Pediatric Preventive Care in Middle-High Resource Countries—The Padova Chart for Health in Children

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Importance: The Padova Chart for Health in Children (PCHC) aims to gather the evidence of healthcare promotion and protection for children and adolescents (i.e., aged <18 y) into a single document in order to guide families, healthcare providers and social actors on healthy choices. No more than 2% of Europeans and North Americans aged <30 y have a healthy lifestyle. This, together with metabolic and brain plasticity during childhood, creates the ideal opportunity to implement preventive strategies. Guided interventions promoting healthy lifestyle in children and families therefore have a key role in abating the unprecedented pandemic of non-communicable diseases (NCDs) in adulthood.

Observations: The PCHC is divided into four sections: nutrition, cardiovascular health, respiratory health, and mental and social health. Each section is structured in an ALICE approach (assessment, lobbying, intervention, call-for-action, evaluation): assessment of necessity, describing relevance to healthcare; lobbying to identify those who can effect the proposed interventions; interventions involving family, school and peers; a call-for-action to define priorities among the proposed interventions; and objective evaluation measures that can be applied on a population basis.

Conclusions and Relevance: Interventions promoting health in childhood require joint action from multiple institutional, local and family representatives, with the shared goal of promoting health across the entire age group. These lifestyle interventions have the potential to change the lifetime risk trajectory for NCDs.

Keywords: pediatric health care, non-communicable chronic diseases, pediatric preventative care, lifestyle related disease, lifestyle and behavior
INTRODUCTION

Optimizing pediatric health is key to reducing social inequality and ensuring sustainable growth. Although 30% of the European and North-American population is younger than 30 years (1), only 2% of this group has a healthy lifestyle, defined as being physically active for at least 60 min/d, consuming fruit and vegetables daily, spending <2 h/d on screen-based activities, and abstaining from alcohol and tobacco (2). This creates the conditions for an unprecedented pandemic of non-communicable diseases (NCDs), many of which start early in life, although not always with an overt onset in childhood or early adulthood (3). NCDs directly or indirectly account for 90% of deaths in middle-to-high income countries (4). More recently, the combination of NCDs (specifically diabetes, obesity, hypertension, chronic lung and cardiovascular diseases, and mental illnesses) and socio-economic disparities have worsened outcomes in those affected by COVID-19, compelling national healthcare systems to target health as the only truly sustainable strategy to “prevent a “syndemic” disease” approach (5, 6). Targeting health promotion in children is ideal, as they have a metabolic (7, 8) and brain plasticity (9, 10) that offers the opportunity to instill life-long healthy habits (11). Interventions promoting healthy lifestyle in childhood are the sole sustainable and effective action to prevent NCDs in adulthood (1, 11).

We therefore decided to gather current evidence and guidance into a single document to inform and promote child health. We identified four areas, based on their potential impact on morbidity and mortality (4). 1. nutrition; 2. cardiovascular health; 3. respiratory health; 4. mental and social health.

METHODS

Each area was investigated by a team of two experts. Research was performed using PubMed, UpToDate, and WebOfScience. Guidelines and position statements published by European and North American scientific societies were also considered, as were position statements from the World Health Organization and Centers for Disease Control, systematic reviews, and Cochrane Reviews. The Chart targets “children” according to the broad UNICEF definition as those aged <18 years.

Each section is formatted using a call-for-action (ALICE) approach: Assessment of necessity, based on current evidence; Lobbying: identifying targets (families, primary healthcare providers and/or schools) to effect the proposed interventions; Interventions and guidance involving family, school and peers; Call for action to define priorities among the proposed interventions; Evaluate: proposed measurable population-level indicators to give a long-term assessment of the effectiveness of the interventions.

DISCUSSION/OBSERVATIONS

Nutrition

Assessment of Necessity

Over the past 30 years, the prevalence of overweight and obesity have increased 10-fold in youth (12, 13), with 20% of those aged 2–19 years now obese (14), and one out of four having impaired glucose metabolism. Childhood obesity increases the risk of NCDs in adulthood, including type 2 diabetes, cardiovascular disease, asthma and other respiratory problems, sleep disorders, and liver disease (15). Further, longitudinal data from the SEARCH for Diabetes in Youth and the Restoring Insulin Secretion studies (16–18) have highlighted the morbidity in children with early type 2 (i.e., obesity-related) diabetes. This is important as more than 50% of those with childhood-onset type 2 diabetes have kidney disease or retinopathy by the age of 30 y (19). Treatment of childhood-onset type 2 diabetes focuses on dietary and behavioral interventions, with limited effective pharmacologic interventions available. Indeed, nutrition and lifestyle interventions remain the key tools to prevent childhood obesity and its comorbidities (20, 21). Ultra-processed food (22) and high-fructose beverages (23) are major sources of energy for children, both of which are associated with higher cardiometabolic risk (24–26). Despite this, children are exposed to the marketing of such products through techniques that exploit their developmental vulnerabilities.

It has been estimated that dietary changes may prevent ~11 millions deaths per year, that represent from the 19% to the 24% of deaths in adulthood. The benefit deriving from a healthy diet may be accounted as direct benefits—when directly impacting the disease determinants (e.g., reducing fat-saturated food directly impact cardiovascular risk) and indirect. These latter include the global impact of choosing sustainable foods, that include preferring plant-based dietary patterns (fruits, vegetables, nuts, seeds and whole grains—while limiting animal source foods), reducing food waste, and improving food production practices. Such an approach would imply a new definition of agricultural priorities and would imply an action at different levels of the food chain.

Sustainability of food results from the action of different “influencers”—determinants (27), that involves the food chain of production, the individual and collective choices and, ultimately, the food consumption. This latter is by itself a major determinant of food sustainability, thereby healthy food choices may drive food production chain in a bidirectional way.

Lobbying

Nutrition interventions should target not only children themselves, but their families and schools, along with food industries. Sustainable food promotion targets consumers but also regional and national authorities deputed to the agriculture to shift the current food-production paradigms.

Interventions

We identified two main intervention areas (20, 21): healthy food choices, education in food preparation. The access to age-appropriate high-quality nutrition is an important step toward combating malnutrition, one of the WHO millennium goals (28, 29). Malnutrition in Europe and North America is largely due to poor-quality nutrition (23). Food marketing, and children’s own food preferences (including their requests for purchase and consumption) are major determinants of the obesity epidemic. Governments in France, Israel, and the United Kingdom have
endorsed labeling policies that provide qualitative information on nutrient content, including highlighting excess salt and fat, and, in certain cases, age-appropriateness. Considering the needs of children when labeling food is a mandatory step if governments are to support healthy choices. Our recommendations combine guidelines from the American Heart Association (AHA) (30), WHO (31), and UNICEF (27), and target the two environments where food is consumed during childhood: schools and homes.

As summarized in Table 1, interventions are meant to guide food choices, instead of defining age-adjusted dietary regimens. This strategy has been proven to be effective in large clinical studies (20, 21) and regional programs.

Table 1: Nutrition.

| Assessment of necessity | • 20% of children aged 2–19 years are obese (14). |
| • 25% of obese children have prediabetes (impaired fasting glucose, impaired glucose tolerance, or both) (32). |
| • Childhood-onset type 2 diabetes is associated with microvascular complications before adulthood (19). |
| • Lifestyle is main risk factor for prediabetes and diabetes (18, 33–35). |

| Interventions | Healthy food choices (20, 21). |
| • Consume vegetables and fruit daily. |
| • Use vegetable oils and margarines that are low in saturated fat and trans fats, instead of butter or other animal fats. |
| • Use wholegrain breads and cereals rather than refined grain products. |
| • Consume skimmed or low-fat milk and dairy products daily. |
| • Eat more fish, especially oily fish, broiled/grilled or baked. |
| • Reduce salt intake, including in processed foods. |
| • Reduce consumption of sugar-sweetened beverages and foods. |
| • Limiting animal source foods (27, 30). |
| • Prefer products from a sustainable food chain (regional diversified vegetables and fruits). |
| • Food preparation education (20, 21). |
| • Promote and support breastfeeding. |

| Call for action | • Mandate food “labeling-for-children” (23, 37, 38). |
| • Introduce legislation supporting accessibility to healthy choices, including subsidies for low-income families (39). |

| Evaluation | • Track regional trends in obesity and glucose intolerance in children. |
| • Introduce quality assessment of school-based nutrition. |

The Call for action includes proposals aimed at communities and industry.

The longitudinal Evaluation of the interventions will rely on regional studies tracking the prevalence of obesity and glucose metabolism impairment. Local authorities are expected to verify quality assessment of school nutrition.

### Cardiovascular Health Assessment of Necessity

The AHA defines good cardiovascular health through seven health behaviors: abstinence from smoking; body-mass index <85th percentile; ≥60 min of moderate or vigorous physical activity daily; a diet emphasizing fruits, vegetables, fish, and whole grains, low in sodium and with few sugar-laden foods and drinks (40, 41); total cholesterol <170 mg/dL; blood pressure <90th percentile; and a fasting plasma glucose level <100 mg/dL (42). Less than 50% of adolescents aged 12–19 y achieve at least five out of these seven behaviors. As ~80% of cardiovascular events (CVD) could be prevented through these health behaviors (43), educational interventions starting in childhood are expected to have the highest impact on the incidence of CVD in adulthood (41). Beside nutrition (see Section Introduction), physical activity and screen time are the two main behavioral interventions able to affect the lifetime trajectory of cardiovascular risk.

### Physical Activity

Physical activity (structured or unstructured) for preschool (44, 45) and school children (46) is a major determinant of pediatric health. Physical activity in preschool age is important to develop large motor skills and foster coordination (important aspects of school readiness), yet infants and preschool children in many middle- and high-income countries spend more than 30% of their time in sedentary activities such as screen time (45, 46).

**Screen time** is defined as the time spent engaging with visual screen-based technologies such as televisions, computers, videogames, smart phones, and tablets, including accessing the Internet and social media. In the last decade, there has been a widespread cultural adoption of media devices in young children; in one French study in 2018, 90% of those aged 2 y used touch-screen devices (47, 48). In this rapidly evolving digital age, much more time is spent in front of screens than previous generations; children’s screen use is a key concern for parents and healthcare providers (49).

Evidence suggests that moderate screen time can be beneficial to children’s wellbeing, widening social connections and improving learning skills, especially from activities including education and early learning. However, excessive use can be detrimental (50, 51), with potential negative impacts on physical, cognitive, emotional, and social wellbeing (48, 52), including a range of adverse physical, psychosocial, and cognitive outcomes (53). Further, the “time displacement hypothesis” suggests that excessive screen time displaces important protective health behaviors such as physical activity, green time, and adequate sleep (54). In addition, excessive screen time and social media use by children is associated with the development of obesity, sleep disturbances/problems (55), language delay, inattention (or attention disorders) (56), and depression (53, 57, 58). Yet,
<20% of pediatricians ask families about their children’s use of electronic devices (59, 60).

Lobbying
Proposed interventions target families, schools and primary healthcare providers.

Interventions to promote physical activity and reducing screen time are summarized in Table 2. Age-specific recommendations are provided and should be explained with oral and written informative factsheets to families. Healthcare providers are the primary information source to effectively promote physical activity in preschool children, and one of the main sources of information in school-aged children along with schools. Universal screening for dyslipidemia at 9–11 years is still controversial (37), though scientific societies convened for the necessity for screening at risk children (overweight/obese children with/without a family history of early CVD) (Table 2) (61).

The Call for action involves institutional local and regional groups to facilitate access to spaces for physical activity.

The Evaluation of the proposed interventions is through the prevalence in children of the seven cardiovascular health behaviors.

Respiratory Health
Assessment of Necessity
Chronic respiratory diseases (CRD)—and in particular chronic obstructive pulmonary disease (COPD) and asthma—contribute significantly to the global burden of NCDs, and are major causes of morbidity and mortality. Tobacco smoking, e-cigarettes (vaping), and air pollution increase the burden of CRD. Further, although e-cigarettes have been proposed as an aid to smoking cessation in adults, there is mixed evidence for their effectiveness (63), and they can be a gateway to tobacco and nicotine use in adolescents naïve to tobacco (64, 65). E-cigarette users outnumber traditional smokers among adolescents (66); in one study 27.5% of high school and 10.5% of middle school students were current e-cigarette users (67), and in another, half of e-cigarette users aged 15–17 y had never used combustible cigarettes (68). This high use of e-cigarettes is of concern, as adolescents using e-cigarettes have an increased incidence of chronic bronchitis and asthma exacerbations compared with non-users (69, 70). E-cigarette use is also becoming more common in pregnant women, thus exposing the developing fetus to nicotine, which crosses the placenta and thus reaches the fetal bloodstream. Nicotine is not only a known teratogen (71, 72), but has been associated with major congenital anomalies such as cleft palate, prematurity and stillbirth (73, 74).

Pollution
Pollution is a major contributor to global morbidity and mortality (75). Children are especially vulnerable to the effects of pollution as they receive a relatively higher dose of toxins in any given environment, and are also more susceptible due to the physiology of their developing airways (76). Further, maternal exposure to pollutants during pregnancy may affect lung development in offspring (75). There is also convincing evidence that air pollution has negative impacts on respiratory health during childhood, and is associated with reduced maximal lung growth function (77, 78), potentially leading to the development of asthma (79) and COPD (80, 81).

Asthma is more common in children exposed to particulate air pollution, and there is evidence of a correlation between traffic-related air pollution and asthma occurrence (82, 83). Ambient air pollution is therefore recognized as a preventable risk factor for a spectrum of pediatric health problems (84).

Lobbying
Interventions should target families, healthcare practitioners and community/social organizations.

Interventions include educational sessions to be delivered through healthcare providers and schools, and local-community programs and regional politics aimed to reduce pollution exposure. Interventions are summarized in Table 3.

The Call for action targets e-cigarette regulatory policies, which are currently highly heterogeneous (85).

The efficacy of the proposed interventions can be evaluated through the prevalence of asthma in childhood and of COPD in adulthood from population studies.

Mental and Social Health
Assessment of Necessity
Neuropsychiatric conditions are the leading cause of disability in young people, with half of all chronic mental illnesses beginning by the age of 14 years. Suicide is the second cause of death in adolescents and young adults, with 10 out of 100,000 adolescents completing suicide each year (86), while attention-deficit/hyperactivity disorder (ADHD), behavior problems, anxiety, and depression are the most common mental disorders in children (87). Further, gender discrimination and economic inequity are key determinants of mental health in children (62, 88, 89).

The COVID-19 pandemic, with the resulting quarantine, social isolation, mortality, and lack of proper education, has dramatically accelerated the course of a variety of childhood mental illnesses. Community includes family, schools, and peers; thus, to achieve optimal mental wellbeing a child needs support across these domains. Gender identity, self-image and family/school environment are the three key areas for childhood mental wellbeing.

Gender interacts with, but is different from, the binary categories of biological sex. Girls (but not boys) are more likely to view girls as victims of discrimination than boys, and children with egalitarian gender attitudes are more likely to perceive discrimination than are their peers (39, 90). Youths with lesbian, gay, bisexual, transgender, or queer (LGBTQ) orientations have higher rates of anxiety and mood disorders, as well as suicide and suicide attempts. Promoting acceptance of gender diversity allows children to develop without the burden of social isolation and discrimination that people may experience surrounding their gender identity.

The health impact of social media on children is greatest on mental health, and specifically self-esteem and wellbeing, with related issues around cyberbullying, with an association between
TABLE 2 | Cardiovascular health.

Assessment of necessity
- >20% of adolescents have high blood pressure, high total cholesterol and low physical activity (41).
- Most adolescents do not achieve at least five of the American Heart Association's seven health behaviors: not smoking; weight; active life; healthy diet; cholesterol; blood pressure; blood sugar.

Intervention 1 (physical activity)
Family and school:
- Play with your children.
- Encourage active toys (balls, jump ropes, outdoor toys).
- Do not overschedule your children's day.
- Discourage eating in front of a screen.
- Avoid high caloric snacks and sugary drinks.
- Do not use food as a reward after physical activity.

Healthcare providers:
- Enquire about physical activity habits of children and their parents/caregivers.
- Describe the benefits to parents and families of an active lifestyle: Strengthen bones; decrease blood pressure; reduce stress and anxiety, and boost self-esteem; prevent obesity and type 2 diabetes; and prevent major cardiovascular events in adulthood.
- Screen for dyslipidemia in all children at 9–11 year in overweight/obese children (61, 62).
- Screen for dyslipidemia in children at 2 year in those with a family history of dyslipidemia or early cardiovascular disease
- Screen for dysglycemia in overweight/obese children.
- Check blood pressure annually.

Age specific physical activity interventions:
- (<1 year):
  - >30 min of tummy time spread throughout the day.
- 3–5-year:
  - Active play.
  - Take account of the child's preferences.
- 6–17 years:
  - ≥1 h moderate-to-vigorous physical activity every day.
  - ≥3 times per week preferred structured physical activity (football, running, gymnastics, group sports).

Intervention 2 (screen time)
Family
- No screens during meals and for 1 h before bedtime.
- Avoid having televisions and screen-based electronic devices in the children's bedroom.
- Parents should be aware of positive and negative effects of screen time and monitor children's media content and the apps that are used or downloaded.

Healthcare providers
- Healthcare providers should regularly inquire about children's social media habits, and be familiar with the social media to which children may be exposed.
- Parents and healthcare providers should ensure that sedentary screen time is not a routine part of child care.
- Unregulated video streaming apps (e.g., YouTube and YouTube Kids) are not recommended in pre-school children.
- Apps to control/limit screen time can be discussed and explored with parents.

Age specific screen-time recommendations:
- <2 years
  - Avoid screen time in children younger than 2 y (except video chatting such as Skype and FaceTime when talking with relatives/family members).
- 2–5 y
  - Limit screen time to max 1 h/d.
  - Co-view with parents is recommended.
- 5–8 years
  - ≤2 h/d recreational screen time.

Call for action
- Provide accessible outdoor spaces for children.
- Encourage school-based physical activity.

Evaluation
- Regional prevalence of childhood overweight/obesity.

the use of social media and self-esteem or body image. One of the more recent impacts of social media during the COVID-19 pandemic has been a sharp increase in eating disorders among children, in particular female teenagers. These vulnerable children restrict food and exercise excessively, presenting to pediatric wards with signs and symptoms of extreme starvation.

Income remains a major determinant of family and individual mental health (88). A population study in Great Britain found that the more debt people had, the more likely they were to have some form of mental disorder, even after adjustment for income and other sociodemographic variables. A review of European population surveys found that depression and anxiety are associated with low educational attainment, material disadvantage and unemployment, and for older people, social isolation. The pattern of social distribution of common mental disorders is observed as a social class gradient and is more marked in women than in men.

The impact of economical inequity goes beyond the paradigm of mental health: families' income impact the access to healthy food and food insecurity is, in turn, a major determinant of pediatric obesity. Thereby, the sociodemographic interactions— as resulting from housing policies, social interactions,
neighboring features—determine the individual risk of pediatric and adulthood obesity (62, 91).

The concept of ACEs—adverse childhood experiences—such as poverty, discrimination, loss of a parent, insecure housing put children at higher risk of poor physical and mental health outcomes in adulthood. Interventions to reduce and mitigate ACEs will have tremendous payoffs as these children grow into working happy and healthy adults.

Exposure to violence and poverty during childhood and adolescence is an independent risk factor for risky behaviors as substance abuse and alcohol use among adolescence. In spite of a transient decrease for substance abuse during the first year of COVID-19 pandemic, almost 5% of youth between 8 and 12th grade use illicit drugs other than marijuana and ~17% of eight graders consume alcohol (92).

**TABLE 3 | Respiratory health.**

| Assessment of necessity                                                                 | Interventions                                                                 |
|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| 27.5% of high school and 10.6% of middle school students use e-cigarettes (87).         | • E-cigarette users have an increased incidence of wheezing, chronic bronchitis and asthma exacerbations (69, 94, 95). |
| E-cigarette users have an increased incidence of wheezing, chronic bronchitis and asthma exacerbations (69, 94, 95). | • Air pollution is associated with reduced lung function (77, 78) and a higher prevalence of asthma (79) and COPD (80–82). |
| Air pollution is associated with reduced lung function (77, 78), and a higher prevalence of asthma (79) and COPD (80–82). | • 10:100,000 adolescents complete suicide each year [88]. |
| School:                                                                                  | • 5% youth use illicit drugs other than marijuana (92).                      |
| • Favoring commitment and engagement over competitive behaviors (such as school marks) through complimentary educational rewards. | • Parenting to parenting.                                                  |
| • Gender-discrimination teaching programs (39).                                          | • Community-based shelter programs.                                         |
| • Parenting to parenting.                                                               | • Community-based family programs.                                          |
| • Supporting parents, especially single parents, in learning new job skills, so they can remain employed and continuing to provide childcare while working. | • Supporting parents, especially single parents, in learning new job skills, so they can remain employed and continuing to provide childcare while working. |
| • Specialized childcare when children are ill, so parents do not need to miss work to provide care. | • Specialized childcare when children are ill, so parents do not need to miss work to provide care. |
| • Discussing income support program accessibility.                                      | • almonds to almonds.                                                     |
| • Sustainable daycare for younger children, and year-round school for older children.   | • Local campaigns targeting family and maternal income-support (fight family poverty). |
| • All schools (public and private schools).                                               | • Public campaign for gender-equality (public reports on gender discrimination, advertisements, fashion, online restrictions) (62, 85, 89). |
| • Financial support of educational activities to minimize social inequality, providing additional support as youths transition through elementary school to high school, college and post-graduate education. | • Addiction-focused educational campaigns (gaming, tobacco, e-cigarettes, social media, alcohol, and other drugs). |
| • Provide academic support for students in college who come from disadvantaged backgrounds. | • Financial support of educational activities to minimize social inequality, providing additional support as youths transition through elementary school to high school, college and post-graduate education. |
| • Gender non-discriminative policies at school and on social media.                      | • Engaging, non-competitive school environment.                            |
| • Engaging, non-competitive school environment.                                          | • Shelter houses for children and mothers.                                 |
| • Tutoring program so that youths struggling academically can reach out to other students for extra help. | • Tutoring program so that youths struggling academically can reach out to other students for extra help. |
| • Provide academic support for students in college who come from disadvantaged backgrounds. | • Develop a quality certification process for public and private schools. |
| • Gender non-discriminative policies at school and on social media.                      | • Loss of school days.                                                     |
| • Engaging, non-competitive school environment.                                          | • Shelter houses for children and mothers.                                 |
| • Shelter houses for children and mothers.                                               | • Tutoring program so that youths struggling academically can reach out to other students for extra help. |

**TABLE 4 | Mental and social health.**

| Assessment of necessity                                                                 | Interventions                                                                 |
|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Neuropsychiatric conditions are the leading cause of disability in children (86).       | • 10:100,000 adolescents complete suicide each year [88]. |
| School:                                                                                  | • 5% youth use illicit drugs other than marijuana (92).                      |
| • School-advisor support (psychologist).                                                 | • Parenting to parenting.                                                  |
| • Favoring commitment and engagement over competitive behaviors (such as school marks) through complimentary educational rewards. | • Community-based shelter programs.                                         |
| • Gender-discrimination teaching programs (39).                                          | • Community-based family programs.                                          |
| • Parenting to parenting.                                                               | • Supporting parents, especially single parents, in learning new job skills, so they can remain employed and continuing to provide childcare while working. |
| • Community-based shelter programs.                                                     | • Specialized childcare when children are ill, so parents do not need to miss work to provide care. |
| • Community-based family programs.                                                      | • Discussing income support program accessibility.                         |
| • Supporting parents, especially single parents, in learning new job skills, so they can remain employed and continuing to provide childcare while working. | • almonds to almonds.                                                     |
| • Providing information about the health risks of e-cigarettes (38).                    | • Local campaigns targeting family and maternal income-support (fight family poverty). |
| Call for action                                                                          | • Public campaign for gender-equality (public reports on gender discrimination, advertisements, fashion, online restrictions) (62, 85, 89). |
| • Ban the sale of e-cigarettes to those <18 years (38).                                 | • Addiction-focused educational campaigns (gaming, tobacco, e-cigarettes, social media, alcohol, and other drugs). |
| • Ban advertising of e-cigarettes.                                                      | • Financial support of educational activities to minimize social inequality, providing additional support as youths transition through elementary school to high school, college and post-graduate education. |
| Evaluation                                                                               | • Engaging, non-competitive school environment.                            |
| • Prevalence of tobacco and e-cigarette use in those aged <18 years.                   | • Shelter houses for children and mothers.                                 |
| • Prevalence of asthma in children and COPD in adulthood.                               | • Tutoring program so that youths struggling academically can reach out to other students for extra help. |

**Lobbying**

Mental health cannot be improved by policies focused only on the most disadvantaged, but should consider the community as a whole, supporting children’s capability to do and to be. Policies should be universal yet proportionate to need. Focusing solely on the most disadvantaged will fail to achieve the required reduction in health inequalities necessary to reduce the steepness of the social gradient in health. Families, schools, communities are the target bodies for interventions aimed to preserve and promote mental and social health of youth.

The interventions are based on the scientific consensus that giving every child the best possible start will generate the greatest societal and mental health benefits (93). Certain subgroups are at a higher risk of mental disorders because of greater exposure and
vulnerability to unfavorable social, economic, and environmental circumstances, interrelated with gender.

Facilitating the access to diagnosis and support for children and families living with mental health disorders is of pivotal importance. Recommended interventions are deployed at schools (presence of advisors and supports), at home to support families within the domestic environment or to ensure a shelter environment as necessary, and in local communities (Table 4). Screening for substance abuse in primary care should be advised starting 8th grade (92).

The call for action to maximize the impact of the proposed interventions involves supporting shelter houses for children and mothers, creating engaging, non-competitive school environments, and gender non-discriminative policies at school and in the media. These interventions are expected to reduce the risk determinants of mental health disorders in children, though their implementation relies on regional and state policies.

Community-based interventions targeting poverty remain a major leverage to promote mental health throughout all the age groups.

The evaluation of the efficacy of regional and state interventions could be quantified through certification processes for schools and educational environments. Additionally, regional school performance could be an indirect measure of effective mental health programs on a regional basis.

**CONCLUSIONS**

Less than 2% of young adults (<30 years) have a healthy lifestyle, and no more than 50% of adolescents aged 12–19 years meet at least five of the seven ideal cardiovascular lifestyle, and no more than 50% of adolescents aged 12–19 years meet at least five of the seven ideal cardiovascular health behaviors. Childhood presents a unique window of opportunity to effect strategic interventions to promote healthy lifestyles, due to the metabolic and brain plasticity of children. Interventions targeting childhood therefore hold the potential to dramatically abate the rising incidence of NCDs and should involve families, schools and community-social groups. The ALICE approach we propose aims to define priority areas, targets and interventions, actions and measurable indicators to be used by primary healthcare providers and pediatricians to address health promotion strategies in childhood.

**AUTHOR CONTRIBUTIONS**

EB and AG designed the project and drafted the manuscript. GP, MG, ASi, and AR contributed to the Mental and Social Health section. AG and SC contributed to the Nutrition section. GD and RV contributed to the Cardiovascular Health section. EB and PS contributed to the Respiratory Health section. LD, CG, ASt, RR, and EB critically revised the manuscript. All authors approved the final version of the document.

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**REFERENCES**

1. Lloyd J, Creanor S, Logan S, Green C, Dean S, Hillsdon M, et al. Effectiveness of the healthy lifestyles programme (HeLP) to prevent obesity in UK primary-school children: a cluster randomised controlled trial. *Lancet Child Adolesc Health*. (2018) 2:35–45. doi: 10.1016/S2352-4642(17)30151-7

2. Marques A, Bordado J, Tesler R, Demetriou Y, Sturm D, de Matos M. A composite measure of healthy lifestyle: a study from 38 countries and regions from Europe and North America, from the health behavior in school-aged children survey. *Am J Hum Biol.* (2020) 32:e23419. doi: 10.1002/ajhb.23419

3. Dabelea D, Stafford JM, Mayer-Davis EJ, D’Agostino R, Dolan L, Imperatore G, et al. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. *JAMA*. (2017) 317:825–35. doi: 10.1001/jama.2017.0686

4. NCD Countdown 2030 collaborators. Worldwide trends in non-communicable disease mortality and progress towards sustainable development goal target 3.4. *Lancet*. (2018) 392:1072–88. doi: 10.1016/S0140-6736(18)31992-5

5. Horton R. Offline: science and politics in the era of COVID-19. *Lancet*. (2020) 396:1319. doi: 10.1016/S0140-6736(20)32221-2

6. Coates MM, Kintu A, Gupta N, Wroe EB, Adler AJ, Kwan GF, et al. Burden of non-communicable diseases from infectious causes in 2017: a modelling study. *Lancet Glob Health*. (2020) 8:e1489–8. doi: 10.1016/S2214-109X(20)30358-2

7. Harper ME, Patti ME. Metabolic terminology: what’s in a name? *Nat Metab.* (2020) 2:476–7. doi: 10.1038/s42255-020-0216-7

8. Galderisi A, Giannini C, Weiss R, Kim G, Shabanova V, Santoro N, et al. Trajectories of changes in glucose tolerance in a multiethnic cohort of obese youths: an observational prospective analysis. *Lancet Child Adolesc Health*. (2018) 2:726–35. doi: 10.1016/S2352-4642(18)30235-9

9. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The adverse childhood experiences (ACE) study. *Am J Prev Med.* (1998) 14:245–58. doi: 10.1016/s0749-3797(98)00017-8

10. Fandakova Y, Hartley CA. Mechanisms of learning and plasticity in childhood and adolescence. *Dev Cogn Neurosci.* (2020) 42:100764. doi: 10.1016/j.dcn.2020.100764

11. Fernandez-Jimenez R, Al-Kazaz M, Jaslow R, Carvajal L, Fuster V. Children present a window of opportunity for promoting health: JACC review topic of the mortality. *J Am Coll Cardiol.* (2018) 72:3310–9. doi: 10.1016/j.jacc.2018.10.031

12. SEARCH for Diabetes in Youth Study Group, Liese AD, D’Agostino RB Jr, Hamman RF, Kullo PD, Lawrence JM, et al. The burden of diabetes mellitus among US youth: prevalence estimates from the SEARCH for diabetes in youth study. *Pediatrics*. (2006) 118:1510–8. doi: 10.1542/peds.20 06-0690

13. Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, et al. SEARCH for diabetes in youth study. Incidence trends of type 1 and type...
2 diabetes among youths, 2002-2012. *N Engl J Med.* (2017) 376:1419–29. doi: 10.1056/NEJMa1610187

14. Centers for Disease Control Prevention. *Childhood Obesity Facts* | *Overweight & Obesity.* (2021). Available online at: https://www.cdc.gov/obesity/data/childhood.html (accessed April 05, 2021).

15. Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med.* (2002) 346:802–10. doi: 10.1056/NEJMoa0212578

16. RISE Consortium. Metabolic contrasts between youth adults with impaired glucose tolerance or recently diagnosed type 2 diabetes: I. Observations using the hyperglycemic clamp. *Diabetes Care.* (2018) 41:1696–706. doi: 10.2337/dc18-0244

17. Imperatore G, Boyle JP, Thompson TJ, Case D, Dabelea D, Hamman RF, et al. Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: dynamic modeling of incidence, mortality, and population growth. *Diabetes Care.* (2012) 35:2515–20. doi: 10.2337/dc12-0669

18. Hamman RF, Bell RA, Dabelea D, D’Agostino RB Jr, Dolan L, Imperatore G, et al. The SEARCH for diabetes in youth study: rationale, findings, and future directions. *Diabetes Care.* (2014) 37:3336–44. doi: 10.2337/dc14-0574

19. TODAY Study Group, Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, et al. Projections of type 1 and type 2 diabetes burden in the U.S. population growth. *Diabetes Care.* (2018) 41:1696–706. doi: 10.1111/diab.ced.13517

20. Savoye M, Caprio S, Dziera J, Camp A, Germain G, Summers C, et al. Reversal of early abnormalities in glucose metabolism in obese youth: results of an intensive lifestyle randomized controlled trial. *Diabetes Care.* (2014) 37:317–24. doi: 10.2337/dc13-1571

21. Savoye M, Shaw M, Dziera J, Tamborlane WV, Rose P, Guandalini C, et al. Effects of a weight management program on body composition and metabolic parameters in overweight children: a randomized controlled trial. *JAMA.* (2007) 297:2697–704. doi: 10.1001/jama.297.24.2697

22. Wang L, Martinez Steele E, Du M, Pomerantz LE, O’Connor JP,errick KA, et al. Trends in consumption of ultra-processed foods among US youth aged 2-19 years, 1999-2018. *JAMA.* (2021) 326:519–30. doi: 10.1001/jama.2021.10238

23. Fidler Mis N, Braegger C, Bronsky J, Campoy C, Domellöf M, Embleton ND, et al. ESPGHAN committee on nutrition. Sugar in infants, children and adolescents: a position paper of the European society for paediatric gastroenterology, hepatology and nutrition committee on nutrition. *J Pediatr Gastroenterol Nutr.* (2015) 61:651–96. doi: 10.1097/MPG.0000000000001733

24. Van Name M, Giannini C, Santoro N, Jastreboff AM, Kubat J, Li F, et al. Blunted suppression of acyl-ghrelin in response to fructose ingestion in children with metabolic syndrome. *Pediatrics.* (2015) 23:653–61. doi: 10.1542/peds.2011-0054

25. Galderisi A, Giannini C, Van Name M, Caprio S, Fructose consumption contributes to hyperinsulinaemia in adolescents with obesity through a GLP-1-mediated mechanism. *J Clin Endocrinol Metab.* (2019) 104:3481–90. doi: 10.1210/jc.2019-00116

26. Morgan RE. Does consumption of high-fructose corn syrup beverages cause obesity in children? *Pediatr Obes.* (2013) 8:249-54. doi: 10.1111/j.2047-6310.2013.00173.x

27. United Nations Children’s Emergency Fund (UNICEF). *Nutrition, for Every Child.* Available online at: https://www.unicef.org/media/92031/file/UNICEF%20Nutrition%20Strategy%202020-2030.pdf

28. Oruambo RS. Child malnutrition and the millennium development goals: much haste but less speed? *Arch Dis Child.* (2015) 100(Suppl. 1):S19–22. doi: 10.1136/archdischild-2013-035584

29. World Health Organization. *Millennium Development Goals (MDGs).* Available online at: https://www.who.int/news-room/fact-sheets/detail/millennium-development-goals-(mdgs) (accessed February 1, 2022).

30. Gidding SS, Dennison BA, Birch LL, Daniels SR, Gillman MW, Lichtenstein AH, et al. Dietary recommendations for children and adolescents: a guide for practitioners. *Pediatrics.* (2006) 117:544–59. doi: 10.1542/peds.2005-2374

31. World Health Organization. *Comprehensive Implementation Plan on Maternal, Infant and Young Child Nutrition: World Health Organization.* (2018). Available online at: https://www.who.int/nutrition/publications/CIP_document/en/ (accessed April 24, 2018).

32. Weinstock RS, Drews KL, Caprio S, Leibel NL, McKay SV, Zeitzer PS, et al. Metabolic syndrome is common and persistent in youth-onset type 2 diabetes: results from the TODAY clinical trial. *Obesity.* (2015) 23:1357–61. doi: 10.1002/oby.21120

33. Food and Agriculture Organization of the United Nations. *Food Labelling.* (2021). Available online at: https://www.fao.org/food-labelling/en/ (accessed February 1, 2022).

34. Lobstein T, Jackson-Leach R, Moodie ML, Hall KD, Gortmaker SL, Swinburn BA, et al. Child and adolescent obesity: part of a bigger picture. *Lancet.* (2015) 385:2510–20. doi: 10.1016/S0140-6736(14)61746-3

35. Deng D, Sexism impacts development. *Adv Child Dev Behav.* (2016) 50:105–33. doi: 10.1016/bse.acb.2015.11.001

36. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association’s strategic impact goal through 2020 and beyond. *Circulation.* (2010) 121:586–613. doi: 10.1161/CIRCULATIONAHA.109.192703

37. Shay CM, Ning H, Daniels SR, Roos CR, Gidding SS, Lloyd-Jones DM. Status of cardiovascular health in US adolescents: prevalence estimates from the national health and nutrition examination surveys (NHANES) 2005-2010. *Circulation.* (2013) 127:1369–76. doi: 10.1161/CIRCULATIONAHA.113.001559

38. Steinberger J, Daniels SR, Hagberg N, Isasi CR, Kelly AS, Lloyd-Jones D, et al. Cardiovascular health promotion in children: challenges and opportunities for 2020 and beyond: a scientific statement from the American heart association. *Circulation.* (2016) 134:e236–55. doi: 10.1161/CIR.0000000000000441

39. Stampler MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med.* (2000) 343:16–22. doi: 10.1056/NEJM200007063430103

40. American Academy of Pediatrics. *Prechuelor - Physical Activity:* @AmerAacpEds. (2020). Available online at: http://www.aap.org/en-us/ advocacy-and-policy/aap-health-initiatives/HALF-Implementation-Guide/Age-Specific-Content/Pages/Prechuelor-Physical-Activity.aspx (accessed February 1, 2022).

41. World Health Organization (WHO). *Guidelines on Physical Activity, Sedentary Behaviour and Sleep for Children Under 5 Years of Age.* (2019). Available online at: https://www.who.int/publications/i/item/9789241550536 (accessed February 1, 2022).

42. Centers for Disease Control Prevention. *How Much Physical Activity do Children Need?* (2021). Available online at: https://www.cdc.gov/physicalactivity/basics/children/index.htm (accessed May 08, 2021).

43. Cristia A, Seidl A. Parental reports on touch screen use in early childhood. *PLOS ONE. (2015) 10(5):e0128338. doi: 10.1371/journal.pone.0128338

44. Straker L, Zabatiero J, Danby S, Thorpe K, Edwards S. Conflict guidelines on young children’s screen time and use of digital technology create policy and practice dilemmas. *J Pediatr.* (2018) 202:300-3. doi: 10.1016/j.jpeds.2018.07.019

45. Dumas D, Screen time in early childhood. *Lancet Child Adolesc Health.* (2020) 4:169-70. doi: 10.1016/S2352-4642(20)30005-5

46. O’Keeffe GS, Clarke-Pearson K. Council on communications and media. The impact of social media on children, adolescents, and families. *Pediatrics.* (2011) 127:800-4. doi: 10.1542/peds.2011-0054
51. Richards D, Caldwell PH, Go H. Impact of social media on the health of children and young people. *Paediatr Child Health*. (2015) 51:1152–7. doi: 10.1111/jpc.13023

52. American Academy of Child & Adolescent Psychiatry. *Screen Time and Children*. 2021. Available online at: https://www.aacap.org/AACAP/Families_and_Youth/Facts_for_Families/FPP-Guide/Children-And-Watching-TV-054.aspx (accessed February 1, 2022).

53. Domingues-Montanari S. Clinical and psychological effects of excessive screen time on children. *Paediatr Child Health*. (2017) 53:333–8. doi: 10.1111/jpc.13462

54. Roberts DF, Henriksen L, Voelker DH, van Vuuren DP. Television and schooling: displacement and distraction hypotheses. *Austr Educ* (1993) 37:198–211. doi: 10.1177/014434049303700207

55. Chindamo S, Bernard JY, Padmapriya N, Ning Y, Cai S, Lança C, et al. Associations of vaporizing cannabis: individual and social network predictors in a restricted market: findings from Ontario, Canada. *Int J Drug Policy*. (2018) 58:9–12. doi: 10.1016/j.drugpo.2018.04.001

56. Bozier J, Chivers EK, Chapman DG, Larcombe AN, Bastian NA, Masso-Silva JA, et al. The evolving landscape of e-cigarettes: a systematic review of recent evidence. *Chest*. (2020) 157:1362–90. doi: 10.1016/j.chestr.2019.12.042

57. McGrath-Morrow SA, Gorkozwski J, Groner JA, Rule AM, Wilson K, Tanasi SE, et al. The effects of nicotine on development. *Pediaiatrics*. (2020) 145:e20191346. doi: 10.1542/peds.2019-1346

58. Hadjipanayis A, Efstathiou E, Altorjai P, Stiris T, Valiulis A, Koletzko B, et al. Prevalence of vaping and smoking among adolescents in Canada, England, and the United States: repeat national cross sectional surveys. *BMJ*. (2018) 360:k2219. doi: 10.1136/bmj.k2219

59. Czoli CD, Goniewicz ML, Palumbo M, White CM, Hammond D. Electronic cigarette nicotine content and labelling practices in a restricted market: findings from Ontario, Canada. *Int J Drug Policy*. (2019) 157:1362–90. doi: 10.1016/j.drugpo.2018.04.001

60. Cameron BM, Bernard JY, Padmapriya N, Ning Y, Cai S, Lança C, et al. Associations of vaporizing cannabis: individual and social network predictors in a restricted market: findings from Ontario, Canada. *Int J Drug Policy*. (2018) 58:9–12. doi: 10.1016/j.drugpo.2018.04.001

61. Landrigan DJ, Fuller R, Acosta NJR, Adey O, Arnold R, Basu NN, et al. The Lancet commission on pollution and health. *Lancet*. (2018) 391:462–512. doi: 10.1016/S0140-6736(17)32345-0

62. Martinez FJ. Early-life origins of chronic obstructive pulmonary disease. *N Engl J Med*. (2016) 375:871–8. doi: 10.1056/NEJMra1603287

63. Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med*. (2004) 351:1057–67. doi: 10.1056/NEJMoa040610

64. Soto-Martinez M, Sly PD. Relationship between environmental exposures in children and adult lung disease: the case for outdoor exposures. *Chron Respir Dis*. (2010) 7:173–86. doi: 10.1177/1479979209345929

65. Gehring U, Wijga AH, Hoek G, Bellander T, Brüske I, et al. Exposure to air pollution and development of asthma and rhinoconjunctivitis throughout childhood and adolescence: a population-based birth cohort study. *Lancet Respir Med*. (2015) 3:933–42. doi: 10.1016/S2213-2600(15)00426-9

66. Gauderman WJ, Rollman LG, Unger J, Urman R, Avol E, Berhane K, McConnell R, Rappaport E, et al. Association of improved air quality with lung development in children. *N Engl J Med*. (2015) 372:905–13. doi: 10.1056/NEJMoa1414123

67. Goldizen FC, Sly PD, Knibbs LD. Respiratory effects of air pollution on children. *Pediatr Pulmonol*. (2016) 51:94–108. doi: 10.1002/ppul.23262

68. Friedman MS, Powell KE, Hutwagner L, Graham LM, Teague WG. Impact of changes in transportation and commuting behaviors during the 1996 summer Olympic games in Atlanta on air quality and childhood asthma. *JAMA*. (2001) 285:897–905. doi: 10.1001/jama.285.7.897

69. McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ, et al. Asthma in exercising children exposed to ozone: a cohort study. *Lancet*. (2002) 359:386–91. doi: 10.1016/S0140-6736(02)07597-9

70. Ramadour M, Burel C, Lanteaume A, Vervloet D, Charpin D, Brisse X, et al. Prevalence of asthma and rhinitis in relation to long-term exposure to air pollutants. *Allergy*. (2000) 55:1163–9. doi: 10.1034/j.1398-9995.2000.00063.x

71. Brumberg HL, Karr CJ. Council on environmental health. Ambient air pollution: health hazards to children. *Pediatrics*. (2021) 147:e2021051484. doi: 10.1542/peds.2021-051484

72. Centers for Disease Control Prevention. *FastStats - Adolescent Health*. (2021). Available online at: https://www.cdc.gov/nchs/fastats/adolescent-health.htm (accessed June, 11, 2021).

73. Centers for Disease Control Prevention. *Data Statistics on Children's Mental Health | CDC: @CDCgov*. (2021). Available online at: https://www.cdc.gov/childrensmentalhealth/data.html?ref (accessed March 22, 2021).

74. Sareen J, Afifi TO, McMillan KA, Asmundson GJ. Relationship between household income and mental disorders: findings from a population-based longitudinal study. *Arch Gen Psychiatry*. (2011) 68:419–27. doi: 10.1001/archgenpsychiatry.2011.155

75. Dobrenov BP, Levav I, Shrouf PE, Schwartz S, Naveh G, Link BG, et al. Socioeconomic status and psychiatric disorders: the causation-selection issue. *Science*. (1992) 255:946–52. doi: 10.1126/science.1546291
90. Spears Brown C, Bigler RS. Children’s perceptions of gender discrimination. *Dev Psychol.* (2004) 40:714–26. doi: 10.1037/0012-1649.40.5.714

91. Andes LJ, Cheng YJ, Rolka DB, Gregg EW, Imperatore G. Prevalence of prediabetes among adolescents and young adults in the United States, 2005-2016. *JAMA Pediatr.* (2020) 174:e194498. doi: 10.1001/jamapediatrics.2019.4498

92. O’Rahilly S, Barroso I, Wareham NJ. Genetic factors in type 2 diabetes: the end of the beginning? *Science.* (2005) 307:370–3. doi: 10.1126/science.1104346

93. Weiss R, Santoro N, Giannini C, Galderisi A, Umano GR, Caprio S. Prediabetes in youth - mechanisms and biomarkers. *Lancet Child Adolesc Health.* (2017) 1:240–8. doi: 10.1016/S2352-4642(17)30044-5

94. Sly PD. Adverse environmental exposure and respiratory health in children. *Pediatr Clin North Am.* (2021) 68:277–91. doi: 10.1016/j.pcl.2020.09.018

95. Ferkol TW, Farber HJ, La Grutta S, Leone FT, Marshall HM, Neptune E, et al. Electronic cigarette use in youths: a position statement of the forum of international respiratory societies. *Eur Respir J.* (2018) 51:1800278. doi: 10.1183/13993003.00278-2018

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