Cohort Profile

Cohort Profile: The Finnish Health in Teens (Fin-HIT) study: a population-based study

Rejane Augusta de Oliveira Figueiredo,1,2*† Sabina Simola-Ström,1† Trine B Rounge,1,2,3 Heli Viljakainen,1,4 Johan G Eriksson,1,5 Eva Roos1,6 and Elisabete Weiderpass1,2,3,7,8

1Genetic Epidemiology Group, Folkhälans Research Center, Helsinki, Finland, 2Faculty of Medicine, University of Helsinki, Helsinki, Finland, 3Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway, 4Department of Food and Environmental Sciences, University of Helsinki, Helsinki, Finland, 5Department of General Practice and Primary Healthcare, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, 6Department of Public Health, University of Helsinki, Helsinki, Finland, 7Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden and 8Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, Arctic University of Norway, Tromsø, Norway

*Corresponding author. Folkhälans Research Center, University of Helsinki, Biomedical 1 - P.O. Box 63, Helsinki 00014, Finland. E-mail: rejane.figueiredo@helsinki.fi
†These authors contributed equally.

Why was the cohort set up?

The prevalence of overweight and obesity in children and adolescents is increasing globally. In high-income countries, the prevalence of obesity has plateaued, although the rate is still high.1,2 Children with overweight and obesity are likely to stay obese into adulthood and tend to develop certain diseases, such as pulmonary, cardiovascular and metabolic diseases, more frequently and at a younger age.3,4 Overweight and obesity develop as a consequence of the imbalance between energy intake and energy expenditure, and they are heavily influenced by poor eating habits, inadequate sleep and low physical activity level.5,6 Only about 20% of 13–15-year-old adolescents worldwide achieve the recommended 60 min per day of moderate-to-vigorous physical activity.7 At the same time, the number of hours per day that children and adolescents sit in front of a screen, especially in front of a computer screen, is increasing.8

The aetiology of overweight and obesity is complex and results from environmental factors, genetic susceptibility and their interaction.9 Whereas 70% of obesity has been estimated to be hereditary, only 1–2% can currently be explained by known genetic risk loci.10–12 There is substantial evidence that epigenetic mechanisms have a role in the regulation of adipogenesis and glucose homeostasis.13–15 However, there is a need for more in-depth understanding, and the associations between DNA methylation and body size also need to be verified, preferably in an age group in which dieting and medication use are less likely. Studies of animal models and humans suggest that the gut microbiome might also be associated with weight regulation.16 Less is known about the role of the oral microbiome and its association with overweight and obesity;17 most studies on the topic are based on animal models.18 Nonetheless, one study showed that some bacteria, such as Campylobacter rectus and Neisseria, are present in the oral microbiome in higher amounts among subjects with obesity than among normal-weight subjects.19 Large studies using independent culturing methods are needed to validate these findings.

Supported by and coordinated at the Folkhälans Research Center in Helsinki, Finland, the Finnish Health in Teens (Fin-HIT) study was initiated with the aim to follow up and
understand long-term changes in body size from adolescence to adulthood. Within this cohort several risk factors for overweight and obesity, such as lifestyle, mental health, family environment and microbial, genetic and epigenetic markers, as well as the association between these factors, are being studied.

Who is in the cohort?
The Fin-HIT Study cohort, initiated in 2011, comprises adolescents aged around 9–12 years at enrolment, together with one adult responsible for each participant (henceforth referred to as ‘parents’), and is planned to be followed for 25 years. This age range was chosen as it denotes a period during which most participants are about to enter puberty. Moreover, according to our own focus group discussions with adolescents, individuals in this age range are cognitively mature enough to participate. Adolescents are defined as individuals 10–19 years old,20 but for simplicity, we will henceforth use the term ‘adolescents’ for all our study participants, including the 9-year-olds. The Fin-HIT-study includes 11 407 adolescents and 9935 parents of these adolescents (one parent per adolescent), the vast majority of whom are mothers (Figure 1).

Baseline recruitment
Geographically, a large part of Finland was represented in the study, including urban and rural areas. Participants come from 44 municipalities, including Finland’s largest cities: Helsinki, Turku, Espoo, Oulu, Jyväskylä, Tampere and Kuopio.

Baseline recruitment was carried out at two time points: in 2011 a pilot study was conducted, in which participants were recruited at home; in 2013–14 the main study went forward, in which participants were recruited at school. The pilot study tested the strategy of home-based recruitment by mailed invitation among 11 000 randomly selected households, but the response rate was 14.5%. Therefore, the main study used a school-based recruitment strategy in which 496 schools agreed to participate and fieldworkers handed out invitations to 27 000 adolescents in those schools. The total participation rate for adolescents at baseline was 30% [14.5%, (n = 1599) in the pilot study and 36% (n = 9808) in the main study, Figure 1].

An adolescent consent forms had to be signed by each adolescent and one of their parents; participating parents also returned their own, separate consent form. The school-based recruitment strategy did not allow us to obtain any information on non-participants (either no consent or non-response). Therefore, it was not possible to compare information between responders and non-responders.

The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the Fin-HIT Study.
Research permission to approach the schools was received from each municipality’s education administration office. Approval to conduct the study was granted by the principal of each school.

How often have they been followed up?

The first active follow-up took place in 2015–16. Criteria for inclusion in the follow-up study were: valid study consent from both the adolescent and parent; valid body mass index (BMI) and/or saliva sample from the adolescent at baseline; and ability to identify personal information for adolescents and parents in the Population Information Center. Therefore 11,044 adolescents and 9,632 parents were invited (Figure 1). There were 5,911 adolescents and 5,357 parents in the follow-up, corresponding to a participation rate of 53.5% and 55.5%, respectively.

The current ethical approval covers a 25-year follow-up period (i.e. until 2035), to which all participants have consented. This will include active follow-up, that is questionnaires and repeated saliva samples; and passive follow-up, that is linkage to national health registers through the participants’ social security number, which will provide us with reliable follow-up data.

What has been measured?

At baseline

Adolescents answered a web questionnaire, provided a saliva sample and had their anthropometric measures (height, weight and waist circumference) taken at the school by fieldworkers. Parents completed a web questionnaire, in which they gave self-reported anthropometric measures. All information collected in the Fin-HIT Study is shown in Table 1.21–39

The fieldworkers followed a standardized measurement protocol for all adolescents. Height was measured to the nearest 0.1 cm with a portable stadiometer (Seca model 217); weight to the nearest 0.01 kg with portable digital scales (CAS model PB) calibrated daily before each series of measurements; and waist circumference midway between the hip bones and the ribs to the nearest 0.1 cm with a measuring tape calibrated against a measure once a week. BMI was calculated as weight (kg)/height (m)2 and the adolescents were classified as underweight, normal weight, overweight or obese (BMI categories) according to age- and sex-specific cut-offs suggested by International Obesity Task Force (IOTF).41 Adolescents from the pilot study or those who were absent from school on the day of data collection (approximately 13% of adolescents) returned self-reported body measurements.

At follow-up

Adolescents and parents answered a web questionnaire and provided a saliva sample. Follow-up web questionnaires for both adolescents and parents collected information on lifestyle factors and anthropometric measures (height, weight and waist circumference) (Table 1). This self-reported follow-up information allowed us to study changes in body size and health status over time, including epigenetic and microbial changes and their associations with body size development. The saliva samples enabled us to study common changes and features in the microbiome and epigenome in a household setting.

Biological samples

Unstimulated saliva samples were collected using the Oragene® DNA Self-Collection Kit (DNA Genotek Inc., Canada), a high-quality method that has been used in studies of molecular epidemiology.42 DNA was extracted for a subset of the saliva samples collected from participants. Two different protocols were used, depending on the research aim. An automated Chemagen protocol (PerkinElmer, UK) was used to enrich human DNA, and both mechanical and enzymatic lysis of all cells was used to ensure access to DNA from all bacteria in the sample.43 We successfully used a targeted bisulphite sequencing (Agilent SureSelectX, Agilent, CA, USA) to assess DNA methylation (n = 136) and 16S rDNA sequencing (1000 baseline saliva samples and 412 follow-up saliva samples) to assess microbial composition using the above-mentioned DNA extracts.

Register data

A proportion of information will be obtained from national health registers. The registers that will be consulted include: (i) the Population Information System at the Population Register Center [https://eevertti.vrk.fi/paivityspalvelut], which contains information on social security number, address, and mother tongue; (ii) the Social Insurance Institution of Finland, [http://www.kela.fi/web/en/492], which includes information on medical prescriptions, purchases of prescription drugs and patient
spending on these drugs; (iii) Statistics Finland [http://www.stat.fi/til/asan_kaikki_en.html], which includes information on occupational status, wages and cause of death; and (iv) the National Institute for Health and Welfare (THL) [https://www.thl.fi/en/web/thlfi-en/statistics/information-for-researchers], which manages the Medical Birth Register, the Care Register for Health Care and the Register of Primary Health Care Visits, which contain information on diseases, pregnancy, newborn health, diagnoses, etc.

Descriptive results

The average age of adolescents was 11.2 (± 0.8) years at baseline and 13.7 (± 1.3) years at follow-up. Of the 11 407 adolescents recruited, 52% (n = 5981) were girls and 48% (n = 5423) were boys, and a similar proportion was found at follow-up (Table 2). This distribution is quite similar to that of the 10–14 years-old Finnish population in 2017 (51.1% boys and 48.8% girls). Information on sex was obtained from the consent form and confirmed through linkage with the Population Information System at the Population Register Center. Social security number was missing for three participants, for whom we do not have information on sex.

At baseline, the prevalence of overweight in Fin-HIT adolescents was 12.6% (n = 1343) and the prevalence of obesity was 2.6% (n = 274), which is in accordance with other studies. At follow-up there was a similar percentage of adolescents with overweight (12.3%; n = 670) and obesity (2.2%; n = 119). In the total cohort, 4.6% (n = 524) of the adolescents reported Swedish as their first language, which is slightly lower than the proportion in the general Finnish population (5–6%). Most adolescents reported having reached puberty (65.9%; n = 5614) but there were a lot of missing data for these questions (25%; n = 2892). Of the non-responders, 47% (n = 1355) were represented by adolescents below age 10 years and not targeted to answer these questions, and 53% (n = 1537) did not want to answer these questions (Table 2).

Both at baseline and at follow-up, most participating parents were female (n = 8568, 86.8%; n = 4701, 87.5%, respectively). The average age for parents was 42.0 (± 5.5) years at baseline and 44.9 (± 5.4) years at follow-up. The prevalence of overweight and obesity among parents at baseline was lower (41.3 %; n = 2431) than the estimated prevalence in the general population in Finland (50% of females and 62% of males). However, this prevalence was higher at follow-up (45.7%; n = 2313). The majority

Table 1. Information collected in the Fin-HIT Study for adolescents and parents at baseline and follow-up

| Adolescent’s information | Parent’s information |
|--------------------------|----------------------|
| Baseline 2011-14         |                      |
| Self-administered web questionnaire |                      |
| Lifestyle and health behaviour: diet, meal patterns, physical activity, parents’ attitudes toward physical exercise, screen time, TV-programmes watched, bullying, sleep patterns |                      |
| Mental health: emotional eating, self-esteem, anxiety, depression, obsessive compulsive disorder, weight perception, disordered eating symptoms, binge eating symptoms, body image |                      |
| Adolescent growth environment: parent-child relationship, alone time during school days, children’s perception of alcohol consumption among adults in their social environment, puberty onset |                      |
| Anthropometric measures | Self-collected saliva sample |
| First follow-up 2015-16  |                      |
| Self-administered web questionnaire |                      |
| Meal patterns, diet, self-esteem, physical activity in free time, screen time |                      |
| Self-reported anthropometric measures | Self-collected saliva sample |
| Second follow-up 2016-17 |                      |
| Self-administered web questionnaire |                      |
| Meal patterns, diet, self-esteem, physical activity in free time, screen time |                      |
| Self-reported anthropometric measures | Self-collected saliva sample |

aHeight, weight, waist circumference.

bOragene® DNA Self Collection Kit.
of the parents reported that they had a university degree with diploma from a university of applied sciences or a degree from a university (54.9%; n = 3200), and the others reported a high school or technical level of education (45.1%; n = 2634) (Table 2).

No substantial differences were found between adolescents with and without their parent’s questionnaire information; however, results showed higher participation among prepubescent adolescents in the group with parental information (36.8%; n = 1784 compared with 30.5%; n = 1117 without parental information) (Table 3).

When some characteristics at baseline were compared between participating and non-participating adolescents in the follow-up (Table 4), only parental educational level differed somewhat: participating adolescents in the follow-up had parents with a slightly higher educational level (57.5%) than the non-participating ones (49.5%). However, this information was available only from 5834 parents.

Of the 5277 adolescents with information on BMI at baseline and follow-up, 80.5% (n = 4247) maintained the same BMI at both time points (Table 5). The highest change was related to adolescents who were underweight at baseline and changed to normal weight at follow-up (6.6%; n = 349). Among normal-weight adolescents at baseline, 2.5% (n = 130) changed their BMI status to underweight, and 4.7% (n = 251) changed to overweight or obese at follow-up.
What has it found? Key findings and publications

Published studies and ongoing projects from the Fin-HIT cohort are briefly described below.

Validity of self-reported height, weight and waist circumference

This study assessed the validity of self-reported anthropometric measurements compared with standardized...
measurements taken at school among adolescents, at base-
line. We found no statistically significant difference in
height or BMI measured at home and at school.49

Maternal alcohol and tobacco consumption and
BMI among adolescents
This cross-sectional study aimed to evaluate whether mater-
nal consumption of alcohol or tobacco is associated with
their children’s BMI. We found that maternal consumption
of tobacco and alcohol is associated with their children’s
BMI. Current maternal smoking was associated with over-
weight among children, and former maternal smoking was
inversely associated with underweight among children.50

DNA methylation and body size
DNA methylation (DNAm) has been analysed among 100
adolescents at baseline: 50 underweight girls and 50 girls
with overweight. An association was found between differen-
tial methylation and body size groups. The two strongest
signals were located near NAV3 and MC2R. Many of the
associated CpG-sites and genomic regions were co-located
with known obesity-related genes, predominantly in the
insulin-melanocortin pathway. The overlap with obesity and
insulin-related genes, including MC2R, IGFBPL1, IP6K1 and IGF2BP1, indicate functional connections be-
tween the saliva methylome and BMI, and vice-versa.51
Replication of these results is ongoing.

Identifying eating habits in Finnish adolescents
In a cross-sectional study, we aimed to identify different
eating habits among adolescents and to evaluate the associ-
bation between these eating habits and meal patterns, break-
fast consumption and sociodemographic characteristics.
We identified three groups: unhealthy eaters (12.3%), fruit
and vegetable avoiders (43.3%) and healthy eaters
(44.1%). Unhealthy eaters showed irregular meal and
irregular breakfast patterns, and had parents with a low
education level. Healthy eaters showed regular meal and
regular breakfast patterns, and had parents with high edu-
cation level (Figueiredo et al., submitted).

Body dissatisfaction and disordered eating
symptoms in Finnish pre-adolescents
The purpose of this cross-sectional study was to evaluate
whether body dissatisfaction is associated with disordered
eating symptoms like dieting or avoiding certain foods,
and to determine the effects of gender and BMI on this as-
sociation. A relevant percentage of adolescents reported
body dissatisfaction: 30.0% wanted a smaller body and
9.3% wanted a larger body. Only 2.2% of the participants
had disordered eating symptoms. We found that body
dissatisfaction was associated with disordered eating symp-
toms, especially among girls and those who were under-
weight and normal-weight (Figueiredo et al., submitted).

Reproducibility and repeatability of six
high-throughput 16S rDNA sequencing
protocols for microbiota profiling
The purpose of the study was to establish methods to in-
vestigate the microbiome in saliva samples collected at
baseline. One of the challenges when using next-generation
sequencing technologies to assess the microbiome is
achieving sufficient reproducibility and repeatability of the
results. High reproducibility and repeatability are mostly
attained through robust polymerase chain reaction (PCR)
amplification. We assessed the reproducibility of saliva
microbiota profiles produced with simplified, in-house 16S
amplicon assays with a large number of barcodes. The
assays included primers modified with Truseq (TS-tailed)
or Nextera (NX-tailed) adapters, with either dual index or

| Table 5. Changes in adolescents’ BMI categorya (IOTF) |
|---------------------------------------------|
| BMI categories (baseline) | Underweight | Normal weight | Overweight | Obese | Total in each row |
|----------------------------|------------|---------------|-----------|------|------------------|
| n, %                       | n, %       | n, %          | n, %      | n, % | n, %             |
| Underweight                | 270 5.1%   | 349 6.6%      | 240 4.5%  | 11 0.2% | 619 11.7% |
| Normal weight              | 130 2.5%   | 3547 67.2%    | 366 7.0%  | 39 0.7% | 3928 74.4% |
| Overweight                 | 1 0.01%    | 217 4.1%      | 39 0.7%   | 105 2.0% | 625 11.8% |
| Obese                      | 4 0.1%     | 4117 78.0%    | 647 12.3% | 112 2.1% | 5277 100.0% |
| Total in each column       | 401 7.6%   | 4117 78.0%    | 647 12.3% | 112 2.1% | 5277 100.0% |

aOnly adolescents with information on BMI at baseline and follow-up.
dual index plus a 6-nt internal index. All amplification protocols produced consistent microbial profiles for the same samples. However, reproducibility was highest for the TS-tailed method, and the repeatability of a TS-tailed, one-step protocol without internal index tested on the HiSeq platform yielded high alpha diversity.

Microbiome and body size

Associations between BMI categories and the saliva microbiome were investigated in 1000 randomly selected saliva samples at baseline. About 104 million 16S rDNA (V3-V4) sequences were obtained and classified into operational taxonomic units (OTUs). Significant differences in microbial abundance at three taxonomic levels (OTU, genus, order) were observed between BMI categories. The following bacteria were significantly more abundant in the BMI categories: Kingella in underweight; Alysiella, Caulobacter and Acidovorax in overweight; Acinetobacter, Kingella and Enhydrobacter in overweight and obese; and Alysiella and Acidovorax in obese. Our results may potentially be used for early identification of persons at risk for developing obesity (Raju et al., submitted).

Diversity in saliva microbiota and body composition of adolescents at baseline and follow-up

We aimed to investigate longitudinal changes in the adolescent saliva microbiome after 4 years of follow-up, and their association with BMI development. The microbiome of 580 follow-up saliva samples will be compared with baseline samples and changes will be studied in four groups: adolescents who maintained normal weight; adolescents who maintained overweight; adolescents who changed from normal weight to overweight; or vice versa; during the 4-year follow-up (Raju et al., in preparation).

Picky eating, a risk factor for underweight in Finnish adolescents

This cross-sectional study focused on the associations of picky eating (PE) and food neophobia (FN) with food consumption and BMI. The overall prevalence of PE and FN in the cohort were 33.6% and 14.1%, respectively. We have shown that PE and FN are real obstacles to healthy eating, as they are clearly associated with unhealthy eating habits. Adolescents with PE and FN had a higher risk for underweight, and those with PE had a lower risk for overweight/obesity (Viljakainen H et al., in preparation).

Eating habits and body size in Finnish adolescents

This cross-sectional study evaluates the associations of eating habits, meal patterns and breakfast consumption with body size, as defined by BMI categories. Fruit and vegetable avoiders were associated with underweight. Adolescents with irregular breakfast consumption had a lower risk of underweight but a higher risk of overweight and obesity (Viljakainen J et al., in preparation).

What are the main strengths and weaknesses

Strengths of the Fin-HIT Study include its sample size, as it is one of the largest prospective population-based studies of 9–12-year-olds and their parents in Finland so far. Moreover, questionnaire data, anthropometric measures and saliva samples are available for both adolescent and parents. The study takes advantage of data linkage from several national registers. The longitudinal study design enables us to observe trends from adolescence to adulthood related to body size, lifestyle factors, the microbiome, genetic and epigenetic aspects and others. The study design also lends to the elaboration of aetiological studies on body size development. The data collection was supervised by trained staff following standard operating procedures, and all management procedures are quality assured.

Weaknesses include a relatively low participation rate at baseline (30%) and first active follow-up, during which only about half of the original 11 407 adolescents participated; thus, selection bias cannot be excluded. Reassuringly, the prevalences of overweight and obesity among Fin-HIT adolescents (13.4%, Table 2) are similar to those observed in other studies. Other studies have reported similar or lower participation rates, which may indicate a more global trend of unwillingness to participate in large epidemiological studies. Another weakness was that information on principal risk factors were self-reported, which may have some bias and thus may provide weaker evidence of causality. However, some parts of the questionnaire data will be confirmed and complemented with data from national registers.

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

The Fin-HIT Study is being conducted at the Folkhälsan Research Center, under the supervision of Professor Elisabete Weiderpass. Details of the cohort can be found at [www.finhit.fi/for-researchers]. We welcome applications to use the Fin-HIT dataset. Interested researchers, please contact Professor Elisabete Weiderpass [e-mail: elisabete.weiderpass@helsinki.fi].
Profile in a nutshell

- The Fin-HIT Study is designed to study environmental, genetic and epigenetic factors in the development of body size and health outcomes over time.
- At baseline (2011–14), 11 407 adolescents aged 9 to 12, living in and around the largest cities in Finland, were enrolled in the study together with 9935 parents.
- The first active follow-up was conducted in 2015–16 and included repeated body measurements and saliva sampling from both adolescents and parents.
- The dataset consists of questionnaire data, anthropometric measures and biological samples. The study database is linked to data from several Finnish national health registers.
- For collaborative studies, please contact Professor Elisabete Weiderpass [e-mail: elisabete.weiderpass@helsinki.fi].

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