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Cohort Profile: The Amsterdam Growth and Health Longitudinal Study

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Summary

The Amsterdam Growth and Health Longitudinal Study (AGHLS) is a unique, multidisciplinary cohort study that was initially set up to examine growth and health among teenagers. Throughout the years, the AGHLS has aimed to answer research questions dealing with the relationships between the (natural) development of anthropometry, lifestyle and health from adolescence into adulthood. The AGHLS specifically focuses on anthropometrics, physical activity and fitness, cardiovascular disease risk, lifestyle, musculoskeletal health, psychological health and well-being. Besides this, many methodological issues related to the analysis of longitudinal data were also explored within the framework of the AGHLS. In 1976, students from two secondary schools from the greater Amsterdam area were included in the study. Between 1976 and 2006, 10 rounds of measurement were performed covering an age range between 13 and 43 years. The huge database collected so far has been primarily used to answer relevant research questions regarding the longitudinal relationship between lifestyle and health. Further information about the study can be obtained from the principal investigator Jos Twisk (jwr.twisk@vumc.nl), and up-to-date information on AGHLS can be found by visiting the website www.aggio.nl.

How did the study come about?

The initial set-up of the Amsterdam Growth and Health Longitudinal Study (AGHLS) was designed in the early 1970s by Prof. Dr Han Kemper and initially funded by the Dutch Prevention Fund and the Dutch Heart Foundation. At the time, authorities were concerned about the unfavourable changes in lifestyle of 45 adolescents. Physical activity levels³¹, for example, were declining and unhealthy dietary intake was increasing³². Especially, the rise in the prevalence of cardiovascular disease (risk factors) among adolescents was of great concern^{31,33,34}. As sufficient physical activity and a healthy diet were seen as reachable targets for reversing this increase in prevalence, several school-based interventions were implemented by authorities. In this light, the observational cohort AGHLS was set up to follow up the natural growth and health and lifestyle in a representative (i.e. both rural and urban) sample of Dutch adolescents of the same age.

What does it cover?

In the first 4 years, the AGHLS was primarily aimed at the investigation of the natural course of dietary intake, physical activity and physical fitness as risk factors for cardiovascular disease, such as cholesterol levels³¹. Over the 4 years, a decline in physical activity levels was a major finding. However, unexpectedly, no changes were found in physical fitness nor in the other cardiovascular disease risk factors³¹. To investigate a possible time lag effect between unfavourable lifestyle habits and biomedical indicators of health status, the AGHLS was expanded with further rounds of measurements after the adolescence period³⁵. At each of these follow-up rounds of measurement, cardiovascular disease risk indicators and lifestyle variables were measured in a similar way to allow longitudinal comparison. Also, new, age-relevant measures for health and lifestyle were added to the test battery at each follow-up round. For example, when subjects were in their 20s, measurements of bone mineral density were added and research questions regarding the relationship between lifestyle and bone health were answered^{35,36}. In their 30s, the test battery was extended with, for example, carotid ultrasound measurements to determine large 30 arterial properties to examine not only the 'clinical' cardiovascular risk factors but also the early preclinical cardiovascular damage^{37,38}. In their 40s, microvascular function was added to the test battery as an even earlier indicator for vascular damage³⁹. Moreover, to study the onset, timing and progression of neuropsychiatric disease, such as Alzheimer's disease (AD), a magnetoencephalogram (MEG), a novel brain scan to assess communication of different brain sections⁴⁰, was added to the test battery. The AGHLS study has also been used to study more methodological research questions. At that time, new methods such as generalized estimation equations (GEE) and mixed models were used to analyse longitudinal relationships^{41,42}. Furthermore, latent class growth

mixture modelling⁴³, multilevel item response modelling, the handling of missing data and the analysis of left-censored variables in longitudinal studies were investigated.

What has been measured?

Participants in their teens

From 1976 until 1979, the AGHLS started with measurements concerning the natural development of growth, health and lifestyle. For instance, anthropometric measurements, age at menarche, psychological variables, personality characteristics, lifestyle (nutrition and physical activity), cardiovascular health indicators and physical fitness measurements were included in the test battery. Regarding physical fitness, both cardiopulmonary fitness and neuromotor fitness were measured extensively. Cardiopulmonary fitness was measured with a running test until exhaustion on a treadmill, whereas neuromotor fitness was measured with the Motor PERFORMANCE (MOPER) test battery⁴⁴.

Highlight: the detailed measurement of dietary intake is one of the highlights of the AGHLS⁴⁵. A cross-checked, dietary history interview of 60–90 min was specifically designed and validated for the AGHLS to assess dietary intake. This method is based on a method developed by Beal⁴⁶ and Marr⁴⁷. With this method, specific food groups as well as the caloric intake and specific macro- and micronutrient intake were assessed in great detail^{36,48}.

Participants in their 20s

As the interests changed from short-term effects on health and fitness into long-term effects of lifestyle during adolescence on adult health, new measurements were added to the test battery^{35,44,49}. In addition to the health and lifestyle measures collected previously, new measures such as work- and stress-related questionnaires and questionnaires on life events and daily hassles were added to the test battery. Furthermore, indicators for osteoporosis (i.e. bone mineral content and density) of the lumbar spine, hip and wrist were added³⁶.

Highlight: the development of a new method to assess tracking. Tracking is defined as the stability of a certain risk factor in time and/or the predictability of future values by early measurements. The new method, developed with the AGHLS, was based on GEE^{41,42,50}.

Participants in their 30s

When participants were in their 30s, interest shifted towards determinants of chronic diseases such as a preclinical status of cardiovascular disease (risk)^{37,38,51–53}. Novel techniques to assess such determinants and (preclinical) disease outcomes were used in the following rounds of measurement. For example, dual energy X-ray absorptiometry (DEXA) scans provided

information that refined previous measurements of fat, lean and muscle mass and body fat distribution^{37,54}. In order to measure preclinical cardiovascular disease, carotid ultrasound imaging was added to the test battery^{37,38}.

Highlight: ultrasound measurements provided detailed information on the carotid vessel wall capacities ascribing intima-media thickness (IMT) (investigating atherosclerotic plaques) as well as vessel wall stiffness and elasticity characteristics (compliance and distensibility)^{37,38}.

Participants in their 40s

The most recent round of measurement took place in 2006, when participants were in their early 40s. Besides measurement of the 'longitudinal' variables, the test battery was extended with parameters to serve as a baseline measure for the investigation of deterioration in health with age. For example, brain function using a MEG scan was assessed in order to describe a baseline measure for a possible early indicator of AD³⁹. Although many parameters can be obtained from a MEG scan, functional connectivity is probably the most important. This parameter can be seen as a measurement of how well different sections of the brain communicate. Measurements related to cardiovascular diseases were extended with the assessment of microvascular function using^{1,55}. These measures can be seen as an early sign of cardiovascular damage^{1,55}.

Highlight 1: as far as we know, a MEG scan has not been performed on such a large scale in apparently healthy individuals.

Highlight 2: microvascular function is measured in the capillaries in the nailfold. This is a method to study, for example, the functional increase in capillaries after oxygen shortage caused by arterial occlusion with a small cuff as an early marker of CVD risk^{1,55}.

Table 1 shows an overview of all the performed measurements over time.

Who is in the sample?

Participants were included by attending one of the two selected secondary schools in The Netherlands. The schools were selected based on location, i.e. one of the schools in a rural area, the other in an urban area, as being representative of the Dutch adolescent population of the 1970s. However, both schools are for pupils with a level of intelligence that is above average for the Dutch population. Pupils and their parents were asked to participate before the new school year started. Informed consent was signed by the school authorities, parents and pupils at each follow-up round. Initially, there were no refusals. Ethical approval was given by the VU Medical Center ethical committee at each follow-up round.

Each of the schools provided approximately 300 participants, resulting in a total of approximately 600 first-grade and second-grade pupils of the three different birth cohorts (1962, 1963, 1964). In the articles generated by the AGHLS over time, different numbers can be found. These numbers are lower

Table 1. Measurements in the AGHLS over time.

Year	77-80	85	91	93	96/97	2000	2006
Age (years)	13-16	21	27	29	32	36	42
Body fatness							
Dexa scan						X	X
Skinfold measurements	X	X	X	X	X	X	X
BMI	X	X	X	X	X	X	X
Waist to hip ratio	X	X	X	X	X	X	X
Birthweight (retrospective)						X	X
Physical activity and fitness							
Maximal oxygen uptake (direct test)	X	X	X	X ^a	X	X	X ^a
Motor Fitness (MOPER)	X	X	X	X	X	X	X
Muscle strength (quadriceps/hamstrings)		X	X	X	X	X	
Lung function	X	X	X	X	X	X	X
Physical activity (accelerometry)	X						X
Physical activity (interview)	X	X	X	X	X	X	X
Sedentary behaviour (questionnaire)			X	X	X	X	X
Postural sway							X
Cardiovascular health							
Traditional blood markers (lipoproteins, triglycerides)	X	X	X	X	X	X	X
Markers of inflammation and endothelial function						X	X
Systolic/diastolic blood pressure	X	X	X	X	X	X	X
Macrovascular function (carotid ultrasound)						X	X
Microvascular function (nailfold capillaroscopy)							X
Lifestyle							
Demographic information (questionnaire)	X	X	X	X	X	X	X
Geographic mobility (interview)							X
Dietary intake (questionnaire)	X	X	X		X	X	X
Smoking (questionnaire; dipstick in 2000)	X	X	X		X	X	X
Alcohol consumption (questionnaire or interview)	X	X	X	X	X	X	X
Coffee consumption (questionnaire)			X	X	X	X	X
TV and computer usage (questionnaire)					X	X	X
Life rhythm (questionnaire)					X	X	X
Sports motivation					X		X
Bone mineral density and osteoporosis							
DEXA scan			X			X	X
Heel bone (ultrasound)			X			X	
Lumbar spine (X-ray)			X		X	X	
Distal radius and femoral head (X-ray)				X			
Musculoskeletal health complaints (questionnaire)	X	X	X	X	X	X	X
Skeletal age (X-ray)	X						

^a for VO₂ max in 1993 and 2006, this was a submaximal performance

Table 1. Continued

Mental health and well-being						
Health-related quality of life (questionnaire)		X	X	X	X	X
Brain function (functional connectivity and cognitive function)						X
Health-care utilization (questionnaire)		X	X	X	X	X
School attitude (questionnaire)	X					
Work environment (questionnaire)				X		
Personality (questionnaires)	X	X	X	X	X	X
Vital exhaustion (questionnaire)			X	X	X	X
Depression (questionnaire)					X	X
Coping (questionnaire)		X	X	X	X	X
Sleep quality (questionnaire)			X	X	X	X
Life events, daily hassles (questionnaire)		X	X	X	X	X
Habit strength (questionnaire)			X	X	X	X

since they specifically mention the total number of participants with complete data on a single variable or a group of variables. Pupils from one school were, in 1976 (at age 13 years), asked to participate in a 4-year, annually repeated study. The other school had only 25% of the pupils measured every year (no repeated measures for each individual). The pupils from this school re-entered the study from 1996 onwards (Figure 1). The pupils from this school did not differ on important parameters from the pupils from the other school at that point⁴⁹. Thereafter, participants from both schools have been analysed together; no distinction has been made between the two initial schools.

How often have the participants been followed up and what is the attrition like?

Up to now, the AGHLS has had 10 detailed rounds of measurements spread out over 35 years (Table 1 and Figure 1). Around 350–375 participants to date have remained in the study. Attrition over the years remained relatively low because rounds of measurement were presented not only for scientific aims, but also because of the social aspects of meeting former school mates during measurement days. We have also organized two reunions of the schools in 2001 and 2007. Detailed information on attrition can be found in Table 2 in which information on differences between responders and non-responders are described in the periods 1976–2006 (long term) and 2000–06 (short term) for several key variables. The results indicate no short- and long-term selective dropout for all key variables shown in Table 2.

Up to now, the AGHLS cohort is not linked to any (inter)national morbidity or mortality systems.

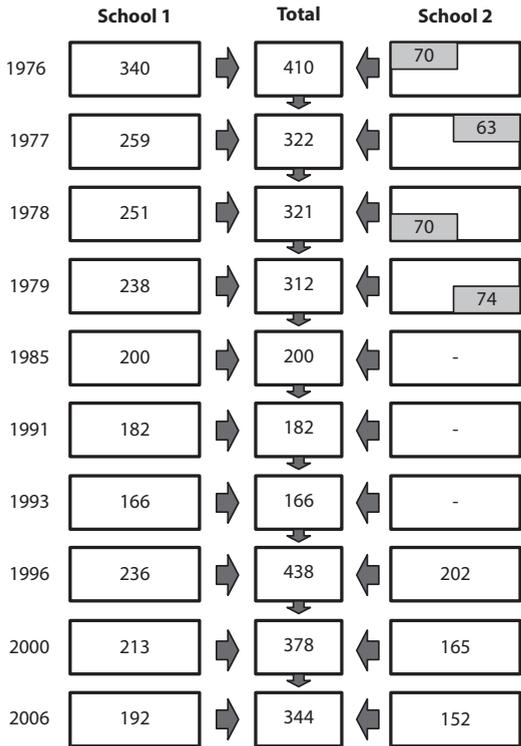


Figure 1. Flow chart of the attending participants per round of measurement.

Table 2. Results of both long- and short-term dropout analyses of several key variables in the AGHLS.

	Group 1 Attended at the age of 13 and 42 years (N = 226)	Group 2 Attended at the age of 13 but not at 42 years (N = 39)	Group 3 Attended at the age of 36 and 42 years (N = 312)	Group 4 Attended at the age of 36 but not at 42 years (N = 66)
Female (%)	52.4	51.2	52.5	50.8
Total cholesterol levels (mmol/l)	4.47 (0.73)	4.49 (0.75)	5.05 (0.99)	5.19 (0.12)
Systolic blood pressure (mmHg)	124.14 (9.24)	124.43 (8.95)	131.17 (13.31)	132.22 (18.47)
Body mass index (kg/m ²)	17.37 (1.89)	17.82 (2.22)	24.09 (3.17)	24.08 (2.87)

^a Characteristics of the participants who attended the rounds of measurements at the age of 13 as well as 42 years are compared with those who did not attend at the age of 42 years (long term) and characteristics of the participants who attended the rounds of measurements at the age of 36 and 42 years with those who did not attend at the age of 42 years (short term).

Results are presented as means (SD) for continuous variables and per cent for categorical variables and variables concern those measured at the age of 13 years (for the comparison of 13 years, age 42 years) and at the age of 36 years (for comparison of 36 years, age 42 years).

What has been found? What are the key findings?

Research with AGHLS data covers a broad, multidisciplinary range of topics. In this section, key findings on most important research themes that the AGHLS cohort has contributed to are presented. Also, a complete database of all AGHLS publications is included and can be found online (www.aggo.nl).

Anthropometrics

Important topics regarding anthropometry are studies incorporating body fat 'distribution' instead of body fat or body weight per se. The AGHLS has great expertise in measuring fat distribution and has contributed to this research field greatly. For example, already in the beginning of the AGHLS, it was shown that a central pattern of body fat was associated with high blood pressure and an unhealthy lipoprotein profile between the ages of 13 and 27 years⁵⁶ and, more recently, at the age of 36–42 years, it has been shown that increases in central fat mass are associated with accelerated arterial stiffness⁵⁷. Regarding birth weight, it was found that 1 kg lower birth weight is associated with ~3mmHg higher systolic blood pressure⁵⁸.

Physical fitness and activity

An important finding concerning the relationship between physical activity and fitness was that, although physical activity did decline during adolescence, physical fitness did not^{33,44}. Further, it was shown that relatively high levels of physical activity during adolescence were related to a lower decrease in bone mineral density at later age⁵⁹. This was especially true for body weight-bearing activities³⁶. Regarding physical fitness, one of the most intriguing findings was the positive relationship between cardiopulmonary fitness during adolescence and arterial properties later in life³⁷. Besides that, it was shown that physical activity was found to be longitudinally related to clustering of CVD risk factors⁶⁰.

Cardiovascular disease risk (factors)

Markers and measures of cardiovascular health and disease remain one of the most important topics within the AGHLS. Many publications have resulted from the analyses of these data and noteworthy findings concern the (longitudinal) analyses of arterial stiffness^{37,38,57}. Moreover, the metabolic syndrome (MS)³⁷ (a clustering of several CVD risk factors) has been studied extensively. It was shown that participants diagnosed with the MS at the age of 36 years had stiffer arteries compared with participants without the MS. Novel markers for CVD risk, such as soluble intercellular adhesion molecule-1 (s-ICAM), interleukin-6 (IL-6) and TNF- α were determined from the age of 36 years onwards and have shown to refine CVD risk quantification⁶¹.

Lifestyle

Besides the decline in physical activity (see physical fitness and activity) during adolescence, unhealthy dietary intake, smoking and alcohol consumption increased dramatically^{32,33}. Throughout the AGHLS, lifestyle variables have been the focus of interest mainly in the research of CVD risk. Longitudinal analyses revealed key health consequences of long-term tobacco smoking, such as deterioration of heart rate response^{53,62}, arterial stiffness^{53,62}, lung function⁴² and physical fitness⁶².

Musculoskeletal health

Surprisingly in the AGHLS, no relationships were found between calcium intake and either bone mineral density or bone mineral^{36,59}. Weight-bearing activities during adolescence seemed to be more important for the prevention of bone mass loss than calcium intake. Besides this, fat-free mass was positively associated with lumbar bone mineral density^{36,59}.

Psychological health and well-being

Multiple measures of psychological health were part of the test battery at each round of measurement. Constructs, such as depression⁶³, coping⁶⁴, life events⁶⁵, workability⁶⁶, personality⁶⁷, quality of life⁶⁸ and sleep quality⁶⁹ were exclusively measured using validated questionnaires. A small number of studies have been conducted with these data and results mostly concern personality and life events⁷⁰⁻⁷². For example, a higher score on the personality characteristics and social inadequacy during adolescence was associated with higher body fatness at later age⁷⁰. More recently, novel markers of brain function, measured by MEG³⁹, have been included in the test battery. Although findings from the AGHLS data are expected in 2012, preliminary results indicate that physical fitness is associated with more healthy brain function parameters. Since MEG scans were performed at the age of 42 years, these measurements could serve as a baseline measurement to study the timing and onset of deterioration of brain function and possibly aid clinicians and researchers in the field of AD and dementia to diagnose and prevent these diseases at an earlier stage. Alongside the measurements for functional connectivity, cognitive function has been determined by IQ tests. Data are expected to be published in 2012. Preliminary results show, for instance, a positive relationship between physical fitness and functional connectivity of the brain.

Methodological issues

Apart from the information on biological, lifestyle, medical and psychological areas of interest, the AGHLS is a suitable cohort to address methodological questions^{50,73}. It is one of the first epidemiological cohort studies in which sophisticated longitudinal data analysing techniques, such as GEE analysis and mixed models, were studied and applied. This was done not only by

analysing longitudinal relationships but also by analysing tracking^{41,42}. Currently, the cohort is also used to study and apply a variety of contemporary analytical techniques. For example, latent class growth mixture modelling is used in the analyses of distinct development trajectories over time and the cohort is used to investigate the necessity of multiple imputations on missing data in longitudinal studies. Furthermore, longitudinal item response theory (IRT) and the longitudinal analyses of left censored data are explored within the AGHLS framework. Most methodological issues described here are concerned with the recently started PhD projects where results should be expected within the next 2 or 3 years.

Future projects

The AGHLS remains an active cohort. When participants are in their early 50s, we plan to perform another detailed measurement round. The AGHLS will continue to focus on important questions regarding the aetiology and prevention of several chronic diseases. Besides that, the consequences of (health) behaviour on several health outcomes will also be studied. Furthermore, the AGHLS database will be used for further methodological research questions.

What are the main strengths and weaknesses?

Nowadays, the AGHLS consists of 35 years of longitudinal data focusing extensively on the (natural) development of anthropometrics, lifestyle and health. The AGHLS is a unique cohort for many reasons. Firstly, the focus is multidisciplinary and involves numerous lifestyle and biological and psychological health determinants over a long period of time, allowing for detailed research. Only few observational cohort studies exist with such an extensive data collection and long duration from the age of 13 years (including information on birth) onwards. Second, many concepts have been measured in similar ways at each round of measurement to make longitudinal comparison with a high-quality data set possible. Also, several constructs were often measured twice at the same occasion to allow for concurrent validation of these measures. Third, the AGHLS has a relatively low loss to follow-up, especially in the most recent years, because of dedicated participants. Fourth, the study design permits the use of multivariable statistical methods and provides the ideal data set for answering many longitudinal research questions. Also, several studies have followed the study design, such as the Young Hearts projects in Northern Ireland⁷⁴, the Ellisras Longitudinal Study in South Africa⁷⁵ and the European Youth Heart Study in four European countries⁷⁶. Last but not least, sophisticated statistical analyses have been applied to the data of the AGHLS. The main weakness of the study is the possible difficulty in generalizing results. The study sample was, and still remains, fairly healthy, highly educated and slightly homogeneous, and in that respect, not really representative of the whole Dutch population. However, if small effects are found in the healthy and

homogeneous AGHLS cohort, this finding can indicate much larger effects in a more heterogeneous study population, and should not remain unnoticed. Furthermore, the population is homogeneous concerning age, which indicates that secular trends cannot be investigated within the AGHLS cohort and, finally, the population of the AGHLS is relatively small.

Can I get hold of the data? Where can I find more?

Specified proposals for collaboration are more than welcome. Further information about the study can be obtained from the principal investigator Jos Twisk (jwr.twisk@vumc.nl). Up-to-date information on AGHLS can be found by visiting the website www.aggo.nl.

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Conflict of interest: None declared.

Key messages

- Findings from the AGHLS cover aspects of growth and health between the ages of 13 and 43 years. Examples of the study's many findings at different stages of the life course include the following:
- Teens: a sharp increase in unhealthy lifestyle habits.
- In their 20s: weight-bearing activities and not calcium intake slow the process of decrease in bone mineral content and density by age.
- In their 30s: a central pattern of body fat was associated with high blood pressure and an unhealthy lipoprotein profile.
- In their 40s: higher central fat mass and lower physical fitness during adolescence are associated with increased arterial stiffness later in life.