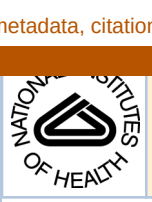

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Social, Behavioral, and Genetic Linkages from Adolescence Into Adulthood

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Abstract

The influence of genetic factors on health and behavior is conditioned by social, cultural, institutional, and physical environments in which individuals live, work, and play. We encourage studies supporting multilevel integrative approaches to understanding these contributions to health, and describe the Add Health study as an exemplar.

Add Health is a large sample of US adolescents in grades 7 to 12 in 1994–1995 followed into adulthood with 4 in-home interviews and biomarker collections, including DNA. In addition to sampling multiple environments and measuring diverse social and health behavior, Add Health features a fully articulated behavioral genetic sample (3000 pairs) and ongoing genotyping of 12 000 archived samples.

We illustrate approaches to understanding health through investigation of the interplay among biological, psychosocial, and physical, contextual, or cultural experiences.

To Understand the Complex

processes underlying human health and development across the life course, successful public health research requires a dynamic systems approach that integrates multiple levels of influence, including genetic and neural activity, as well as cognition, life experiences, behavior, and the physical, social, and cultural aspects of the environment in a longitudinal framework.[1–4] To progress toward this scientific ideal, this article argues for integrative research designs linking genes and environments, and their intersections with health and behavioral trajectories over time.[5–10] This is a fruitful area in which to begin integrative research, because growing evidence indicates that the influence of genetic factors on health is conditioned by the social, cultural, institutional, and physical environments in which individuals live, work, and play,[11–18] and increasingly rich and diverse environmental data are now available in national, longitudinal health studies.

To date, molecular genetic research has taken 2 general paths, neither of which typically incorporates a longitudinal or systems approach: (1) traditional pedigree-based linkage studies and candidate gene approaches, which are focused on genetic variants thought to be important contributors to phenotypes, and (2) the common disease–common variant (i.e., 5% or more of the population) model, which assumes common diseases are caused by multiple genetic variants that individually have small effects. Technological advances now allow for genome-wide association studies, based on the common disease–common variant model. However, a strictly additive or static model is at odds with the wealth of theoretical and empirical evidence demonstrating time-varying gene-environment (G × E) interactive influences on health and behavior.[10,14,19–21] Furthermore, the necessity of large sample sizes to capture sufficient numbers of common variants and to have the power to detect small “main effects” has, because of logistical and financial constraints, limited the collection of contextual and experiential data that are vital to understanding the intersecting systems that influence health.

Advancing the public health knowledge base depends upon research grounded in prospective contextual and lifestyle or experiential information collected in long-term longitudinal designs that include theoretically derived measures. Such designs, especially if available with larger representative samples, allow for the investigation of critical public health problems with life course approaches that capture cumulative exposures, G × E correlations (relative gene expression [rGE], which is selecting into different social

environments that may be associated with genotype over time), and the presence and timing of G × E interplay. Therefore, understanding how genetic factors and G × E interactions (accounting for rGE) contribute to health, life experiences, and the social and physical environments requires a detailed, multilevel, and longitudinal assessment of health and the environment. Relatively few studies offer all of these necessary strengths to implement an integrative systems approach to understanding public health issues.

This article is a call for researchers to develop integrative, longitudinal research designs that facilitate a dynamic systems approach to understanding genetic contributions to public health, and to capitalize on existing data allowing such research. As an example of what such designs might entail, we describe an innovative study that provides unique opportunities for the broad scientific community to advance understanding of social, behavioral, and genetic linkages across the life course using a dynamic, longitudinal, multilevel integrative approach to health.[5] The National Longitudinal Study of Adolescent Health (Add Health) is an ongoing study of a nationally representative sample of more than 20000 individuals that began with in-school questionnaires administered to adolescents in grades 7 to 12 in the United States during 1994–1995, followed by 4 waves of in-home interviews in 1995 (wave I), 1996 (wave II), 2001–2002 (wave III) and 2008–2009 (wave IV).

Add Health was originally designed to understand the causes of health and behavior with special emphasis on the role of the environment. Innovative features of the research design facilitated this purpose by providing independent measurements of multiple social contexts and biological markers of health, including DNA as fundamental components of the complex dynamic system of health and well-being.

Add Health Design

Add Health used a primary sampling frame derived from the Quality Education Database (QED) to select adolescents from a stratified list of all high schools in the United States in 1994. An in-school questionnaire was administered to more than 90 000 students in grades 7 to 12 who attended these schools during the 1994–1995 school year. In a second stage of sampling, an age-and gender-stratified prospective longitudinal sample of adolescents was selected from the schools' rosters to participate in an in-home interview and together with supplemental oversamples drawn based on ethnicity, genetic relatedness to siblings, adoption status, and disability, resulting in a total sample size of 20 745 adolescents at wave I (79% response rate [RR]). In most cases, one parent was also interviewed at wave I. The in-home adolescent sample has been followed up with interviews in 1996 (wave II, 89% RR), 2001–2002 (wave III, 77% RR) and 2008–2009 (wave IV, 80% RR). The longitudinal design of Add Health is shown in Figure 1. See Harris[22] for more details on the design of Add Health.

To understand the factors influencing health, Add Health sampled the multiple environments in which young people lived their lives, gathering information from adolescents themselves, their parents, siblings, friends, romantic partners, fellow students, and school administrators. Existing databases with information about the neighborhoods and communities of the adolescents were merged with Add Health data. Add Health contains extensive longitudinal phenotypic information, with a particular focus on causes and consequences of health and health behavior, including multiple longitudinal indicators of health promotion, general health, chronic illness, overweight status and obesity, physical activity, mental health, and disability. Add Health has obtained objective measures of reproductive and cardiovascular health across all waves, including height and weight (among other anthropometrics), sexually transmitted infections and HIV test results, and an expanded set of markers at wave

IV, including biomarkers of cardiovascular health (blood pressure, pulse), metabolic processes (waist circumference, HbA1c, blood glucose, lipids), immune function (Epstein–Barr virus), inflammation (high-sensitivity C-reactive protein) and a medications log. Add Health incorporates prospective longitudinal measures to document change over time in each of these phenotype domains, as well as in context and life experience. Figure 2 shows the environmental and biological data available across waves. A more detailed description of these environment and context data is provided elsewhere.[22]

Add Health pioneered the potential for genetic analysis by embedding a fully articulated behavioral genetic sample, including more than 3000 pairs of adolescents with varying degrees of genetic relatedness (e.g., twins, full siblings, half siblings, and adolescents who grew up in the same household but had no biological relationship).[23] In 2001–2002, buccal cell DNA was collected from the twins and full siblings in the genetic pairs sample (n∼2500) and saliva DNA collection was expanded to include the entire sample in 2008–2009 (n = 15 701), affording greater statistical power for genetic analyses, especially G × E interactions and opportunities for replication. Selected candidate genes associated with dopaminergic and serotoninergic pathways were genotyped and disseminated to the scientific community for gene candidate analyses, and genome-wide genotyping is currently under way for 12 000 archived samples. Add Health Genome-Wide Association Study data will be deposited into the database of Genotypes and Phenotypes (dbGaP; http://www.ncbi.nlm.nih.gov/gap) when genotyping is completed.

Large, representative national studies are critical for public health research that integrates genetics and the physical, social, and behavioral sciences. However, the power of even the large sample size G × E interaction studies is typically inadequate, and studies that are limited to 1 environment are also limited in their ability to identify the environmental factors that suppress or enable complex molecular processes linked to an individual's genotype. Statistical power and ability to capture diverse environmental features across the life course are far greater for multivisit, longitudinal study designs. Because nonrepresentative studies do not capture the geographic, demographic, biological or genetic, and health diversity of a population, findings on G × E interaction may be biased or unique to a specific sample, and therefore, are not replicable.[24,25] Initial reports of candidate gene associations or G × E interactions often do not survive rigorous replica-tion.[26] As Hewitt[25] noted, the reasons for this are complex, but include the likelihood that effect sizes of individual polymorphisms are small, that studies have therefore been underpowered, and that multiple hypotheses and methods of analysis have been explored; [therefore] these conditions will result in an unacceptably high proportion of false findings.[27]

The multilevel, multidimensional, and longitudinal design features of Add Health make it uniquely suited to not only identify and replicate G × E interactions in the US population (e.g., initial findings based on wave III DNA can now be tested for direct replication with adequate power in the much larger independent nonpairs component of the wave IV sample), but also to explain G × E effects with its wealth of longitudinal social, behavioral, and biological data across the early life course. Add Health has national representation of young people who live in all 50 states and come from every race, ethnic, immigrant, geographic, and socioeconomic subgroup in the United States. This design feature allows for detailed study of population stratification by race and ethnicity, and the important opportunity to further explore genetic variation within socially defined groups such as racial/ethnic groups. Add Health is one of the few national studies that prospectively follows a young cohort as they embark on independent lives, experience diverse environments, and explore new lifestyles–formulating their future health and well-being trajectories into adulthood–and providing unique research insights into the precursors of future health disparities and public health impact for their prevention.

Integrating Genetics and Social and Behavioral Sciences

Researchers planning to develop multilevel, longitudinal research designs should also consider data-sharing approaches to maximize the scientific utility of the data. Add Health has an enlightened dissemination policy that has significantly multiplied the research opportunities for a wide range of researchers worldwide. Broad dissemination has enabled prolific research production of unparalleled disciplinary and interdisciplinary breadth, with findings contributing to social and health sciences and public policy.

Reflecting increasing scholarly awareness and commitment to understanding the linkages between the environment, behavior, health, and genes,[19,28,29] hundreds of research studies based on Add Health have used either a behavioral or molecular genetics approach, or both (http://www.cpc.unc.edu/projects/addhealth/pubs). Genetic research in Add Health has been published in a wide range of social and biomedical journals on many public health topics, including substance use and dependence,[30–32] depression,[33] sexual behavior,[34–36] body mass index and obesity,[37,38] crime and delinquency,[39] suicide,[40] aggression,[41,42] attention deficit hyperactivity disorder,[43] and conduct disorder and self-control.[44,45] More than half of these publications examine G × E interactions and their effects on health and behavior. We present some illustrative findings in the following section.

Illustrative Findings in Add Health

Capitalizing not only on the genetic data but also on a wide range of risk behaviors measured over time, Guo et al.[14] examined how the dopamine transporter gene (*DAT1*) interacts with age (or life course stage) in relation to risk behavior (including delinquency, number of sex partners, substance use, and seatbelt use) from adolescence into young adulthood, using data from waves I, II, and III of Add Health. They reported a protective effect of the 9R/9R genotype in the Variable Number Tandem Repeat (VNTR) of *DAT1* on risky behavior; individuals with *DAT1**9R/9R compared with *DAT1**Any10R reported lower levels of risky behaviors. However, as illustrated in Figure 3, this protective effect varied according to age and life course stage, such that genetic protection was evident when the risk behavior was illegal (e.g., alcohol use and smoking in adolescence), but vanished when the behaviors were legal or more socially tolerated (e.g., alcohol use and smoking in adulthood). This research is important because it demonstrated how legal and social contexts can enhance or diminish genetic associations with a spectrum of risky behaviors at different stages of the life course.

Boardman et al.[11] explored the design of Add Health to investigate peer and school environment interactions with genetic factors associated with smoking cigarettes among adolescents. In the Add Health in-school survey, respondents nominated up to 10 of their friends who were also in-school survey participants. Adolescents receiving the most friendship nominations could be classified the “most popular” students who shaped smoking norms for the larger school community because of their social status and social connections.[46] Boardman et al.[11] assessed the smoking behavior of the most popular students and found that school norms favoring smoking (i.e., prevalence of daily smoking among the most popular students) enhanced the associations between genetic factors and daily smoking among all students. Thus, genetic contributions might not emerge unless the environment actively engages individuals in behaviors and reinforces these behaviors. Because the relative contribution of genetics to the daily use of cigarettes is conditional upon school norms related to cigarette use, there are policy opportunities to influence these norms to curb smoking behavior during the critical stage of adolescence, when initiation of smoking can set trajectories for continued use into adulthood.

Future Directions

The notions of "plasticity" or "differential susceptibility,"[47] are being increasingly applied in research examining G × E interactions. In general, differential susceptibility models assume that some individuals will be more sensitive to both unfavorable and favorable effects of negative and positive environments.[48] Most genetic research applying this model has focused on "risk alleles" and their intersection with unsupportive environments. However, examples of differential favorable effects are beginning to appear in the literature. For example, Brody et al.,[48] in an evaluation of a family-centered intervention to prevent initiation of risk behavior among rural African American young adolescents, found that youths were thought to be "at risk" because they carried the short allele of the variable nucleotide repeat polymorphism in the promoter region of the SLC6A4 gene. (This is 5HTT, which is also referred to as 5-HTTLPR. 5HTT is an important key regulator of serotonergic neurotransmission. The polymorphism in the promoter region results in 2 variants, a short and a long allele with the short allele resulting in lower serotonin transporter availability, and potentially higher risk in unfavorable environments.) These youths were considered most likely to benefit from the intervention. Those at risk in the control condition initiated significantly more risk behaviors at long-term follow-up than did those without "genetic risk" and those at risk in the intervention condition. The findings of Brody et al.[48] have important implications for heterogeneous effects of public health interventions, and the ability to maximize the promotion of positive youth development and, in turn, competent and healthy adults.

A second example of the relationship between plasticity alleles and both unfavorable and favorable effects is provided by Beaver and Belsky[49] in their examination of the role of plasticity alleles from 4 genes measured in Add Health: the 10R allele of *DAT1*, A1 allele of DRD2, the 7R allele of DRD4, and the short allele of 5HTTLPR, in the prediction of future parenting experience from parenting experienced as an adolescent. They found that respondents with higher numbers of plasticity alleles (0–4) reported the highest levels of parent stress in young adulthood when they were exposed to higher levels of negative parenting during adolescence, but the lowest levels of parent stress when they were exposed to positive parenting during adolescence.

To illustrate the potential of new research designs and the potential of existing data, we next discuss possible research inquiries that could capitalize on the multifaceted longitudinal data and the geospatial data in Add Health.

Longitudinal Data

Observational studies like Add Health offer measures of "positive" or protective contexts, as well as the unsupportive environments that are the focus of most literature today, allowing for more holistic examinations, including genetic information, of pathways to health. Because Add Health captured diverse experiences at multiple periods during the life course, including information about the prenatal period, it is possible to examine time-varying interactions of what might be better called "plasticity" alleles[50] and varied environments that themselves affect neurologic functioning and, in turn, developmental plasticity.

Consider "sexual risk taking" as an illustration. Multiple aspects of sexual behavior were measured 4 times from adolescence into adulthood in Add Health. To understand the genetic, experiential, and environmental interactions that contribute to the development, continuation, or cessation of various sexual behaviors over time, genetic and biological contributors such as plasticity alleles in the serotonergic and dopaminergic systems can be examined,[35,36] as well as prenatal factors (e.g., maternal smoking and alcohol use that may alter pre- and postnatal hormonal processes[51]). For example, various aspects of a poor

uterine environment may lead to fetal growth restriction, and subsequently, adaptive changes in neonatal hormonal and metabolic profiles. These and other complex changes can affect pubertal timing,[52–54] among other aspects of reproductive maturation, which may have important implications for timing of sexual initiation and contraceptive practices.

At present, there is little information about how these complex hormonal and neuropsychological changes may affect sexual function and relationship formation, and existing findings are mixed. There have been reports that very low birth weight females are less sexually active, have lower pregnancy rates, and show significantly less drug and alcohol abuse.[55,56] However, other studies have failed to document these associations (e.g., Cook[57]). Multifactorial linkages between preterm birth and personality in adolescents and young adults have also been suggested.[58] To examine this possibility, biological factors and processes can be combined with factors within the home environment during adolescence (e.g., parenting style and relationship quality, maltreatment experiences) and the broader environment (e.g., protective experiences with conventional institutions, neighborhood features such as adult monitoring, involvement with older sexual partners) to allow for a multilevel systems analysis of sexual development. Given Add Health's large sample size, it is possible to model complex interactions of time-varying measures of these factors to examine developmental change in sexual risk-taking and how sexual risk taking may be associated with other aspects of health and well-being (e.g., sexually transmitted infections, depression) at different points in the life course.

Similar opportunities are available in Add Health to understand the genesis of health promoting behavior. For example, it is possible to model change in multiple indicators of a leading health indicator, physical activity or inactivity, which are fundamental to understanding the important public health problem of obesity, which is well-documented in the Add Health cohort. Activity or inactivity has been measured from adolescence to adulthood, and it is possible to examine a variety of factors that contribute to physical activity over time. One possible approach is illustrated in Figure 4. The physical environments (e.g., presence of parks, recreation centers, sidewalks) in which the respondent lives at various life stages may contribute directly to physical activity (e.g., via access). The physical environment may also influence the social environment (e.g., group sports, general culture promoting activity), the values and activities that the respondent's family models and supports, and peers' participation in and opinions about activities. The physical environment could also interact directly with genetic factors to influence activity. Each of the social and interpersonal environments, in turn, affects the others.

Add Health data offer many opportunities to directly test the differential susceptibility hypothesis. In this physical activity or inactivity example, bidirectional relationships between plasticity alleles or gene expression and both the multiple environments and the respondent's physical activity can be examined (Figure 4). Individuals with plasticity alleles who are more sensitive to their environments and exposed to environments that promote activity are hypothesized to engage in greater physical activity than those with less-sensitive plasticity alleles. Activity is thus ultimately a product of a constellation of integrated actions of genes, cognitive processes (not shown), and physical and social environments, all of which may be changing over time.

Geospatial Data

The opportunities to add to basic public health knowledge and, therefore, evidence-based health policy are enormous. For example, numerous epidemiological studies have documented the association between cardiovascular disease (CVD) and ambient air pollution, yet few have examined genetic susceptibility to its adverse cardiovascular effects, or examined how environmental exposures could change gene expression. Those studies that

have examined such factors tend to be underpowered, unreplicated analyses based on a handful of candidate genes and conducted within environmentally homogeneous study populations without awareness of pertinent metabolic, behavioral, or socioeconomic modifiers. The Clean Air Act (42 US Code 7408–9) legislatively requires the US Environmental Protection Agency (EPA) to establish and enforce National Ambient Air Quality Standards that have a margin of safety requisite to protect the health of the public. In establishing the margin of safety for particulate matter (PM) air pollution, the EPA emphasizes subpopulations that are susceptible to its adverse effects, regardless of whether susceptibility is developmental or genetic in origin. EPA's Integrated Science Assessment of PM underscores the potential importance of G × E interactions in the study of PM health associations.[59] The size of genetically susceptible populations, as well as the likelihood and severity of the adverse PM effects they experience, are particularly important from this perspective. Add Health can provide estimates of genotype-specific health effects of nationwide reductions in PM concentrations using epidemiological measures of population burden (e.g., markers of metabolism [glucose, glycosylated hemoglobin, cholesterol, triglycerides], inflammation [e.g., high sensitivity C-reactive protein], and biometric data [systolic and diastolic blood pressure, mean arterial pressure, pulse pressure, and pulse rate]). Such measures can provide quantitative insight into the proportion of PM-attributable cardiovascular, metabolic, inflammatory, and immune abnormalities that could be reduced by establishing and complying with stricter National Ambient Air Quality Standards.

Because of its diverse population and respondent-specific linkage to geographic units for which ambient air quality has been documented, Add Health can test potential differential individual susceptibility to, and context-dependent effects of, air pollution on CVD. This strategy is central to understanding the mechanisms linking pollution to acute CVD events, whether they are autonomic, metabolic, inflammatory, or immune in nature. It is also central to identifying the major genetic factors influencing susceptibility to the effects of air pollution on CVD mortality, and the ways in which environmental pollution may facilitate epigenetic changes.

Conclusions

The health of individuals and populations is the manifestation of a complex dynamic system involving a mix of genetic, psycho-social, and environmental factors operating at multiple levels and interacting with each other over hours, days, months, years, and life stages.[1,60] No aspect of health is determined by a single factor, and not all developmental or disease processes yield linear changes in health status. Although it is increasingly acknowledged that pathways to health are embedded in complex biosocial systems, and that such complexity must be included in research to understand health, past work has often been limited by the lack of longitudinal, varied, and multilevel data for samples that are large and sufficiently diverse to support appropriate modeling and replication. As we have illustrated, the Add Health data set, which is prospective, longitudinal, and captures information from all system levels for a large and diverse sample of individuals, offers unparalleled opportunities to expand holistic examinations of health processes across the life course and can serve as one example for future data collection efforts.

Social, behavioral, and genetic public health researchers are poised to take advantage of these data resources to unravel the time-dependent, bidirectional, multidimensional, evolving, and often nonlinear causal pathways of health and well-being. Add Health research has made significant strides toward better understanding the important role of environmental conditioning of genetic influences across a range of environments (family, school, peer, neighborhood, legal, institutional) and for an array of health and behavioral outcomes across the early life course–when the precursors of future chronic disease begin.

Understanding the underlying processes in predisease pathways for diverse, representative samples will furthermore inform health policy and identify early life interventions to improve population health and reduce societal health care costs.

Findings indicate that environmental influence and its interactions with genetic factors occur at multiple levels, at different life course stages, and vary by scale. Researchers can no longer ignore the environmental complexities related to space, time, and age in a system approach to health and disease, for we have the theory, tools, and data to advance knowledge at the intersections of genetics and social and behavioral sciences.

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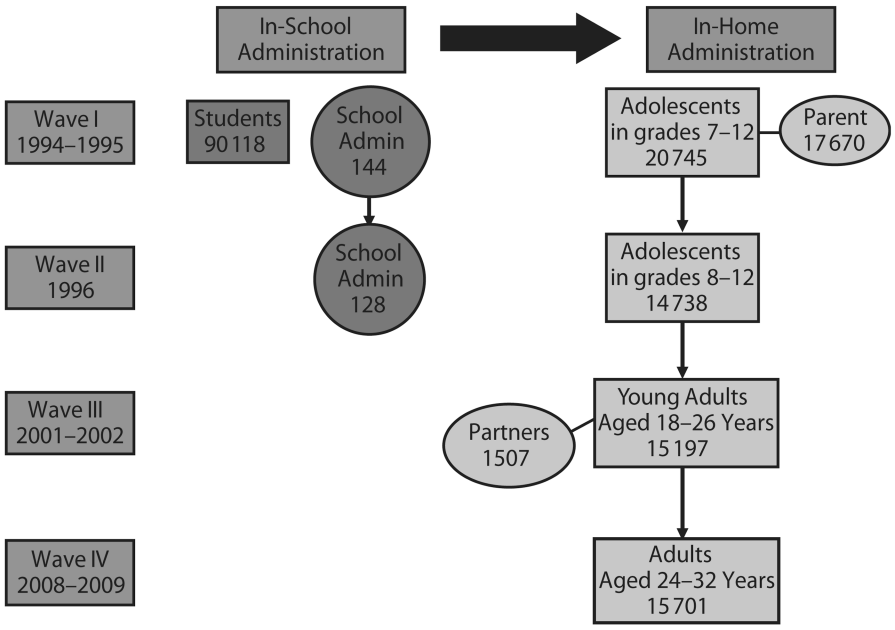
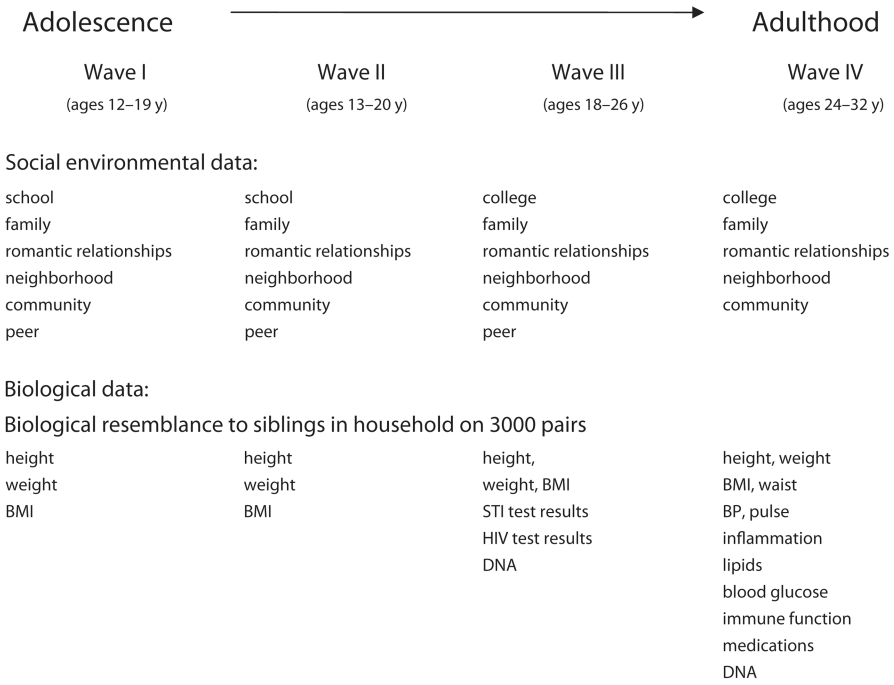


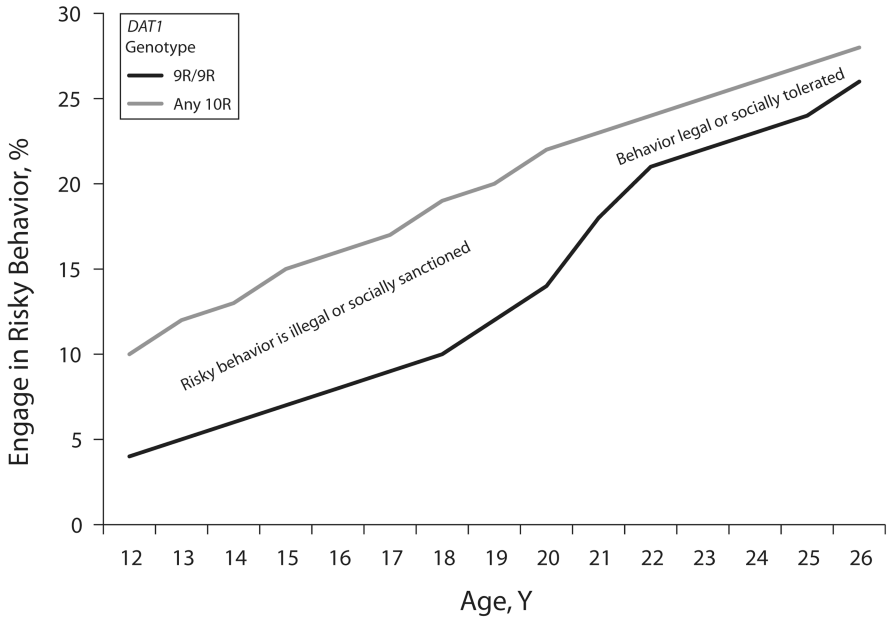
Note. Admin = administrators.

Figure 1.
Add Health longitudinal design: United States, 1994–2009.



Note. BMI = body mass index; BP = blood pressure; STI= sexually transmitted disease.

Figure 2.
Longitudinal data in Add Health.



Source. Visual representation of findings from Guo et al.[14]

Figure 3.
Genetic association with risky behavior and the legal and social context related to life course age: Add Health, United States, 1994–2009.

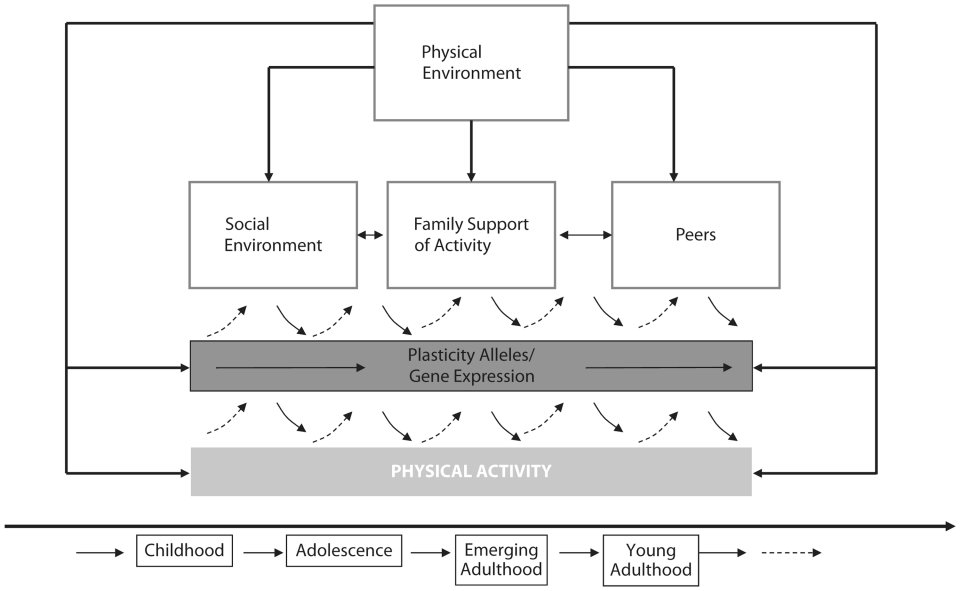


Figure 4.
Multilevel time-varying system of contributors to physical activity.