

Gen3G We thank all participants who have contributed to Gen3G, many that are still be actively followed by our research team. Gen3G research team also acknowledges the Blood sampling in pregnancy clinic at the Centre Hospitalier Universitaire de Sherbrooke (CHUS); the assistance of clinical CHUS Research Centre research nurses and research assistants for recruiting women and obtaining consent for the study; the CHUS biomedical laboratory for performing assays; and the Research in obstetrics services for helping our placenta and cord blood collection. Gen3G has been supported by American Diabetes Association accelerator award #1-15-ACE-26, Fonds de recherche du Québec en santé #20697; Canadian Institute of Health Research #MOP 115071, and Diabète Québec grants.

Generation R Study The generation and management of GWAS genotype data for the Generation R Study was done at the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Netherlands. We thank Pascal Arp, Mila Jhamai, Marijn Verkerk, Lizbeth Herrera and Marjolein Peters for their help in creating, managing and QC of the GWAS database. The general design of Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam, the Netherlands Organization for Health Research and Development (ZonMw), the Netherlands Organisation for Scientific Research (NWO), the Ministry of Health, Welfare and Sport and the Ministry of Youth and Families. This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant agreements No. 633595 (DynaHEALTH) and 733206 (LIFECYCLE).

GINplus The GINplus study team wishes to acknowledge the following: Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg (Heinrich J, Brüske I, Schulz H, Flexeder C, Zeller C, Standl M, Schnappinger M, Ferland M, Thiering E, Tiesler C); Department of Pediatrics, Marien-Hospital, Wesel (Berdel D, von Berg A); Ludwig-Maximilians-University of Munich, Dr von Hauner Children's Hospital (Koletzko S); Child and Adolescent Medicine, University Hospital rechts der Isar of the Technical University Munich (Bauer CP, Hoffmann U); IUF-Environmental Health Research Institute, Düsseldorf (Schikowski T, Link E, Klümper C).

GLAKU GLAKU cohort has been supported by the Academy of Finland, Hope and Optimism Initiative, the Signe and Ane Gyllenberg Foundation, the Emil Aaltonen Foundation, the Foundation for Pediatric Research, the Foundation for Cardiovascular Research, the Juho Vainio Foundation, the Sigrid Jusélius Foundation, the Yrjö Jahnsson Foundation, and the University of Helsinki Research Funds.

HBCS The Helsinki Birth Cohort Study (HBCS/HBCS 1934-44) thanks Professor David Barker and Tom Forsen. Major financial support was received from the Academy of Finland (project Grants 209072, 129255 Grant) and British Heart Foundation. The DNA extraction, sample quality control, biobank up-keep and aliquotting were performed at the National Institute for Health and Welfare, Helsinki, Finland.

Health2006 The Health2006 study was financially supported by grants from the Velux Foundation; the Danish Medical Research Council, Danish Agency for Science, Technology and Innovation; the Aase and Ejner Danielsen Foundation; ALK-Abello A/S (Hørsholm, Denmark), Timber Merchant Vilhelm Bangs Foundation, MEKOS Laboratories (Denmark) and Research Centre for Prevention and Health, the Capital Region of Denmark.

INMA This study was funded by grants from Instituto de Salud Carlos III (Red INMA G03/176; CB06/02/0041; PI041436; PI081151 incl. FEDER funds; PI12/01890 incl. FEDER funds; CP13/00054 incl. FEDER funds, FIS-FEDER: PI03/1615, PI04/1509, PI04/1112, PI04/1931, PI05/1079, PI05/1052, PI06/1213, PI07/0314, PI09/02647, PI11/01007, PI11/02591, PI11/02038, PI13/1944, PI13/2032, PI14/00891, PI14/01687, and PI16/1288; Miguel Servet-FEDER CP11/00178, CP15/00025, CPII16/00051, FIS-PI06/0867, FIS-PI09/00090, FIS-PI13/02187, 97/0588; 00/0021-2; PI061756; PS0901958; PI14/00677 incl. FEDER funds), CIBERESP, Generalitat de Catalunya-CIRIT 1999SGR 00241, Generalitat de Catalunya-AGAUR (2009 SGR 501, 2014 SGR 822), Fundació La marató de TV3 (090430), Spanish Ministry of Economy and Competitiveness (SAF2012-32991 incl. FEDER funds), Agence Nationale de Securite Sanitaire de l'Alimentation de l'Environnement et du Travail (1262C0010), EU Commission (261357, 308333, 603794, 634453, FP7-ENV-2011 cod 282957 and HEALTH.2010.2.4.5-1), Beca de la IV convocatòria de Ayudas a la Investigación en Enfermedades Neurodegenerativas de La Caixa, EC Contract No. QLK4-CT-2000-00263, Generalitat Valenciana: FISABIO (UGP 15-230, UGP-15-244, and UGP-15-249), Department of Health of the Basque Government (2005111093, 2009111069, 2013111089 and 2015111065), and the Provincial Government of Gipuzkoa (DFG06/002, DFG08/001 and DFG15/221) and annual agreements with the municipalities of the study area (Zumarraga, Urretxu, Legazpi, Azkoitia y Azpeitia y Beasain). ISGlobal is a member of the CERCA Programme, Generalitat de Catalunya.

Inter99 The Inter99 study was funded by the Danish Research Councils, Health Foundation, Danish Centre for Evaluation and Health Technology Assessment, Copenhagen County, Danish Heart Foundation, Ministry of Health and Prevention, Association of Danish Pharmacies, Augustinus Foundation, Novo Nordisk, Velux Foundation, Becket Foundation, and Ib Henriksens Foundation.

LISA The LISA study team wishes to acknowledge the following: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Munich (Heinrich J, Schnappinger M, Brüske I, Ferland M, Lohr W, Schulz H, Zeller C, Standl M); Department of Pediatrics, Municipal Hospital "St. Georg", Leipzig (Borte M, Gnodtke E); Marien Hospital Wesel, Department of Pediatrics, Wesel (von Berg A, Berdel D, Stiers G, Maas B); Pediatric

Practice, Bad Honnef (Schaaf B); Helmholtz Centre of Environmental Research – UFZ, Department of Environmental Immunology/Core Facility Studies, Leipzig (Herberth G, Lehmann I, Bauer M, Röder S, Schilde M, Nowak M, Herberth G, Müller J, Hain A); Technical University Munich, Department of Pediatrics, Munich (Hoffmann U, Paschke M, Marra S); Clinical Research Group Molecular Dermatology, Department of Dermatology and Allergy, Technische Universität München (TUM), Munich (Ollert M).

MAAS This report includes independent research supported by National Institute for Health Research Respiratory Clinical Research Facility at Manchester University NHS Foundation Trust (Wythenshawe). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health. MAAS was supported by the Asthma UK Grants No. 301 (1995–1998), No. 362 (1998–2001), No. 01/012 (2001–2004), No. 04/014 (2004–2007), the BMA James Trust and Medical Research Council, UK (G0601361) and The Moulton Charitable Foundation (2004-current); the Medical Research Council (MRC) Grants G0601361, MR/K002449/1 and MR/L012693/1, and Angela Simpson is supported by the NIHR Manchester Biomedical Research Centre. The authors would like to acknowledge the North West Lung Centre Charity for supporting this project.

MOBA The Norwegian Mother and Child Cohort Study are supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research, NIH/NIEHS(contract noN01-ES-75558), NIH/NINDS (Grant No. 1 UO1 NS 047537-01 and Grant No. 2 UO1 NS 047537-06A1).

MUSP The authors thank the National Health and Medical Research Council (NHMRC).

NTR Data collection in the NTR was supported by NWO: Twin-family database for behavior genetics and genomics studies (480-04-004); "Spinozapremie" (NWO/SPI 56-464-14192; "Genetic and Family influences on Adolescent psychopathology and Wellness" (NWO 463-06-001); "A twin-sib study of adolescent wellness" (NWO-VENI 451-04-034); ZonMW "Genetic influences on stability and change in psychopathology from childhood to young adulthood" (912-10-020); "Netherlands Twin Registry Repository" (480-15-001/674); "Biobanking and Biomolecular Resources Research Infrastructure" (BBMRI – NL (184.021.007). We acknowledge FP7-HEALTH-F4-2007, Grant agreement No. 201413 (ENGAGE), and the FP7/2007-2013 funded ACTION (Grant agreement No. 602768) and the European Research Council (ERC-230374). Part of the genotyping was funded by the Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health, Rutgers University Cell and DNA Repository (NIMH U24 MH068457-06), the Avera Institute, Sioux Falls, South Dakota (USA) and the National Institutes of Health (NIH R01 HD042157-01A1, MH081802, Grand Opportunity Grants 1RC2 MH089951 and 1RC2 MH089995).

NFBC1966 and NFBC1986 The following are key grants for data collections and for laboratory work.

NFBC1966 (31 years study) received financial support from University of Oulu Grant No. 65354, Oulu University Hospital Grant No. 2/97, 8/97, Ministry of Health and Social Affairs Grant No. 23/251/97, 160/97, 190/97, National Public Health Institute, Helsinki Grant No. 54121, Regional Institute of Occupational Health, Oulu, Finland Grant No. 50621, 54231, NHLBI Grant 5R01HL087679-02 through the STAMPEED program (1RL1MH083268-01), NIH/NIMH (5R01MH63706:02).

NFBC1966 (46 years study) received financial support from University of Oulu Grant No. 24000692, Oulu University Hospital Grant

No. 24301140, ERDF European Regional Development Fund Grant No. 539/2010 A31592.

NFBCC1986 study has received financial support from EU QLG1-CT-2000-01643 (EUROBLCS) Grant No. E51560, NorFA Grant No. 731, 20056, 30167, USA / NIH 2000 G DF682 Grant No. 50945, NIHM/MH063706, H2020-633595 DynaHEALTH action and Academy of Finland EGEA-project (285547).

PIAMA The PIAMA study was supported by The Netherlands Organization for Health Research and Development; The Netherlands Organization for Scientific Research; The Netherlands Lung Foundation (with methylation studies supported by AF 4.1.14.001); The Netherlands Ministry of Spatial Planning, Housing, and the Environment; and The Netherlands Ministry of Health, Welfare, and Sport.

Project Viva This study was supported by the National Institutes of Health (UG3OD23286, R01 HD034568, and R01 AI102960).

Qtwin These studies have been supported from multiple sources: National Health and Medical Research Council (901061, 950998, 241944, 1103603), Queensland Cancer Fund, Australian Research Council (A79600334, A79801419, A79906588, DP0212016) Human Frontiers Science Program (RG0154/1998-B) and Beyond Blue.

Raine The Raine Study acknowledges the National Health and Medical Research Council (NHMRC) for their long term contribution to funding the study over the last 25 years. Core Management of the Raine study has been funded by the University of Western Australia (UWA), Curtin University, the UWA Faculty of Medicine, Dentistry and Health Sciences, the Raine Medical Research Foundation, the Telethon Kids Institute, the Women's and Infants Research Foundation, Edith Cowan University, Murdoch University, and the University of Notre Dame. This study was supported by the National Health and Medical Research Council of Australia [Grant Numbers 572613, 403981 and 003209] and the Canadian Institutes of Health Research [Grant Number MOP-82893]. The authors gratefully acknowledge the assistance of the Western Australian DNA Bank (National Health and Medical Research Council of Australia National Enabling Facility). This work was supported by resources provided by the Pawsey Supercomputing Centre with funding from the Australian Government and the Government of Western Australia.

SKOT This project was carried out as part of the research program "Governing Obesity" funded by the University of Copenhagen Excellence Programme for Interdisciplinary Research (<http://www.go.ku.dk>). The SKOT studies were supported by grants from The Danish Directorate for Food, Fisheries and Agri Business as part of the 'Complementary and young child feeding (CYCF)—impact on short- and long-term development and health' project.

STRIP Supported by Academy of Finland (206374, 294834, 251360, 275595); Juho Vainio Foundation; Finnish Cultural Foundation; Finnish Foundation for Cardiovascular Research; Sigrid Jusélius Foundation; Yrjö Jahnsson foundation; Finnish Diabetes Research Foundation; Novo Nordisk Foundation; Finnish Ministry of Education and Culture; Special Governmental Grants for Health Sciences Research, Turku University Hospital; and University of Turku Foundation

TCHAD Supported by The Swedish Council for Working Life and the Swedish Research Council

TDCOB This present study was supported with funds from the Region Zealand Health Sciences Research Foundation, the Innovation Fund Denmark (Grants 0603-00484B and 0603-00457B), and the Novo

Nordisk Foundation (Grant Number NNF15OC0016544) and is part of the research activities in the Novo Nordisk Research Foundation Center for Basic Metabolic Research, University of Copenhagen (<http://metabol.ku.dk/>), and the Danish Childhood Obesity Biobank; Clinical Trials.gov ID-no: NCT00928473.

TEDS TEDS is supported by a program grant to RP from the UK Medical Research Council (MR/M021475/1 and previously G0901245), with additional support from the US National Institutes of Health (AG046938). The research leading to these results has also received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ Grant agreement No. 602768 and ERC Grant agreement No. 295366. RP is supported by a Medical Research Council Professorship award (G19/2). SS is supported by the MRC/IoPPN Excellence Award and by the US National Institutes of Health (AG046938). High performance computing facilities were funded with capital equipment grants from the GSTT Charity (TR130505) and Maudsley Charity (980).

TRAILS TRAILS (TRacking Adolescents' Individual Lives Survey) is a collaborative project involving various departments of the University Medical Center and University of Groningen, the University of Utrecht, the Radboud Medical Center Nijmegen, and the Parnassia Bavo group, all in the Netherlands. TRAILS has been financially supported by grants from the Netherlands Organization for Scientific Research NWO (Medical Research Council program Grant GB-MW 940-38-011; ZonMW Brainpower Grant 100-001-004; ZonMw Risk Behavior and Dependence Grant 60-60600-97-118; ZonMw Culture and Health Grant 261-98-710; Social Sciences Council medium-sized investment Grants GB-MaGW 480-01-006 and GB-MaGW 480-07-001; Social Sciences Council project Grants GB-MaGW 452-04-314 and GB-MaGW 452-06-004; NWO large-sized investment Grant 175.010.2003.005; NWO Longitudinal Survey and Panel Funding 481-08-013); the Dutch Ministry of Justice (WODC), the European Science Foundation (EuroSTRESS project FP-006), Biobanking and Biomolecular Resources Research Infrastructure BBMRI-NL (CP 32), the participating universities, and Accare Center for Child and Adolescent Psychiatry. Statistical analyses are carried out on the Genetic Cluster Computer (<http://www.geneticcluster.org>), which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003) along with a supplement from the Dutch Brain Foundation.

Young Finns The Young Finns Study 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).

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