



Rationale and design of the school-based SI! Program to face obesity and promote health among Spanish adolescents: A cluster-randomized controlled trial

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Background Unhealthy habits in adolescents are increasing at an alarming rate. The school offers a promising environment in which to implement effective preventive strategies to improve adolescents' lifestyle behaviors. The SI! Program is a multilevel multicomponent school-based health-promotion intervention aimed at all stages of compulsory education in Spain. We present the study design of the SI! Program for Secondary Schools, targeting adolescents aged 12 to 16 years.

Aim The main goal of this study is to evaluate the impact of the SI! Program educational intervention on adolescent lifestyle behaviors and health parameters.

Methods The study was designed as a cluster-randomized controlled intervention trial and enrolled 1326 adolescents from 24 public secondary schools in Spain, together with their parents/caregivers. Schools and their students were randomly assigned to the intervention group (the SI! curriculum-based educational program over 2 or 4 academic years) or to the control group (usual curriculum). The primary endpoint will be the change from baseline at 2-year and 4-year follow-up in the composite Ideal Cardiovascular Health (ICH) score, consisting of four health behaviors (body mass index, dietary habits, physical activity, and smoking) and three health factors (blood pressure, total cholesterol, and glucose). Secondary endpoints will include 2-year and 4-year changes from baseline in ICH score subcomponents, the Fuster-BEWAT health scale, adiposity markers (waist circumference and body composition), polyphenol and carotenoid intake, and emotion management.

Discussion The overarching goal of the SI! Program is to instill healthy behaviors in children and adolescents that can be sustained into adulthood. The SI! Program for Secondary School is a comprehensive health-promotion intervention targeting 12–16-year-old adolescents and their immediate environment. The present study addresses the optimal timing and impact of the educational intervention on health in adolescence. (Am Heart J 2019;215:27-40.)

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RCT# NCT03504059.

Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov/identifiers/NCT03504059) identifier NCT03504059. Registered (<https://clinicaltrials.gov/show/NCT03504059>).

Sources of funding: This study was supported by the Fundació la Marató de TV3 (369/C/2016), the "la Caixa" Foundation (LCF/PR/CE16/10/700001), and the SHE Foundation.

VF is a recipient of funding from the American Heart Association under grant No 14SFRN20490315. R.F.J. is a recipient of funding from the European Union Horizon 2020 Research and Innovation Programme under Marie Skłodowska-Curie grant No 707642. We would like to thank the Ministerio de Ciencia, Innovación y Universidades for supporting the project AGL2016-75329-R; and Generalitat de Catalunya. The CNIC is supported by the Instituto de Salud Carlos III (ISCIII), the Ministerio de Ciencia, Innovación y Universidades (MCNU) and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (SEV-2015-0505).

Submitted December 17, 2018; accepted March 28, 2019.

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<https://doi.org/10.1016/j.ahj.2019.03.014>

Cardiovascular disease (CVD) is the leading cause of death and disability in the world,¹ largely because of risk factors modifiable by changes in behavior.^{2,3} Behavioral risk factors start in childhood and adolescence,^{4,6} and lack of physical activity⁷ and an unhealthy diet⁸ in particular have contributed significantly to the growing problem of youth obesity.⁹⁻¹¹ This will manifest as an increased CVD risk decades later.¹²⁻¹⁴ Early prevention interventions able to positively impact health-related behaviors in young people represent one of the most promising approaches to combating obesity and promoting health and thereby preventing CVD in adulthood.¹⁵⁻¹⁸

The school is probably the most appropriate setting for such an intervention¹⁹⁻²¹ because no other institution has as much influence on children during their first two decades of life.²² Adolescence is a critical period for the initiation of unhealthy behaviors. Few school-based interventions have been tested in randomized trials targeting adolescents, suggesting mild effectiveness.²³⁻²⁵ Most studies focused on a single lifestyle component and targeted weight loss rather than overall health promotion. The elements identified as necessary for an effective intervention include evidence-based approaches;^{26,27} development of personal, social and emotional abilities;²⁸ and a focus on the students, their families, and the school.^{29,30}

The SI! Program (*Salud Integral*-Comprehensive Health) is a multidimensional educational intervention, designed by the SHE Foundation, that adapts principles of the Transtheoretical Model of Change³¹ to promote lifelong cardiovascular health and good quality of life by instilling healthy lifestyle behaviors from early childhood through to adolescence.³²⁻³⁵ The intervention adopts a multicomponent approach to health that, unlike many childhood interventions in school-age adolescents, goes beyond the prevention of obesity through fitness education or dietary advice.³⁶ Uniquely, the intervention introduces emotion management as a cohesive component aimed at enhancing the uptake of healthy behaviors and instilling protective behavioral mechanisms against substance abuse.

In this article, we describe the rationale, objectives, and methods used to design the SI! Program for Secondary Schools, a cluster randomized intervention trial aimed at promoting health and combating obesity among Spanish adolescents.

Study objectives

The main objectives of the SI! Program for Secondary Schools are as follows: (1) to characterize lifestyle behaviors (dietary habits, physical activity and sedentary patterns, smoking and substance abuse, and emotion management) and health parameters among adolescents aged 12 to 16 years in a large sample of schools in Spain; (2) to evaluate the impact of different timings and intensities of the SI! Program educational intervention on adolescent lifestyle behaviors and health; (3) to study

the association between lifestyle behaviors, with special focus on dietary and physical activity habits, obesity, and other clinical parameters; and (4) to study the influence of the school environment and sociodemographic and lifestyle characteristics at the family level on adolescent lifestyle behaviors and health change.

Methods

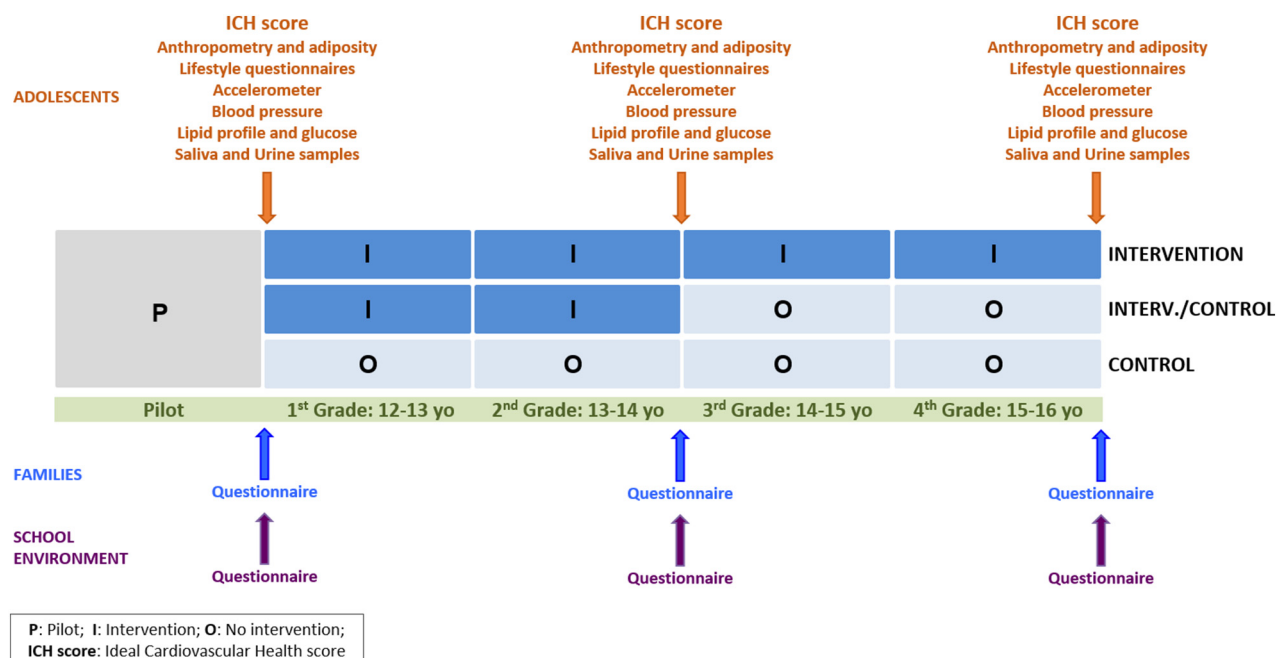
Study design, population, and randomization process

The SI! Program for Secondary Schools study was designed as a cluster-randomized controlled intervention trial in which the units of randomization were the participating schools. Secondary schooling in Spain includes education for adolescents aged from 12 to 16 years in grades 1 to 4. The eligible schools must meet all the inclusion criteria: status as a public school located in Barcelona or Madrid, provision of education from grades 1 through 4, and 3 to 5 classes in grade 1. The study aimed to enroll 24 secondary schools and a minimum of 1200 adolescents. To evaluate the effects of two different exposures to the program, schools were randomly allocated for intervention in all secondary-school levels (long-term intervention group) or only the first 2 levels (grades 1 and 2; short-term intervention); a group of control schools continued with their usual curriculum (Figure 1).

The Barcelona and Madrid regional government education committees invited all head teachers from eligible schools ($n = 146$) to a presentation of the SI! Program study design. The final 24 schools were those that agreed to participate, and they were subsequently allocated 1:1:1 to one of the two intervention arms or to the control group using a simple randomization scheme, thus ensuring an equal number of schools in each study arm. The allocation sequence was generated by an independent researcher who has no interaction with schools or participants during the study. Schools were informed of their allocation group by e-mail. Within each school, the study included those adolescent students and their parents or legal guardians who signed the informed consent form.

In the 24 schools, all 1st grade students and their families were invited to participate. Informed consent forms were provided to the teachers, who distributed them to parents, collected the completed forms, and returned them to the research team. Additional consent was provided for dual energy X-ray absorptiometry (DEXA). Upon completion of this process, the participant was considered enrolled in the study. The actual flow chart of the study schools and adolescent participants is shown in Figure 2. Participating parents or caregivers, adolescent students, and school boards have the right to withdraw from the study at any time. Based on adherence criteria established by the SHE Foundation coordination team, schools unable to deliver 75% of the program curriculum may be excluded from the study. Whether they are in an intervention arm or control arm,

Figure 1



Study design of the SI! Program for Secondary Schools.

participating schools are discouraged from running concomitant health-related programs during the course of the trial. Participating schools are advised to inform investigators about interest in any other health-related programs, and investigators additionally monitor these periodically.

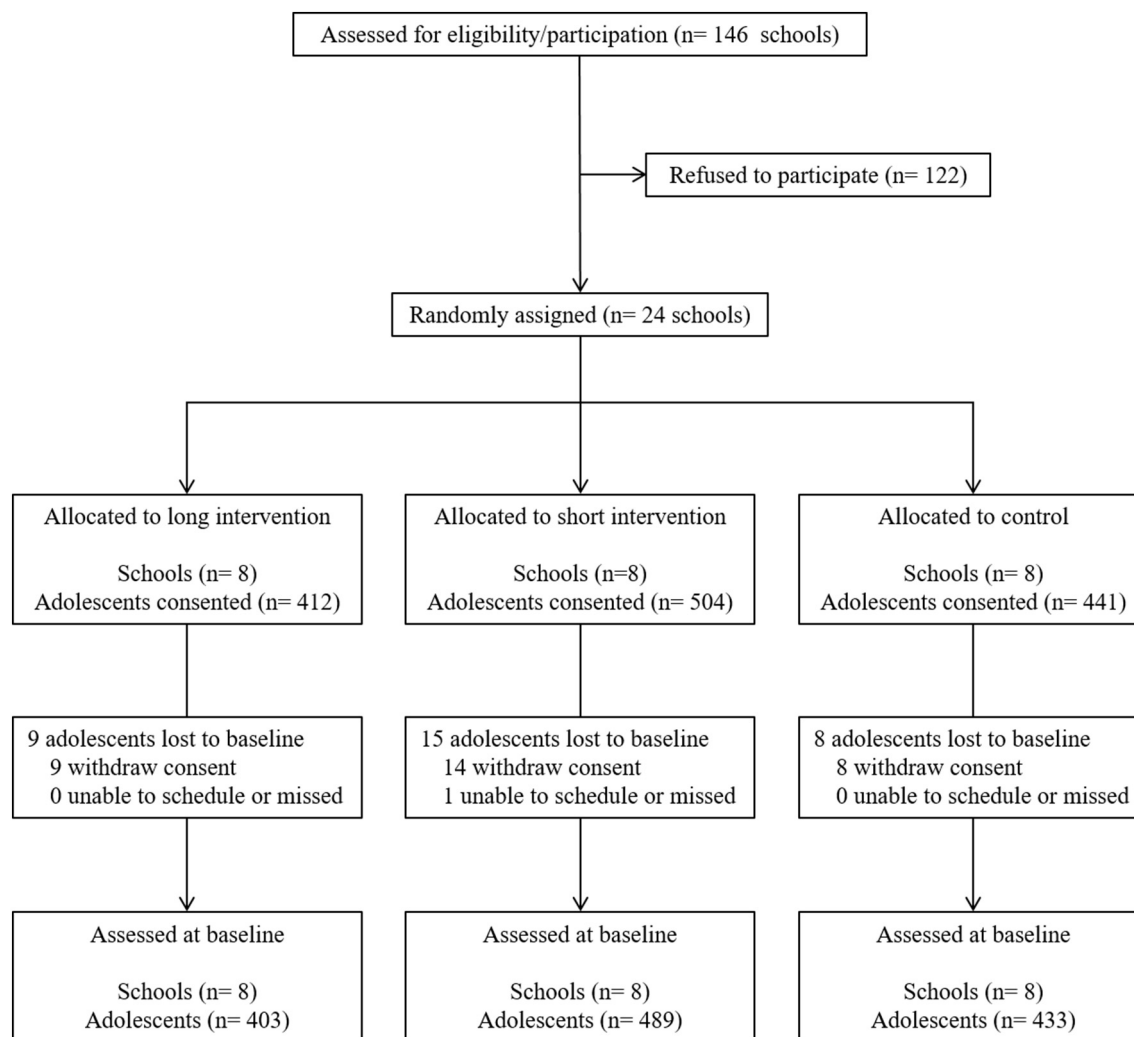
The study was approved by the Committee for Ethical Research (CEI) of the *Instituto de Salud Carlos III* in Madrid (CEI PI 35_2016) and by the CEI of the Fundació Unió Catalana d'Hospitals in Barcelona (CEI 16/41) and the University of Barcelona Bioethics Committee (IRB00003099). Data will be collected and handled according to Spanish Law 15/1999 on the Protection of Personal Data, ensuring the confidentiality of all participants' data. The study is registered at [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT03504059. The reporting of this study protocol adheres to the SPIRIT guidelines.^{37,38} The authors are solely responsible for the drafting and editing of the manuscript and its final contents. There was no specific funding provided for the creation of this manuscript.

Intervention

The levels and components comprising the educational and behavioral intervention are summarized in [Table I](#). The SI! Program for Secondary Schools is tailored to the curriculum content at this educational stage, with adaptation of strategies and materials. Materials were developed by the SHE Foundation using innovative teaching methodologies³⁹ aimed at inculcating a critical

attitude among adolescents, and thereby leading to better self-control of their own behavior.⁴⁰ The intervention materials, strategies and assessments were tested during 2017 in 2 pilot schools in Barcelona and Madrid. The teachers implementing the SI! Program in their classes completed a survey with specific questions about the program activities. The results of this pilot study (not published) helped to finesse the intervention materials and strategy before starting the randomized trial.

Adolescent-level intervention. The core intervention consists of teacher-led computer-based simulations and games (virtual trip) targeting the different age groups (grades 1-2 or 1-4). The minimum intervention load is 18 hours per year in the short-term intervention group and 12 hours per year in the long-term intervention group. The health challenge topics (healthy eating, physical activity, and substance abuse avoidance) are integrated into the regular curricular subjects (science, physical education, etc.) and are designed to stimulate a range of motivational pathways related to the diverse content through a shared methodology. The classroom activities are carried out in 3 teaching units per academic year, each focused on healthy eating, physical activity, or substance abuse avoidance (protective factors). For the healthy eating unit, the classroom intervention mostly focuses on the Mediterranean diet pyramid, the recommended quantities of different food types, alternatives to sugar-sweetened drinks, the healthiest kinds of dietary fats, food labeling, and emotional eating. For the physical

Figure 2

SI! Program for Secondary Schools flow chart.

activity unit, the classroom intervention tackles learning different sports, discovering abilities, planning training sessions, learning about the benefits of aerobic activities, and the importance of rest. Lastly, for the protective factors unit, participating adolescents work mainly on self-esteem, assertiveness, and self-efficacy. The intervention provides strategies to identify and deal appropriately with emotions such as stress and anxiety. The students also learn how to identify talents and hobbies that support healthy leisure activities. Body acceptance is integrated into all activities in the 3 teaching units. At the end of each main activity, students complete a diary describing what they have learned.

The educational resources for the intervention are introduced through an interactive game (to be downloaded on a

personal computer, mobile phone, or tablet). In the game, the student, through a personalized avatar, embarks on a virtual trip, during which he or she faces a series of challenges. Individuals earn points by registering their out-of-school physical activity, and these points are converted to kilometers for the virtual trip. Additional points can be awarded by the teacher based on each student's participation in the different program activities in the classroom. The teachers can also give additional rewards as the students reach specific points milestones. All the teachers in the intervention group have online access to the materials and a detailed teaching guide via the SI! Program website (schools are provided with a password at the beginning of the academic year).

Family-level intervention. The family-level intervention will be carried out through three newsletters per

Table I. SII Program for Secondary Schools: Levels of intervention and goals.

Level	Goal	Strategy	Supporting Materials
Adolescents	Instill a healthy lifestyle	Healthy activities at school and physical activity out of school	- Web app for recording extra-curricular physical activity. - Classroom materials: teaching units, including audiovisual resources, games, etc. - Health Fair
Families	Instill a healthy lifestyle	Newsletters with recommendations Participation in the school Health Fair	- Newsletters related to nutrition, physical activity and protective factors - SII Program website - Health Fair
Teachers	Instill healthy lifestyle contents in the curriculum	Formal training Continued counseling from the SHE Foundation educational team	- Teaching guide classroom materials - Proposal for the Health Fair - SII Program website
School environment	Promote a healthy school environment	Health recommendations for schools	- Healthy School Management - Guidance for the Healthy Fair - SII Program web site

course related to nutrition, physical activity, and protective factors. The content is focused on improving parents' knowledge about key messages in these areas and how they can help to instill healthy habits in their children.

Teacher-level intervention. At least one teacher at each school will receive training in the promotion of cardiovascular health in the school setting. This health coordinator will be the role model for the other participating teachers. All of the team will work together on the program activities.

School environment-level intervention. For the school-level intervention, schools will be provided with a set of recommendations to be implemented in specific domains, such as increasing physical activity during recess, improving dietary choices in vending machines and the cafeteria, and promoting conflict resolution. A health day will be held in each academic year and will include participation of teachers, adolescents and families.

Monitoring intervention adherence. Adherence will be monitored through regular meetings between a coordinator from the SHE Foundation and the designated health coordinator, together with the other participating teachers at the school. These meetings will provide information about implementation as well as useful guidance for teachers. In addition, the health coordinator will prepare an annual report on the school's adherence to the program curriculum.

Data collection

Timeline and general considerations. The schedule of enrollment, interventions, and assessments planned in the SII Program for Secondary Schools is summarized in Figure 3, and conforms to SPIRIT 2013 recommendations.^{37,38} All participating students will be evaluated at baseline and at 2 and 4 years thereafter with the same battery of questionnaires and measurements, unless otherwise specified. Every effort will be made to follow up all participants, including those who have changed

school. Assessment of adolescents will include a detailed assessment of health behaviors and health factors, including the following: anthropometry and body composition; diet (using a food frequency questionnaire that includes questions to assess polyphenol and carotenoid intake, as well as polyphenol quantification in saliva and urine samples); physical activity (including accelerometry); smoking and substance abuse; emotion management; blood pressure; and blood glucose and lipid profiles. The assessment at the family and school environment levels will include surveys and questionnaires. Adolescents' lifestyle behaviors and health will be assessed through self-reported questionnaires unless otherwise specified. A trained team of nurses and nutritionists will guide the adolescents through the questionnaires, perform measurements, and collect samples during school hours. Families and school principals will complete online questionnaires sent by e-mail via a dedicated data management application. For families without an e-mail address or internet access, printed questionnaires will be supplied by regular mail.

Anthropometry and body composition. Body weight will be measured with an OMRON BF511 electronic scale and height with a Seca 213 portable stadiometer, with the participant wearing light clothes and no shoes. Height measurements will be accurate to 0.1 cm and weight to 0.1 kg. Body mass index (BMI) will be calculated as body weight divided by height squared (kg/m^2). Waist circumference will be measured at the end of a gentle expiration with a Holtain tape accurate to 0.1 cm. Total fat content will be estimated by bioelectrical impedance analysis with a tetrapolar OMRON BF511 device. A subsample of ~300 control and intervened adolescents recruited in schools in the Barcelona area will undergo a DEXA examination using a GE Lunar iDXA Whole-Body Scanner (GE Healthcare) to obtain accurate estimates of total body fat, regional fat (android, gynoid, and visceral), and lean body mass.⁴¹ The regions of

Figure 3

TIMEPOINT	STUDY PERIOD								
	Enroll ment	Alloc ation	Post-allocation						
	May- June'17	July' 17	Sept- Oct'17	Oct'17 - Jan'18	Jan'18- June'18	Oct'18 - Feb'19	Feb- May'19	Oct'19 - Feb'21*	Feb- May'21
ENROLLMENT:									
Eligibility screen	X								
Information meeting	X								
School recruitment & allocation	X	X							
Informed consent from participants			X						
INTERVENTION:									
SI! Program, grades 1-2									
SI! Program, grades 1-4									
ASSESSMENTS:									
Student questionnaires				X			X		X
Student measurements				X			X		X
Parent questionnaire				X			X		X
School environment questionnaire				X			X		X

Enrollment, intervention, and assessment schedule in the SI! Program for Secondary Schools. *Oct'19-June'20 and Oct'20-Feb'21.

interest for regional body composition will be defined using the software provided by the manufacturer.

Diet. Changes in diet and adherence to the Mediterranean diet among adolescents will be assessed using the validated Children's Eating Habits Questionnaire - Food Frequency Questionnaire (CEHQ-FFQ).⁴²⁻⁴⁴ This information will be complemented with a validated 157-item Food Frequency Questionnaire (FFQ) to be filled out by the families.⁴⁵ Additional validated shorter questionnaires will be used to assess attitudes to food.⁴⁶ We will estimate dietary polyphenol intake from the 157-item FFQ complemented with data on the polyphenol content of foods, obtained from the Phenol-explorer database (<http://www.phenol-explorer.eu/>) and other sources.⁴⁵ With this methodology, we will obtain individual estimates of the uptake of total polyphenols and of the different polyphenol classes. As a

reference method, total phenolics will be estimated in saliva and urine samples by the Folin-Ciocalteu method, and their metabolites will be measured by solid-phase extraction and ultra-high performance liquid chromatography coupled to mass spectrometry.⁴⁷ Saliva and urine samples will be collected at the schools in specific containers and then aliquoted on-site and transported for storage at -80°C for subsequent use. Carotenoid and retinol consumption will be estimated from the 157-item FFQ. Total energy and micronutrient intake will be estimated using Food Processor Nutrition and Fitness Software (ESHA Research, Salem, OR).

Physical activity and sedentary habits. To register and calculate the amount and intensity of physical activity and sleep patterns, participants will wear an Actigraph wGT3X-BT accelerometer for 7 consecutive days per evaluation time-point. To complement this information, participants

will complete a diary questionnaire about the type, intensity, and amount of physical activity per week during the periods when they are not wearing the accelerometer. In addition, we will assess selected items from the validated QPACE survey for the quantification of individual physical activity.⁴⁸ The accelerometer and questionnaire-based information will be complemented with an assessment of sedentary habits, based on measures of leisure time spent with the computer, console, TV, or cell phone.⁴⁹

Smoking and substance abuse. Attitudes toward substance abuse will be assessed with a validated questionnaire.⁵⁰ An additional questionnaire will be used to assess self-efficacy,⁵¹ participant smoking status,⁵² and smoking in the participant's immediate environment.⁵³

Emotion management. A validated questionnaire will assess self-image perception and profile participants' body acceptance and the ideals of beauty in this age group.⁵⁴ Additional validated questionnaires will evaluate self-esteem,⁵⁵ emotional eating,⁵⁶ and mood.⁵⁷

Blood pressure. Blood pressure will be measured with an OMRON M6 monitor. Once the adolescent is comfortable with the monitor, blood pressure will be measured 3 times at 2–3 minute intervals according to a standardized protocol.⁵⁸

Glucose and lipid profile. Blood glucose, total cholesterol (TC), high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol, and triglyceride levels will be measured using the CardioCheck Plus device and PTS-Panels test strips⁵⁹ in capillary blood sampled with a lancet.

A brief medical report will be sent to families detailing the results obtained and making recommendations for further assessment by their primary physician if needed.

Families and school environment. The questionnaires addressing the families and school environment were also tested and adjusted during the pilot study. Parents/caregivers will complete a survey that includes questions related to sociodemographic parameters (education level, occupation, and household income) and lifestyle parameters (smoking, dietary habits, physical activity, BMI, and blood pressure). For the evaluation of the school environment, the school principal will complete a survey containing questions related to recommendations made by the SI! Program. These questions will deal with the type of foods permitted on the school premises (including products offered in the cafeteria or vending machines), measures to promote active commuting to and from school (walking or cycling) and physical activity during recess, and conflict resolution.

Definition of health scores

Ideal cardiovascular health. We will use American Heart Association measures of ideal cardiovascular health (ICH) in children and adolescents.^{60,61} Briefly, age- and sex-adjusted BMI percentiles will be calculated according to Centers for Disease Control standards,⁶² with ideal, intermediate, and poor BMI defined as <85th percentile,

85–95th percentile, and >95th percentile, respectively. The healthy diet score used for dietary profiling will include thresholds of fruits and vegetables ≥ 4.5 servings/day, fish ≥ 2 servings/week, fiber-rich whole grains ≥ 1 servings/day, and sugar-sweetened beverages ≤ 1 L/week.^{60,61} Participants who meet all 4 healthy diet criteria will be classified as having an ideal diet, while those meeting 2–3 or only 0–1 of the criteria will be classified as having an intermediate or poor diet, respectively. Alternatively, fruit and vegetable intake will serve as a proxy for overall diet in the definition of ICH, as used in previous studies,^{63–65} with participants classified as having an ideal, intermediate, or poor diet if they report an intake of ≥ 4.5 servings/day, 2.5–4.4 servings/day, or <2.5 servings/day, respectively.

Physical activity will be primarily categorized according to accelerometer data, complemented with diary and questionnaire information.^{66,67} Ideal physical activity is defined as ≥ 60 min/day moderate to vigorous activity, intermediate activity as any activity <60 min/day, and poor physical activity as no reported physical activity.

Adolescents who report never tried smoking will be categorized as having an ideal smoking status; all other participants will be classified as having a poor smoking status.

Blood pressure percentiles will be calculated according to blood pressure reference data from the American Academy of Pediatrics.⁶⁸ Ideal, intermediate, and poor BP is defined as <90th percentile, 90–95th percentile, and >95th percentile, respectively. Ideal total cholesterol will be TC <170 mg/dL, intermediate TC 170–199 mg/dL, and poor TC ≥ 200 mg/dL.^{60,61} Finally, ideal fasting blood glucose will be <100 mg/dL, intermediate glucose 100–125 mg/dL, and poor glucose ≥ 126 mg/dL.^{60,61}

These 7 cardiovascular health factors and health behaviors will be classified according to the cardiovascular health score devised by Huffman et al⁶⁹ and used by others⁷⁰ into 3 levels: poor = 0 points; intermediate = 1 point; ideal = 2 points. Based on the total score between 0 and 14 points, participants will be further categorized into 3 cardiovascular health groups: poor (0–4 points), intermediate (5–9 points), and ideal (10–14 points).

Additionally, we will use the metrics and criteria for individual ideal health factors and behaviors to calculate the ICH score corresponding to the American Heart Association criteria.⁷¹ This score will be calculated by assigning a value of 1 to each metric meeting the criterion for ideal cardiovascular health and a value of 0 to metrics not meeting the criterion. Scores will thus range from 0 to 7, with a higher score indicating a better cardiovascular health profile. A low cardiovascular health score will be defined as ≤ 3 ideal metrics, an intermediate score as 4 or 5 ideal health metrics, and an ideal score as 6 or 7 ideal health metrics.⁷¹

Fuster-BEWAT. We will also use the metrics of the Fuster-BEWAT health scale.^{32,72,73} The Fuster-BEWAT score collects clinical information on lifestyle and risk factors, including blood pressure (B), exercise/physical

activity (E), body weight/BMI (W), nutrition/diet regarding fruit and vegetable intake (A), and smoking (T). Unlike the ICH, the Fuster-BEWAT does not require laboratory results, making it easier and more suitable for global use. We will calculate this score in both adolescents and parents/caregivers participating in the study. The 5 Fuster-BEWAT components will be divided into 4 categories ranging from 0 to 3.^{32,72,73} Similar to ICH, the Fuster-BEWAT score will be analyzed as a continuous variable with total score ranging from 0 to 15 points. Additionally, each component will be categorized as ideal (3) or nonideal (0 to 2), and participants will be classified as having poor, intermediate, or ideal cardiovascular health based on the total number of ideal components (0 to 1 = poor, 2 to 3 = intermediate, 4 to 5 = ideal).⁷²

Hypothesis and endpoints

The main study hypothesis is that adolescents in the intervention groups (short-term or long-term) will see an improvement in health parameters compared with the control group. The primary study endpoint will be the change from baseline in the composite ICH score at 2-year and 4-year follow-up. Secondary endpoints will include 2-year and 4-year changes from baseline in the following: ICH subcomponents, the Fuster-BEWAT score, adiposity markers (waist circumference and body fat composition), polyphenol and carotenoid intake, emotion management, and family lifestyle and school environment characteristics. Additional secondary endpoints will include the following: a cross-sectional study of baseline lifestyle behaviors and health scores among adolescents and their families; association studies exploring links between adolescent lifestyle behaviors (with emphasis on dietary components), obesity and other clinical parameters; an analysis of determinants of the intervention effect at the school and family levels; a comparison between the short-term and long-term educational interventions, and; the exploratory analysis of the impact of the intervention on parents/caregivers' health and risk factors.

Statistical methods

Sample size calculation. The sample size and the number of schools needed to detect a mean difference between similar-sized control and intervention groups were calculated with a cluster design using the user-written command *clustersampsi* (Stata version 12.0). Based on the results of the HELENA study,⁷⁴ we calculated a minimum sample size of 21 schools (7 schools per study arm) for the detection of a significant difference of 0.5 absolute points in the ICH score between groups. In addition to the effect size, other parameters used for the calculation were as follows: a significance level of 0.05, statistical power of 80%, 50

students per school, a standard deviation in the ICH score of 1.12, and an intraclass correlation coefficient of 0.05.⁷⁵ In anticipation of potential loss to follow-up due to the long study duration, a total of 24 schools (8 schools per study arm) were included and randomized, corresponding to an expected minimum of ~1200 adolescents recruited in the study.

Statistical analysis plan. Post-intervention changes will be evaluated by analyzing data obtained at baseline and at 2-year and 4-year follow-up. The intervention effect will be determined as the mean difference in the change from baseline between the intervention and control groups by using multilevel linear mixed-effects models.^{34,76,77} This methodology will allow us to account for the hierarchical cluster randomized design of the study and to adjust for baseline variables. For the primary endpoint, the dependent variable will be the defined overall ICH score for adolescents. A priori fixed effects in each model will be the corresponding baseline score and treatment group. Schools will be handled as random effect. Interaction models will be run to identify potential age-by-treatment or sex-by-treatment effects for the main outcome variable, as well as to study the influence of other variables on the overall results at the adolescent, family, and school environment levels. The same mixed-linear models strategy will be used to evaluate secondary outcomes. Using a similar approach, multilevel logistic and ordered logistic mixed-effects models will be used for the analysis of categorical data. Both intention-to-treat and per protocol analyses will be performed.

The SI! Program for Secondary Schools is a randomized trial consisting of repeated measurements of variables related to lifestyle behaviors and health. This design allows simultaneous testing of different hypotheses; for each hypothesis, the investigators will draft a specific statistical analysis plan and select the appropriate data treatment and models to study associations and consider potential confounders. Cross-sectional associations between independent variables and outcomes of interest will be analyzed using multivariate linear regression models for continuous variables and logistic regression models for categorical variables. The adjustment variables will be defined a priori, depending on the research question, and will be entered into the model upon combination of the clinical and statistical criteria.

All statistical analyses will be performed using Stata version 12.0 or superior (StataCorp, College Station, Texas, USA) or a similar available statistical software program.

Discussion

The SI! Program for Health Promotion in Secondary Schools seeks to provide evidence that a multilevel, multicomponent school-based educational intervention can induce long-lasting changes toward a healthy lifestyle

among adolescents. Our ultimate goal is to provide effective health promotion strategies for young people, thus helping to combat the alarming increase in risk factors contributing to the CVD epidemic. Schools and their students will be randomized to a long-term or short-term intervention or to a control arm. The schools allocated to the short-term intervention group will run the educational program students during their first 2 years of secondary school, coinciding with the age range from 12 to 14 years, the critical period for the initiation of unhealthy behaviors.^{52,78} A demonstration of similar beneficial effects with the shorter and longer interventions would facilitate scale-up of the educational program. The study will additionally provide a comprehensive characterization of lifestyle behaviors and health in a large sample of adolescents in Spain and will explore the association between these lifestyle behaviors. This analysis will have a particular focus on dietary components and patterns, including examination of obesity and other clinical parameters though detailed assessment of habits and analysis of biological samples.

The magnitude of the problem: current lifestyle behavior and health trends in adolescents

The global prevalence of ideal health behaviors and health factors among adolescents is low.^{6,71,79,80} Of particular concern is the low proportion of individuals having an ideal status for the diet and physical activity components, reflected in alarming rates of overweight and obesity in this age group. According to recent estimates, 1 in 3 adolescents in Spain are overweight or obese,¹⁹ and similarly worrying rates are reported worldwide.^{6,9,80} This problem is predicted to have a highly negative societal impact because obesity is strongly linked to mortality and multiple comorbidities, mainly related to early CVD.⁸¹ Our study will complement available data by providing a cross-sectional in-depth analysis of the lifestyle behaviors and health in one of the largest samples of adolescents examined to date in Spain.

A new paradigm: from primary prevention to primordial prevention and health promotion

Clinical practice in asymptomatic populations has focused on primary prevention through the modification of already present cardiovascular risk factors.⁸² While this approach is undoubtedly positive, it does not go far enough. To achieve optimal cardiovascular health and minimize the risk of long term CVD, programs are needed to prevent the development of risk factors through lifestyle changes starting in early childhood (primordial prevention).^{15,83} Likewise, the accumulation of obesity and other risk factors during the transition to adulthood leads to higher rates of adverse outcomes.^{9,13,18} Reduction of these risk factors, even in children entering

adolescence with low cardiovascular health, has been shown to be beneficial.^{13,84} Prevention strategies focused on promoting and maintaining a healthy lifestyle in children and adolescents, and that can continue into adulthood,⁸⁵ are likely to have a decisive influence on long-term health and justify intervention efforts at early stages.^{86,87} On this basis, we will test the hypothesis that a health promotion intervention targeting adolescents will induce long-lasting beneficial changes in relevant health behaviors and health factors.

School-based interventions for health promotion in adolescents

Although there have been many studies of school-based interventions, few were validated in randomized trials targeting adolescents.²³⁻²⁵ Furthermore, most studies focused on a single lifestyle component such as diet or physical activity through structured diet or exercise interventions and targeted weight loss rather than overall health promotion. Systematic reviews suggest mild effectiveness of school-based interventions in preventing adolescent obesity; however, this analysis is limited by heterogeneity of interventions, variable design quality, and lack of longer-term follow-up.²³⁻²⁵ Moreover, two recent large school-based cluster-randomized controlled trials showed no evidence of an intervention effect on behavioral or weight outcomes at long-term follow-up,⁸⁸⁻⁹⁰ suggesting that effective interventions may require upstream intervention at the family, school environment, and societal levels.

The SI! Program: a holistic school-based health promotion intervention for the young

The SI! Program has been designed to promote long-lasting healthy lifestyle behaviors and cardiovascular health through the implementation of innovative evidence-based multilevel and multicomponent educational strategies from early childhood to adolescence.⁹¹ The educational program includes not only the participating children and adolescents but also key elements of their immediate environment, including family and the school environment. The program content is adapted to each educational stage according to the transtheoretical model of sequential behavior change (Knowledge to Attitudes to Habits),³¹ and aims to empower the individual toward healthy living.^{32-35,76,92,93} Thus, among preschoolers (3 to 5 year-olds), the aim is to promote enjoyable knowledge acquisition about healthy eating and exercise through the use of storybooks, coloring kits, and emotion cards featuring characters from Sesame Street and Cardio (the SI! Program mascot).⁹³ Children respond positively to this curriculum because they enjoy it and identify with the characters.⁹⁴ Later, children beginning their Elementary schooling (at the age of 6) begin to develop their attitudes and abilities to make conscious choices, and

become less dependent on external factors. Parents/caregivers and teachers are still crucial to providing support and encouragement to children, including access to healthy food and opportunities for physically activity.⁹⁵ Finally, in the adolescence, individuals begin to exercise their independence from parental monitoring, formulating their own judgements and decisions about lifestyle habits that will eventually continue into adulthood.⁹⁶ Adolescence also marks the stage of rapid physical development when tangled notions of appearance and perceptions become especially important as adolescents develop self-esteem and self-conceptions of body image, which can be both consequence and cause of changes in diet and exercise patterns in this phase.⁹⁷ In a health promotion intervention during adolescence, emotion management is a crucial cohesive component for enhancing the uptake of healthy behaviors and self-esteem and instilling protective behavioral mechanisms against substance abuse. In parallel, adolescents can be effectively engaged in learning about healthy lifestyles through gamification strategies.^{98,99} In summary, our health promotion intervention relies on the potential of the adolescent to have a positive impact on their own health that will be reinforced by the family and school environment.

Exploring the intersection between diet and obesity in adolescents

The Mediterranean diet is a healthy eating pattern culturally rooted in the countries of the Mediterranean basin; however, there is an increasing prevalence of poor adherence to the Mediterranean diet among young people in Spain,¹⁰⁰ and food consumption patterns among adolescents are increasingly characterized by a low intake of fruits and vegetables and a high intake of foods high in saturated fat, sugar, and salt.¹⁰¹ These dietary patterns are independently associated with adiposity,¹⁰² low cardiorespiratory fitness, and poor cardiovascular health profiles.¹⁰³ In contrast, adherence to the Mediterranean diet is related to lower obesity rates than found in individuals with low adherence across their life span.^{104,105} Furthermore, the Mediterranean diet has been shown to be effective in reducing CVD¹⁰⁶ and other chronic diseases.¹⁰⁷

In addition to changes in food choices and macronutrients, adherents to a Mediterranean diet have a significantly increased intake of several bioactive compounds, including polyphenols and carotenoids.¹⁰⁶ Polyphenols are naturally distributed in plant-derived foods such as vegetables, fruits, seeds, coffee, wine, and tea.¹⁰⁸ Epidemiological studies and meta-analyses strongly suggest that dietary polyphenols offer protection against CVD, diabetes, osteoporosis, cancer, and neurodegenerative diseases; however, data on the potential efficacy of polyphenols to modulate obesity in humans are limited and inconsistent.¹⁰⁹ Only a few human studies

have reported a relationship between polyphenol intake and protection against obesity, suggesting that these compounds could reduce body weight through different mechanisms,¹¹⁰ including the upregulation of energy expenditure.¹¹¹ Carotenoids comprise a group of lipophilic pigments produced by plants and certain photosynthetic microorganisms and are responsible for the red, yellow, and orange coloration of fruits, vegetables, and some animal tissues.¹¹² One of the main known functions of carotenoids in the human diet is to serve as precursor of vitamin A, which plays an important physiological role.¹¹³ Carotenoid consumption has been linked to a reduced risk of several chronic diseases, including CVD, age-related macular degeneration, and some types of cancer.¹¹⁴⁻¹¹⁷ An emerging perspective on the function of carotenoids and carotenoid-derived products such as retinoids suggests a connection between these compounds and the control of body fat accumulation; this interaction involves the modulation of adipocyte biology and body adiposity through several mechanisms and has implications for the management of obesity and obesity-related metabolic disturbances.¹¹⁸⁻¹²⁰

By studying the impact of the intake of key nutrients on adiposity and other health parameters, our study may help to explain the beneficial impact of specific dietary components and patterns on adolescent health.

Limitations and strengths

The major limitation of the trial is its long duration; however, this can also be seen as a strength. Another limitation is the regular changeover in school boards, which usually takes place every 4 years, introducing the possibility of changing priorities. Likewise, teacher mobility in Spain is high and could require re-initiation of the training and familiarization process. In addition, families may move home during the study period, resulting in study dropouts. To minimize the impact of this issue, the sample size calculation accounted for potential loss to follow-up and dropouts, and we will perform an intention-to-treat analysis. Because the included population consists of adolescents, the outcome/endpoint does not include clinical events. However, as mentioned, CVD has its origins during childhood and adolescence; therefore, primordial prevention strategies promoting healthy behaviors in childhood and adolescence are to be especially encouraged.^{12,15,60,82,91,121} These limitations will to some degree be obviated by the implementation of strategies allowing us to follow up participants beyond the end of the study period.

The study also has significant strengths. This cluster-randomized controlled trial will include a large sample of adolescents in Spain and a detailed assessment of health behaviors and health factors. The educational intervention is supported by several unique features, including the accessibility of materials on the SI! Program website,

the projected low relative cost of a large-scale implementation, the inclusion of emotional management as a major behavioral component, and the implementation of the program by the adolescents' own teachers. The SI! Program is flexible and can easily be adapted to different countries, income settings, languages, and children's cognitive functional level.³²⁻³⁵ These characteristics make the SI! Program educational intervention highly suitable for worldwide implementation and offer the potential to curtail the current CVD epidemic through the promotion of healthier behaviors and lifestyles.

Ethics approval and consent to participate

The study was approved by the Committee for Ethical Research (CEI) of the *Instituto de Salud Carlos III* in Madrid (CEI PI 35_2016), the CEI of the Fundació Unió Catalana d'Hospitals (CEI 16/41), and the Bioethics Committee of the University of Barcelona (IRB00003099). Informed consent forms are provided to the teachers, who distribute them to parents, collect the completed forms, and return them to the research team. Participating parents/caregivers, adolescents and school boards have the right to withdraw from the study at any time. Data will be collected and handled according to Spanish Law 15/1999 on the Protection of Personal Data, and updated to the EU General Data Protection Regulation 2016/679, ensuring the confidentiality of all participants' data. The study is registered in [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT03504059. The reporting of this study protocol adheres to the SPIRIT guidelines.^{37,38}

Availability of data and material

The data and materials presented and referred to in publications can be requested from the principal investigators.

Disclosure

None.

Author contributions

VF conceived the overall study. RF-J, GS-B, AT-R, PB, MdM, BI, CS, MD, RE, JF-A, and RL-R made substantial conceptual contributions to the overall study design and coordination, and drafted proposals for obtaining competitive funding. GS-B, AT-R, PB, MdM, VC, DH, CS, MD, RE, JF-A, and RL-R coordinated recruitment of schools and participants, the consent process, and/or data collection. CR, VC, XO, DH, and IC contributed to the study design and coordinated the development and implementation of the educational program. AdC generated the allocation sequence and assisted with data management and statistical methodology. RF-J drafted the first version of

the manuscript along with GS-B, RE, JF-A, and RL-R. All authors revised the manuscript critically for intellectual content and approved the published version.

Acknowledgements

The authors thank the SHE Foundation (intellectual owner of the SI! Program) and its collaborators: Ramona Martínez, Emilia Gómez-Pardo, Yolanda Sánchez, Mi Querido Watson, Fontventa and the Gasol Foundation. We would like to thank the working group of "Programa de salut a l'ESO", coordinated by the Department of Education of the Generalitat de Catalunya (Spain). We especially thank adolescents and their families, teachers, and schools participating in the study. Simon Bartlett (CNIC) provided English editing.

Appendix. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ahj.2019.03.014>.

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