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Clinical and physical characteristics of thinness in adolescents: the HELENA study

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1 **Article title:** Clinical and physical characteristics of thinness in adolescents: The HELENA Study

2 **Short running head:** Thinness in adolescents

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ABSTRACT

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Purpose: Thinness in adolescence has not been studied as extensively as overweight or obesity. The aim of this study was to assess the prevalence, characteristics, and health **impacts** of thinness in a European adolescent population.

Methods: This study included 2711 adolescents (**1479 girls**, 1232 boys). Blood pressure, physical fitness, sedentary behaviors, physical activity (PA), and dietary intake were assessed. A medical questionnaire was used to report any associated diseases. A blood sample was collected in a subgroup of the population. **Thinness and normal weight were identified using the IOTF scale.** Thin adolescents were compared with adolescents of normal weight.

Results: Two hundred fourteen adolescents (7.9%) were classified as being thin; the prevalence rates were 8.6% in girls and 7.1% in boys. Systolic blood pressure was significantly lower in adolescents with thinness. The age at the first menstrual cycle was significantly later in thin female adolescents than in those with normal weight. Upper-body muscular strength measured in performance tests and time spent in light PA were significantly lower in thin adolescents. The Diet Quality Index was not significantly lower in thin adolescents, but the percentage of adolescents who skipped breakfast was higher in adolescents with a normal weight (27.7% vs 17.1%). Serum creatinine level and HOMA-insulin resistance were lower and vitamin B12 level was higher in thin adolescents.

Conclusions: Thinness affects a notable proportion of European adolescents with **no physical** adverse health consequences.

Keywords: *Thinness; Youth; Prevalence; Europe; Characteristics; Lifestyle*

74 **Introduction**

75 Thinness in children and adolescents is clinically defined as a low body mass index (BMI) using
76 international age- and sex-specific cutoff points [1]. A recent systematic review and meta-analysis
77 showed that the prevalence of thinness in children and adolescents increased in several European
78 countries between 2000 and 2017 [2]. Based on the International Obesity Task Force (IOTF)
79 definitions, it has been estimated that about 10% of European children and adolescents are thin [2].
80 The Childhood Obesity Surveillance Initiative has also reported an increase in the prevalence of
81 thinness, particularly in Eastern Europe [3], which raises concerns about possible adverse health
82 consequences. Thinness is associated with a poor quality of life, lower physical fitness level,
83 amenorrhea, decreased bone mineral content, scoliosis, negative body image, and fatigue in childhood
84 and adolescence, and with increased mortality in later life [4–8]. However, most epidemiological
85 studies have not separated the pathological (e.g., anorexia nervosa) from nonpathological thinness
86 characterized by resistance to weight gain.

87 Thinness in adolescence has not been studied as extensively as overweight or obesity, and there
88 is a lack of information about the characteristics and associated factors, including lifestyle factors
89 such as physical activity (PA), sedentary behaviors, dietary habits, and physical fitness. We
90 hypothesized that thinness is constitutional in European adolescents and has no adverse health
91 consequences for lifestyle habits.

92 **Materials & Methods**

93 *Study design*

94 The present ancillary study is based on the Healthy Lifestyle in Europe by Nutrition in
95 Adolescence (HELENA) study. The aim of the HELENA study was to obtain a broad range of
96 standardized, reliable, and comparable nutrition and health-related data from a random sample of
97 European adolescents aged 12.5–17.5 years. The HELENA study was performed from 2006 to 2007

98 in 10 European cities: Vienna (Austria), Ghent (Belgium), Lille (France), Athens (Greece), Heraklion
99 (Greece), Pecs (Hungary), Rome (Italy), Dortmund (Germany), Zaragoza (Spain), and Stockholm
100 (Sweden). Details of the recruitment, sampling, standardization, and harmonization processes were
101 published elsewhere [9,10].

102 The aims and objectives were explained carefully to each adolescent and their parents. Written,
103 informed consent was obtained from the adolescent and their parents. The HELENA study was
104 approved by the local ethics committee for each country, and all procedures were performed in
105 accordance with the ethical standards of the Helsinki Declaration of 1975 as revised in 2008 [11].

106 A summary of the recruitment process is shown in Figure 1. All participants were recruited at
107 school and met the general HELENA inclusion criteria. From the total population of 3528
108 adolescents, a subsample of 2711 (76.8%) was included in the present analysis after exclusion of
109 adolescents with overweight (n = 619) or obesity (n = 198). Based on the International Obesity Task
110 Force (IOTF) definitions and among the 2711 adolescents, 214 with thinness and 2497 with a normal-
111 weight status, and the latter were classified as the control group. From a total of 3528 adolescents
112 included in the HELENA study, one third of the school classes were randomly selected in each center
113 for blood collection, and a total of 846 adolescents (62 with thinness and 784 as controls) were
114 included in a subsample analysis.

115 *Measurements*

116 Anthropometric measures

117 Anthropometric measurements were obtained using standard techniques [12]. Weight was
118 measured with the participant in underwear and without shoes to the nearest 0.1 kg using an electronic
119 scale (Seca 871; Seca, Hamburg, Germany). Height was measured with the participant barefoot
120 without shoes in the Frankfurt plane to the nearest 0.1 cm using a telescopic height-measuring
121 instrument (Seca 225). BMI was calculated from weight (kg) divided by squared height (m²).

122 Thinness and normal weight were identified using the IOTF scale [1]. **The IOTF cut-offs link BMI**
123 **values at 18 years to centiles in childhood, giving: thinness <18.5 kg/m² and normal weight between**
124 **≥18.5 kg/m² and <25 kg/m² [1].**

125 Prenatal and birth factors

126 A parental questionnaire was developed to collect information about exclusive breastfeeding
127 duration, gestational duration, and birth weight and height [13]. Parents were asked to recall this
128 information based on their child's health record booklets. Exclusive breastfeeding duration was
129 reported in four categories: no breastfeeding, <3 months, ≥3 to <6 months, and ≥6 months [14]. The
130 gestational duration was reported in three categories: <35 weeks, 35–40 weeks, and >40 weeks. The
131 questionnaire was sent to parents before study inclusion and was collected at their adolescent's
132 examination.

133 Body composition

134 Indices of fat and fat-free mass were assessed by two methods. Fat mass was evaluated using
135 the bicipital, tricipital, subscapular, suprailiac, thigh, and medial calf skinfold thicknesses measured
136 on the left side of the body to the nearest 0.2 mm with a Holtain caliper (Holtain, Ltd., Wales, UK).
137 Measurements were performed three consecutive times, and the mean was used for the analysis. Fat
138 mass was calculated using skinfold thickness and Slaughter's equation, **validated in children and**
139 **adolescents**, and is expressed as a percentage of body weight [15]. Total fat-free mass was estimated
140 after a 10-h overnight fast using bioelectrical impedance analysis (BIA) (Akern[®], BIA101 Akern,
141 Pontassieve Italy). Shoes, socks, watches, and jewelry were removed. Participants were **fasted** and
142 were requested to void the bladder before testing. Electrode tape, conductivity gel, and current
143 electrodes were placed on the dorsal surfaces of the right hand and foot at the distal metacarpals and
144 metatarsals, respectively. Detector electrodes were applied at the right pisiform prominence of the
145 wrist and between the medial and lateral malleoli at the ankle [16]. The BIA value was expressed in

146 resistance and was used to calculate fat-free mass using the equation of Houtkooper et al., **validated**
147 **in youth aged 10-19 years** [17].

148 Social factors

149 Parental educational level was classified using a specific questionnaire completed by the
150 mothers. This questionnaire was adapted from the International Standard Classification of Education
151 (ISCED)
152 ([https://ec.europa.eu/eurostat/statisticsexplained/index.php/International_Standard_Classification_o](https://ec.europa.eu/eurostat/statisticsexplained/index.php/International_Standard_Classification_of_Education_ISCED)
153 [f_Education_ISCED](https://ec.europa.eu/eurostat/statisticsexplained/index.php/International_Standard_Classification_of_Education_ISCED)). Educational level was scored as 1 = primary and lower education (levels 0, 1,
154 and 2 in the ISCED classification); 2 = higher secondary (levels 3 and 4 in the ISCED classification);
155 and 3 = tertiary (levels 5 and 6 in the ISCED classification) [18].

156 The family affluence scale was included in a questionnaire completed by the adolescents. This
157 scale is an indicator of material affluence and considers parameters such as car ownership, having
158 one's own bedroom, internet availability, and computer ownership. The score ranges from 0 (lowest)
159 to 8 (highest), and these scores were recategorized as low (0–2), medium (3–5), and high (6–8) [19].

160 Medical history and clinical and biological assessments

161 Each **participant** underwent a detailed medical examination. Medical history and medications
162 were recorded in a specific case report form for each participant. Pubertal status was assessed by
163 direct observation according to Tanner and Whitehouse, **performed by a well-trained pediatrician.**
164 **Signs of puberty were scored according to pubic hair status using the standard pictures of pubic hair**
165 **development from the Tanner scale.** For girls, the age at the first menstrual cycle was obtained in a
166 questionnaire. Blood pressure was measured twice (Omron M6, HEM 70001; Omron, Kyoto, Japan).
167 For blood pressure measurement, the participant was seated with the back supported and feet on the
168 ground in a separate quiet room for 10 min. Two readings of systolic blood pressure were taken after
169 10-min intervals of quiet rest, and the lower of the two was recorded for analysis. Blood samples were

170 collected by venipuncture after an overnight fast. Heparinized tubes were used for blood collection
171 and centrifuged within 30 min (3500 rpm for 15 min) to avoid hemolysis. Samples were stored and
172 transported at 4–7°C to the central laboratory of the study (Bonn, Germany) and stored there at –80°C
173 until assayed.

174 Lifestyle factors

175 The lifestyle factors assessed in our study included daily PA, sedentary behaviors, sleep habits,
176 and the dietary profile including dietary quality, total energy intake, and breakfast consumption
177 (skipping or consuming).

178 PA was assessed using accelerometry, an objective measure for use with youth [21]. The
179 accelerometer used was the ActiGraph® monitor (ActiGraph®, GT1M®, Pensacola, FL, USA). The
180 epoch interval for the ActiGraph monitor was set at 15 s. Adolescents wore the accelerometer on their
181 lower back beneath their clothing using an elastic belt with adjustable buckle for 7 consecutive days.
182 Participants who did not record at least 3 days with a minimum of 8 h of activity per day were
183 excluded from the analyses. Zero-activity periods of 20 min or longer were interpreted as “not worn
184 time”, and these periods were removed from the summation of activity. The PA patterns were
185 assessed using the thresholds used in previous studies of adolescents. The assessment of time spent
186 in each PA level was based on cutoff points of 0–500, 501–1999, 2000–2999, and >2999 counts/min
187 [22].

188 Sedentary behaviors were assessed using a structured questionnaire that included questions
189 about the amount of time spent habitually in front of the television or a computer, or playing video
190 games during school days and school-free days. The questionnaire used questions such as, “On
191 weekdays, how many hours do you usually spend watching television?”, “On weekdays, how many
192 hours do you usually spend on computers?”, and “On weekdays, how many hours do you usually
193 spend playing video games?”. The answers were classified into two categories: 0–2 h/day and >2

194 h/day [23,24]. This measure has been shown to provide a reliable (intraclass correlation = 0.82; 95%
195 CI 0.75–0.87) and valid (criterion validity = 0.3) tool for assessing sedentary time [24].

196 Sleep habits were estimated using a questionnaire that included two questions on sleep duration,
197 “During weekdays, how many hours (and minutes) do you usually sleep?” and “During weekend
198 days, how many hours (and minutes) do you usually sleep?”.

199 Dietary intake was assessed using two nonconsecutive 24-h recalls performed on any two
200 convenient days of the week [25]. The 24-h recalls were recorded using a self-administered,
201 computer-based HELENA Dietary Intake Assessment Tool (HELENA-DIAT) that has been validated
202 in European adolescents [26]. Detailed descriptions of the data collection and analysis have been
203 published elsewhere [18,27–29]. The Diet Quality Index for Adolescents (DQI-AM) was used to
204 assess the overall quality of the diet. The DQI-AM comprises four components: quality, diversity,
205 equilibrium, and meal frequency [18,27–29]. A score was calculated for each day, and the mean daily
206 score was taken as the participant’s overall index. The intakes of foods and nutrients were calculated
207 for each adolescent. A breakfast assessment was also performed. Adolescents reported their breakfast
208 habits by responding to the following statement, “I often skip breakfast”, which had seven possible
209 answers ranging from strongly disagree (1) to strongly agree (7). The participants were categorized
210 into three groups: consumers (answer 1 or 2); occasional consumers (answer 3, 4, or 5); and skippers
211 (answer 6 or 7).

212 Smoking status was recorded using a questionnaire. There were four possible answers and the
213 participants were categorized into three groups: regular consumer (answer 1); occasional consumer
214 (answer 2 or 3); and nonsmoker (answer 4).

215 Physical fitness

216 Health-related physical fitness components were assessed by incorporating the Eurofit and
217 FitnessGram tests. The protocols and procedures to assess health-related physical fitness in the

218 HELENA study have been published elsewhere [30]. Briefly, cardiorespiratory fitness was assessed
219 using the 20-m shuttle run test, upper- and lower-body muscular strength were assessed by measuring
220 handgrip strength and the standing long jump test, respectively, and speed–agility was assessed using
221 the 4 × 10-m shuttle run test. All tests were performed twice, and the best score was recorded except
222 for the cardiorespiratory fitness test, which was performed only once. **Good reliability has been**
223 **reported in young people for all tests used in this study using the Bland-Altman plots [31]. It has been**
224 **shown that the systematic error when fitness assessment was performed twice was nearly 0 for all the**
225 **tests [31].**

226 *Statistical analysis*

227 Categorical variables are reported as frequency (percentage) and continuous variables as mean
228 ± standard deviation (SD) for data with a normal distribution or as median (interquartile range)
229 otherwise. Normality was assessed graphically and using the Shapiro–Wilk test. To evaluate the
230 magnitude of the differences in characteristics according to thinness status, the absolute standardized
231 differences were calculated, and an absolute standardized difference >20% was interpreted as a
232 meaningful imbalance. Each outcome was compared between adolescents with thinness and controls
233 using linear regression models for continuous outcomes (after applying a log or rank transformation
234 if needed) and logistic regression models for categorical outcomes (binary or multinomial logistic
235 according to the number of modalities). For these analyses, pubertal status (I + II vs III vs IV vs V)
236 and center were included as confounding factors. From these models, effects sizes and 95%
237 confidence intervals (CIs) were estimated as the odds ratios for categorical outcomes and as
238 standardized differences (Cohen’s d) for continuous outcomes. According to Cohen, a standardized
239 difference <0.2 is considered as null, 0.2–0.5 as small, 0.5–0.8 as medium, and >0.8 as large [32]. All
240 effect sizes were calculated using adolescents with normal weight as the reference group. P values
241 were corrected for multiplicity by controlling the false discovery rate using the Benjamini Hochberg
242 procedure applied to a set of outcomes in the same domain. All comparisons were performed

243 separately for boys and girls as a sex-stratified analysis using the same methodology. All statistical
244 analyses were performed using SAS software (release 9.4; SAS Institute, Cary, NC, USA).

245 **Results**

246 A total of 2711 adolescents were included. The prevalence of thinness was 7.9% in the overall
247 population (95% CI = 6.9 to 8.9; n = 214): 7.1% in boys (95% CI = 5.6 to 8.5; n = 87/1145) and 8.6%
248 in girls (95% CI = 7.2 to 10.0; n = 127/1352). The adolescents' characteristics are presented in Table
249 1. The mean ages of the 214 adolescents with thinness and 2497 normal-weight adolescents were 14.8
250 \pm 1.2 and 14.9 \pm 1.2 years, respectively. No between-group differences were observed with respect
251 to sex, age, height, socioeconomic status, or mother's educational level, except for anthropometric
252 data such as weight and body composition. Thin adolescents had lower fat and fat-free masses, and
253 weight compared with controls. Pubertal status was delayed in the thin group (16% with pubertal
254 status V compared with 29% in controls). Medical history (antecedents and actual diseases) did not
255 differ between the thin and normal-weight groups. The data for neonatal characteristics are also
256 presented in Table 1. No meaningful differences were found between the two groups for weight and
257 height at birth, gestational duration, or breastfeeding duration.

258 The comparisons of clinical characteristics between adolescents with thinness and controls are
259 presented in Table 2. Relevant differences were observed between the two groups for systolic blood
260 pressure and the age at the first menstrual cycle. Systolic blood pressure was lower in thin adolescents
261 ($d = -0.43$; 95% CI = -0.57 to -0.29). Similar results were found in the sex-stratified analyses (in
262 boys, $d = -0.56$; 95% CI = -0.78 to -0.35 ; in girls, $d = -0.31$; 95% CI = -0.50 to -0.12) (Supplemental
263 Figure 1). At the age at the first menstrual cycle, female adolescents with thinness were older (13.1
264 years) than those with a normal weight (12.5 years) ($d = 0.47$; 95% CI = 0.25 to 0.70).

265 The comparisons of lifestyle behaviors and physical fitness between the thin and control
266 adolescents are shown in Table 3. No relevant differences were found between thin and normal-

267 weight adolescents for sleep duration and time spent in sedentary behaviors. No meaningful
268 differences were found for time spent at different daily PA levels, except for light PA (LPA). Thin
269 adolescents spent less time in LPA compared with controls ($d = -0.23$; 95% CI = -0.39 to -0.06);
270 despite the similar effect sizes in boys and girls, this difference was no longer significant in the sex-
271 stratified analyses (Supplemental Figure 2). Upper-body muscular strength was lower in thin
272 adolescents than in controls ($d = -0.43$; 95% CI = -0.57 to -0.29). Similar results were found in the
273 sex-stratified analyses (in boys, $d = -0.51$; 95% CI = -0.70 to -0.32 ; in girls, $d = -0.47$; 95% CI = $-$
274 0.66 to -0.28 ; Supplemental Figure 2).

275 The comparisons of dietary profiles between thin- and normal-weight participants are presented
276 in Table 4. No relevant differences were found. Sex-stratified analyses shows that thin girls had higher
277 energy intake ($d = 0.29$; 95% CI = 0.07 to 0.50), fat intake ($d = 0.30$; 95% CI = 0.10 to 0.50), and
278 carbohydrate intake ($d = 0.31$; 95% CI = 0.11 to 0.51) and skipped breakfast less often (OR = 0.51 ;
279 95% CI = 0.30 to 0.89) compared with normal-weight girls (Supplemental Figure 3).

280 The comparison of biological characteristics between thin and control adolescents are shown in
281 Table 5. Compared with controls, thin adolescents had lower serum levels of creatinine ($d = -0.46$;
282 95% CI = -0.71 to -0.21) and insulin ($d = -0.41$; 95% CI = -0.67 to -0.14), and HOMA-insulin
283 resistance ($d = -0.39$; 95% CI = -0.66 to -0.13), but a higher vitamin B12 level ($d = 0.28$; 95% CI =
284 0.11 to 0.64). In the sex-stratified analyses, only creatinine level was lower in thin girls compared
285 with normal weighted girls ($d = -0.57$; 95% CI = -0.91 to -0.22 ; Supplemental Figure 4).

286 **Discussion**

287 *Prevalence of thinness in European adolescents*

288 In the present study, we found a high prevalence of thinness in European adolescents, which
289 was slightly higher in girls than in boys; the prevalence rates are consistent with those reported in a
290 recent systematic review and meta-analysis [2]. Sex differences in body composition, patterns of

291 weight gain, hormone biology, and susceptibility to certain social, ethnic, genetic, and environmental
292 factors may explain the differences in the prevalence of thinness between boys and girls [33]. The
293 HELENA study excluded all youth with a chronic medical condition, and the medical history did not
294 differ between the thin and normal-weight participants [10]. In addition, the PA patterns did not differ
295 between thin and normal-weight adolescents in this study. We note that anorexia nervosa is
296 characterized by high levels of PA, hyperactivity, and compulsive or excessive exercise [34]. In
297 addition, the food records and dietary habits did not reveal any eating disorders or feeding restrictions
298 in the thin adolescents in this study. We are therefore confident that our results support the idea that
299 the thinness identified here reflects constitutional thinness.

300 *Health-related fitness and lifestyle habits (PA and sedentary behaviors) in thin European*
301 *adolescents*

302 Physical fitness and PA are two important determinants of health. Our results suggest that
303 thinness in European adolescents is not associated with changes in PA or in time spent in sedentary
304 activities. In our study, the only difference was that thin adolescents spent significantly less time in
305 LPA compared with normal-weight adolescents, which may be advantageous for their future health
306 [35–37] because medium and high levels of LPA are associated with a 2.89- and 3.07-years longer
307 predicted life expectancy, respectively, and a decreased risk of death [37,38]. However, the difference
308 between groups in our study was small (on average 6 min) and may be considered as not clinically
309 relevant. Taken together, our results suggest that thin European adolescents do not differ in their
310 lifestyle habits compared with those of normal weight.

311 Although cardiorespiratory fitness, lower-body muscular strength, and speed–agility were
312 similar in thin and normal-weight adolescents in this study, thin adolescents had a lower upper-body
313 muscular strength than controls, a finding that is consistent with previous reports [39,40]. One
314 possible explanation for this difference is the lower fat-free mass in thin adolescents, which has also
315 been reported [39,40].

316 *Dietary habits of thin European adolescents*

317 Except for a higher fat intake, diet quality and total energy intake were similar in thin and
318 normal-weight adolescents in this study. This finding suggests that the thin adolescents exhibited
319 resistance to weight gain, which is a characteristic of a constitutionally thin population. A recent
320 systematic review and meta-analysis confirmed that constitutionally thin adults also have a normal
321 energy intake [41]. We also found no differences in micronutrient intake between the thin and normal-
322 weight adolescents. Unexpectedly, a lower percentage of thin adolescents than controls skipped
323 breakfast. Breakfast skipping in adults is associated with cardiometabolic risk, as shown by the
324 metabolic risk profile, overweight, obesity, hypertension, diabetes mellitus, and presence of
325 cardiovascular disease [42–44]. Similarly, in children and adolescents, regular breakfast consumption
326 promotes good nutritional status, weight maintenance, cognitive performance, and well-being [45–
327 47]. We have no clear explanation for this difference and note that this does not appear to be linked
328 to differences in the mother’s educational level or the family’s socioeconomic status.

329 *Metabolic profiles of thin European adolescents*

330 Our study found, for the first time, that adolescents with thinness have a better metabolic profile,
331 as shown by lower inflammatory markers, lower systolic blood pressure, and better insulin sensitivity,
332 compared with normal-weight adolescents. Similar findings have been reported for adults with
333 constitutional thinness; for example, adults with constitutional thinness have lower levels of insulin-
334 like growth factor 1, estradiol, growth hormone, follicle-stimulating hormone, and luteinizing
335 hormone [41]. Although having anorexia nervosa **or** a BMI <20 kg/m² is associated with impaired
336 glucose tolerance [48,49], we found greater insulin sensitivity in the adolescents with constitutional
337 thinness in our study (**J curve relationship**). The low serum creatinine concentration in adolescents
338 with thinness in our study is not surprising because it reflects the muscle mass, which was probably
339 lower in the thin adolescents, as reflected by the lower fat-free mass and upper-body muscular
340 strength compared with the normal-weight participants.

341 *Clinical characteristics in thin European adolescents*

342 In our study, thinness was associated with pubertal delay, as previously reported [50,51].
343 Underweight can delay the onset and progression of puberty and menarche [50]. Body composition
344 is dependent on age, sex, and sexual maturation, and delayed sexual maturation may have contributed
345 to thinness in these adolescents. The consequences for future health remain to be determined.
346 Previous studies have shown that a delay in puberty can be protective for cardiometabolic health,
347 although other studies have reported an increased risk of coronary heart and other vascular diseases
348 [53–56].

349 *Strengths and limitations*

350 The major strengths of this study are the strict standardization of the fieldwork across the
351 different centers of the HELENA study and the careful medical examination and assessment of any
352 associated chronic diseases [10]. All assessments were valid, reliable, and harmonized between each
353 center using standardized procedures. However, our study also has some limitations. First, the limited
354 sample size of the thin group reduced the power of our analyses. The observations of the present study
355 are also limited by the cross-sectional design nature, and causality cannot be determined. **Lastly, even**
356 **though the HELENA-DIAT has been validated against dietary recall with an interviewer, the main**
357 **limitation is the subjectivity of the assessment of dietary intake that was evaluated only by the**
358 **adolescent participants.**

359 **Conclusions**

360 Thinness affects a notable proportion of European adolescents. However, thinness is not
361 associated with reduced energy intake, increased PA level, or any adverse health consequences.

362

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368

369 **Conflict of Interest**

370

371 The authors declared no conflict of interest.

372

373

374 **Author contributions**

375

376 FG, SD, AK, KW, MK, MGG and LM designed research; JV, LB, MJC, AK, DM, CB and KW
377 conducted research; ED analyzed data; JV, LB, and FG wrote the paper; ED analyzed data and
378 performed statistical analysis; FG had primary responsibility for final content. All authors read and
379 approved the final manuscript.

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Table 1. Characteristics of participants

	Overall n=2711	Thin n = 214	Controls n = 2497	ASD (%)*
Sex				10.5
Boys	1232 / 2711 (45.4)	87 / 214 (40.7)	1145 / 2497 (45.9)	
Girls	1479 / 2711 (54.6)	127 / 214 (59.3)	1352 / 2497 (54.1)	
Age (yrs) ¹	14.8 ± 1.2	14.8 ± 1.2	14.9 ± 1.2	4.0
Weight (kg)	54.7 ± 8.7	44.2 ± 6.0	55.6 ± 8.3	157.1
Height (cm)	165.8 ± 9.1	164.2 ± 8.8	165.9 ± 9.1	19.4
Body Mass Index (kg/m²)	19.8 ± 2.0	16.3 ± 1.0	20.1 ± 1.8	261
Smoking consumption				7.0
Regular smoker	245 / 2637 (9.3)	17 / 211 (8.1)	228 / 2426 (9.4)	
Occasional consumer	220 / 2637 (8.3)	17 / 211 (8.1)	203 / 2426 (8.4)	
No smoker	2172 / 2637 (82.4)	177 / 211 (83.9)	1995 / 2426 (82.2)	
Body composition				
Fat Free Mass (% ²)	45.0 ± 7.6	39.7 ± 5.2	45.4 ± 7.6	87.7
Fat Mass (% ³)	20.4 ± 6.7	15.3 ± 4.5	20.8 ± 6.7	98.0
Mother Education level**				8.3
I	828 / 2556 (32.4)	62 / 202 (30.7)	766 / 2354 (32.5)	
II	788 / 2556 (30.8)	59 / 202 (29.2)	729 / 2354 (31.0)	
III	940 / 2556 (36.8)	81 / 202 (40.1)	859 / 2354 (36.5)	
Socioeconomic status				10.2
Low	471 / 1851 (25.4)	38 / 152 (25.0)	433 / 1699 (25.5)	
Medium	1005 / 1851 (54.3)	77 / 152 (50.7)	928 / 1699 (54.6)	
High	375 / 1851 (20.3)	37 / 152 (24.3)	338 / 1699 (19.9)	
Neonatal characteristics				
Weight (kg) ⁴	3.3 ± 0.6	3.4 ± 0.6	3.3 ± 0.6	12.4
Height (cm) ⁵	50.4 ± 3.2	50.6 ± 3.1	50.4 ± 3.2	5.7
Exclusive breastfeeding				10.1
Never	465 / 2054 (22.6)	33 / 157 (21.0)	432 / 1897 (22.8)	
< 3 months	718 / 2054 (35.0)	61 / 157 (38.9)	657 / 1897 (34.6)	
3 to 5 months	646 / 2054 (31.5)	49 / 157 (31.2)	597 / 1897 (31.5)	
> 6 months	225 / 2054 (11.0)	14 / 157 (8.9)	211 / 1897 (11.1)	
Underlying disease				4.9
Yes	1358 / 2711 (50.1)	112 / 214 (52.3)	1246 / 2497 (49.9)	
No	1353 / 2711 (49.9)	102 / 214 (47.7)	1251 / 2497 (50.1)	
Pubertal status				43.0
I	9 / 2456 (0.4)	2 / 204 (1.0)	7 / 2252 (0.3)	
II	144 / 2456 (5.9)	23 / 204 (11.3)	121 / 2252 (5.4)	
III	585 / 2456 (23.8)	68 / 204 (33.3)	517 / 2252 (23.0)	
IV	1031 / 2456 (42.0)	78 / 204 (38.2)	953 / 2252 (42.3)	

V	687 / 2456 (28.0)	33 / 204 (16.2)	654 / 2252 (29.0)
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Values are expressed as n. / N. (percentage) or mean \pm standard deviation.

* ASD: an absolute standardized difference >20% was interpreted as a meaningful imbalance.

** lower education (I); higher secondary education (II); higher education or university degree (III).

¹ 29 missing values. ² 54 missing values. ³ 138 missing values. ⁴ 568 missing values. ⁵ 621 missing values.

Abbreviations: ASD, absolute standardized difference; BMI, body mass index.

Table 2. Comparisons of clinical characteristics according to weight status

	Thin n = 214	Controls n = 2497	Effect size (95% CI) ¹	P ¹
Blood pressure (n=2656) ²				
Systolic (<i>mmHg</i>)	109.3 ± 11.3	115.0 ± 12.5	-0.43 (-0.57 to -0.29)	<0.001
Diastolic (<i>mmHg</i>)	63.6 ± 8.9	64.3 ± 8.3	-0.02 (-0.16 to 0.13)	0.81
First menstrual cycle *(<i>yrs</i>) (n=1281)	13.1 ± 1.1	12.5 ± 1.2	0.47 (0.25 to 0.70)	<0.001

Values are expressed as frequency (percentage) or mean ± standard deviation.

*only for girls

Effect size are standardized differences using normal weight as reference.

P-values are corrected using false discovery rate adjustment.

¹ adjusted for center and pubertal status.

² 3 missing values for thin group and 52 missing values for controls group.

Table 3. Comparisons of lifestyle behaviors and physical fitness between thin and controls

	Thin n = 214	Controls n = 2497	Effect size (95% CI) ¹	P ¹
Physical activity (n=1735) ²				
Sedentary (<i>min.day</i> ⁻¹)	549.0 ± 73.3	543.2 ± 80.3	0.07 (-0.10 to 0.24)	0.76
Light (<i>min.day</i> ⁻¹)	160.5 ± 37.7	166.7 ± 40.7	-0.23 (-0.39 to -0.06)	0.043
Moderate (<i>min.day</i> ⁻¹)	38.0 ± 14.5	39.4 ± 14.3	-0.13 (-0.30 to 0.04)	0.57
Vigorous (<i>min.day</i> ⁻¹)	19.7 ± 12.4	19.7 ± 14.0	0.01 (-0.16 to 0.18)	0.90
MVPA (<i>min.day</i> ⁻¹)	57.7 ± 23.3	59.1 ± 23.9	-0.07 (-0.24 to 0.10)	0.76
Sedentary behaviors (n=2613) ³				
≥ 2 h.day ⁻¹ in school days	116 (55.5)	1322 (55.0)	1.09 (0.81 to 1.47)	0.76
≥ 2 h.day ⁻¹ in weekend days	160 (76.9)	1868 (77.8)	0.96 (0.68 to 1.37)	0.90
Physical Fitness (n=2544) ⁴				
Cardiorespiratory fitness (<i>mL.kg.min</i> ⁻¹)	41.9 ± 6.9	41.8 ± 7.5	-0.05 (-0.21 to 0.10)	0.76
Lower muscular strength (<i>cm</i>)	165.8 ± 31.5	167.7 ± 34.9	-0.04 (-0.19 to 0.10)	0.76
Upper muscular strength (<i>kg</i>)	25.9 ± 6.9	30.4 ± 8.6	-0.43 (-0.57 to -0.29)	<0.001
Speed/Agility (<i>sec</i>)	12.1 ± 1.1	12.1 ± 1.3	-0.03 (-0.17 to 0.12)	0.86
Sleep duration (<i>hours</i>) (n=2558) ⁵	8.2 ± 1.1	8.0 ± 1.2	0.05 (-0.09 to 0.20)	0.76

Values are expressed as frequency (percentage) or mean ± standard deviation.

Effect size are standardized differences for quantitative variables and odds-ratio for categorical variables using normal weight as reference.

P-values are corrected using false discovery rate adjustment.

¹ adjusted for center and pubertal status.

² 71 missing values for thin group and 905 missing values for controls group.

³ 5 missing values for thin group and 93 missing values for controls group.

⁴ 14 missing values for thin group and 153 missing values for controls group.

⁵ 12 missing values for thin group and 141 missing values for controls group.

Table 4. Comparisons of dietary profile between normal weight and underweight participants

	Thin n = 206	Controls n = 2239	Effect size (95% CI) ¹	P ¹
DQI-AM	62.0 ± 13.5	62.2 ± 13.8	-0.04 (-0.20 to 0.11)	0.67
Energy intake (<i>kcal.day⁻¹</i>)	2269 (1748 ; 2854)	2102 (1605 ; 2780)	0.19 (0.02 to 0.36) ²	0.091
Protein intake (<i>g.day⁻¹</i>)	77.9 (58.8 ; 105.4)	80.3 (57.6 ; 107.7)	0.07 (-0.09 to 0.22) ²	0.53
Fat intake (<i>g.day⁻¹</i>)	82.8 (62.2 ; 116.9)	80.3 (55.5 ; 114.0)	0.20 (0.05 to 0.36) ²	0.091
Carbohydrates intake (<i>g.day⁻¹</i>)	274.3 (211.5 ; 351.7)	254.5 (186.1 ; 342.7)	0.17 (0.01 to 0.32) ²	0.091
Meat (<i>g.day⁻¹</i>)	120.5 (60.0 ; 217.2)	123.1 (60.0 ; 205.0)	0.05 (-0.10 to 0.19) ³	0.63
Eggs consumption (<i>Yes</i>)	57 (27.7)	741 (33.1)	0.80 (0.56 to 1.14)	0.39
Fish consumption (<i>Yes</i>)	50 (24.3)	554 (24.7)	0.97 (0.68 to 1.38)	0.86
Vitamin B12 (<i>μg.day⁻¹</i>)	4.3 (2.9 ; 6.7)	4.3 (2.7 ; 6.7)	0.11 (-0.04 to 0.27) ²	0.35
Vitamin B6 (<i>μg.day⁻¹</i>)	1474 (1103 ; 2037)	1487 (1065 ; 2079)	0.08 (-0.07 to 0.24) ²	0.44
Alcohol consumption (<i>Yes</i>)	0	30 (1.3)	NA	NA
Breakfast consumption				0.091
Consumer	115 (61.5)	1014 (49.2)	1.00 (ref.)	
Occasional consumer	40 (21.4)	477 (23.1)	0.57 (0.37 to 0.87)	
Skipper	32 (17.1)	572 (27.7)	0.84 (0.56 to 1.27)	

Values are expressed as frequency (percentage), mean ± standard deviation or median (interquartile range).

Effect size are standardized differences for quantitative variables and odds-ratio for categorical variables using normal weight as reference.

P-values are corrected using false discovery rate adjustment.

¹ adjusted for center and pubertal status.

² calculated on log-transformed variable.

³ calculated on rank-transformed variable.

Abbreviations: NA, non-applicable.

Table 5. Biological characteristics between normal weight and underweight participants

	Thin n = 62	Controls n = 784	Effect size (95%CI) ¹	P ¹
White Blood Cell (<i>G.L⁻¹</i>)	5.9 (5.1 ; 7.2)	6.0 (5.2 ; 7.0)	0.00 (-0.27 to 0.26) ²	0.97
Neutrophil (<i>G.L⁻¹</i>)	3.0 (2.1 ; 4.0)	3.1 (2.5 ; 4.0)	-0.11 (-0.39 to 0.16) ²	0.82
Lymphocyte (<i>G.L⁻¹</i>)	2.2 ± 0.5	2.2 ± 1.2	-0.01 (-0.28 to 0.25)	0.97
Red Blood Cell (<i>G.L⁻¹</i>)	4.8 ± 0.4	4.9 ± 0.5	-0.13 (-0.40 to 0.13)	0.77
Hemoglobin (<i>g.dl⁻¹</i>)	13.8 ± 1.1	14.0 ± 1.3	-0.10 (-0.36 to 0.16)	0.84
Hematocrit (%)	40.6 ± 2.9	41.2 ± 3.6	-0.11 (-0.38 to 0.14)	0.82
Platelet (<i>G.L⁻¹</i>)	259.5 ± 47.0	260.9 ± 59.7	-0.05 (-0.31 to 0.22)	0.97
Blood glucose (<i>mg/dL</i>)	91.0 ± 7.1	90.8 ± 7.3	-0.05 (-0.31 to 0.22)	0.97
Triglycerides (<i>mg/dL</i>)	58.0 (47.0 ; 80.0)	58.0 (44.5 ; 79.0)	-0.03 (-0.30 to 0.24) ²	0.97
Total Cholesterol (<i>mg/dL</i>)	159.7 ± 28.1	160.4 ± 27.3	-0.05 (-0.32 to 0.21)	0.97
HDL-C (<i>mg/dL</i>)	56.6 ± 9.4	56.5 ± 10.7	-0.04 (-0.30 to 0.23)	0.97
LDL-C (<i>mg/dL</i>)	92.9 ± 29.6	92.8 ± 24.1	-0.01 (-0.27 to 0.26)	0.97
TC/HDL-C	2.9 ± 0.8	2.9 ± 0.6	0.02 (-0.25 to 0.29)	0.97
LDL/HDL-C	1.7 ± 0.8	1.7 ± 0.6	0.06 (-0.21 to 0.32)	0.97
Creatinine (<i>mg/dL</i>)	0.67 ± 0.13	0.74 ± 0.14	-0.46 (-0.71 to -0.21)	0.010
Uric acid (<i>mg/dL</i>)	4.1 ± 1.1	4.4 ± 1.1	-0.28 (-0.54 to -0.01)	0.22
Albumin (<i>g.L⁻¹</i>)	48.0 ± 3.4	47.8 ± 3.9	-0.01 (-0.27 to 0.25)	0.97
GGT (<i>UI/L</i>)	15.0 (13.0 ; 18.0)	15.0 (13.0 ; 18.0)	-0.10 (-0.36 to 0.17) ²	0.84
TGO (<i>UI/L</i>)	22.0 (17.0 ; 24.0)	21.0 (18.0 ; 25.0)	-0.11 (-0.38 to 0.15) ²	0.82
TGP (<i>UI/L</i>)	18.0 (15.0 ; 21.0)	19.0 (16.0 ; 23.0)	-0.25 (-0.52 to 0.02) ²	0.30
Vit D (<i>nmol.L⁻¹</i>)	61.4 ± 26.4	58.8 ± 23.1	0.07 (-0.20 to 0.35)	0.87
Vit B12 (<i>pmol/L</i>)	388.5 (284.0 ; 529.0)	322.5 (241.0 ; 446.0)	0.28 (0.11 to 0.64) ²	0.048
Vit C (<i>mg/L</i>)	11.0 ± 3.1	10.4 ± 3.4	0.18 (-0.09 to 0.45)	0.57
C3 (<i>g.L⁻¹</i>)	1.06 ± 0.12	1.12 ± 0.17	-0.32 (-0.60 to -0.04)	0.17
IgA (<i>mg.dl⁻¹</i>)	130.0 (98.0 ; 165.0)	123.0 (93.0 ; 164.0)	-0.17 (-0.11 to 0.45) ²	0.62
IgG (<i>mg.dl⁻¹</i>)	1011 ± 261.2	1004 ± 214.9	-0.03 (-0.31 to 0.25)	0.97
IgM (<i>mg.dl⁻¹</i>)	114.0 (74.0 ; 153.0)	95.0 (72.0 ; 126.0)	0.20 (-0.07 to 0.48) ²	0.52
Basophil (<i>G.L⁻¹</i>)	0.03 (0.02 ; 0.05)	0.02 (0.01 ; 0.04)	0.19 (-0.08 to 0.45) ³	0.54
Insulin (<i>μUI/mL</i>)	6.8 (4.7 ; 9.4)	8.1 (6.0 ; 11.0)	-0.41 (-0.67 to -0.14) ²	0.040
Ferritin (<i>μg/L</i>)	28.1 (12.1 ; 39.9)	26.0 (15.5 ; 42.5)	-0.07 (-0.35 to 0.20) ²	0.97
Homa-Insulin Resistance	1.6 (1.1 ; 2.2)	1.8 (1.3 ; 2.5)	-0.39 (-0.66 to -0.13) ²	0.040
C-Reactive Protein (<i>mg.L⁻¹</i>)	0.25 (0.10 ; 0.65)	0.32 (0.16 ; 0.80)	-0.24 (-0.52 to 0.04) ³	0.35

Values are expressed as mean ± standard deviation or median (interquartile range).

Effect size are standardized differences using normal weight as reference.

P-values are corrected using false discovery rate adjustment.

¹ adjusted for center and pubertal status.

² calculated on log-transformed variable.

³ calculated on rank-transformed variable.

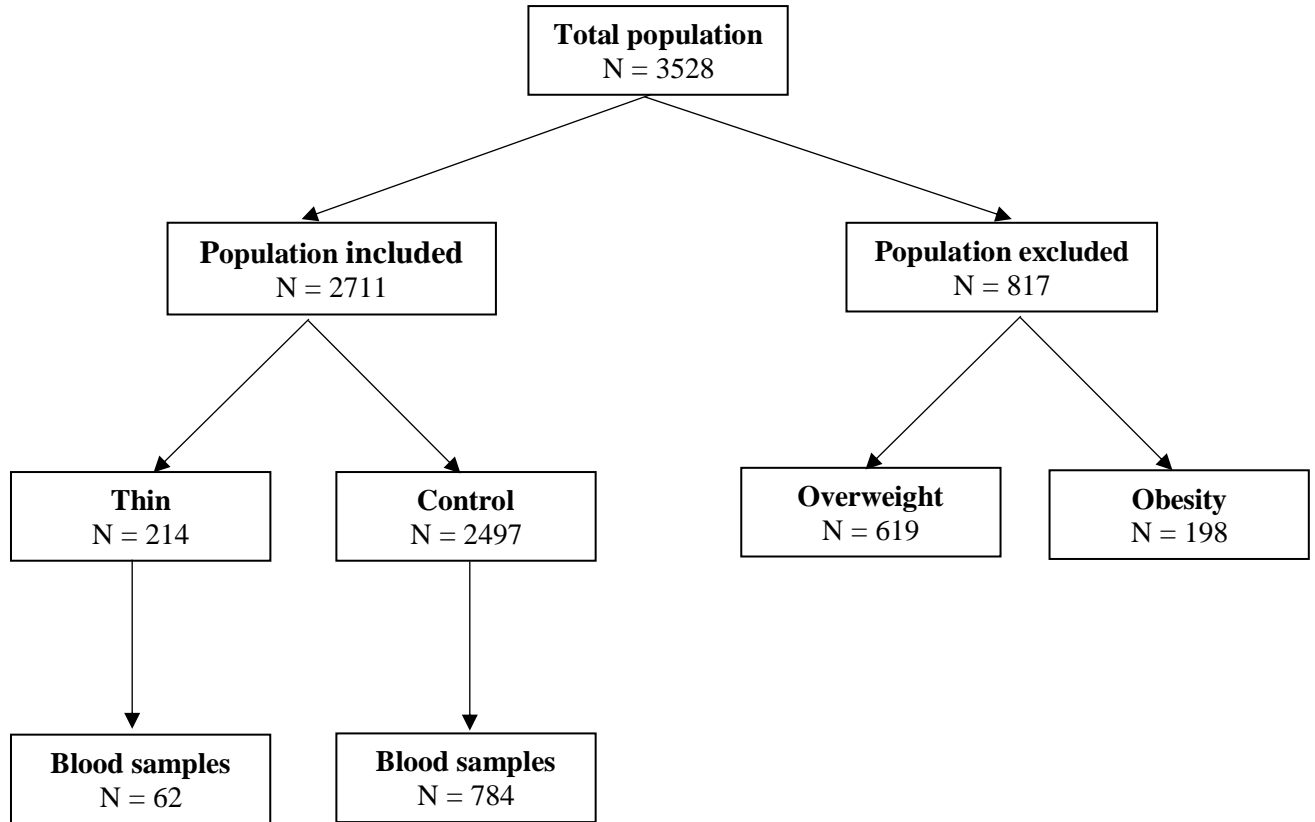


Figure 1. Flow chart of study