



How strong is the evidence supporting the WHO guidelines on physical activity, sedentary behaviour and sleep in early childhood?

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Abstract

Background: The WHO issued recommendations about the ideal amount of physical activity, sedentary behaviour and sleep in infants, toddlers and preschool children. To facilitate their interpretation and translation into public health policies, we analysed the quantity and quality of the evidence that supported the development of each WHO recommendation.

Methods: All data for each exposure-outcome pair analysed in the studies informing WHO guidelines were extracted, and predefined criteria, based upon GRADE methodology, were used to classify each outcome and study result.

Results: Among the 237 studies that could be included, 37 were experimental and 200 were observational, yielding 920 analyses of exposure-outcome associations. Sixty-two analyses used a relevant outcome, with or without significant results. Five of the 10 WHO recommendations were based upon zero analyses with significant results on relevant health outcomes. The remaining recommendations were mostly based upon analyses evaluating obesity-related outcomes. Eight of the 10 GLs thresholds were not supported by any significant analysis on clinically relevant outcomes.

Conclusion: While these findings should not be interpreted as an attempt to disprove the benefits of healthy lifestyle habits in early childhood, neither to minimize the work of the experts in this complex research field, very limited evidence currently supports the adoption of recommended thresholds as behavioural surveillance and public health interventions targets. Therefore, until further data are available, public health interventions should be developed balancing whether to focus on the achievement of specific targets that are still not supported by high-quality evidence or on the general promotion of healthy behaviours.

Alessandro Bianconi and Matteo Fiore equally contributed to this work.

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KEYWORDS

early childhood, physical activity, screen time, sedentary behaviour, sleep, WHO guidelines

1 | INTRODUCTION

Many interventions related to lifestyle have been proposed to enhance health and reduce the risk of diseases.¹ In recent years, there has been an increasing interest in the formulation of evidence-based guidelines promoting healthy lifestyles among diverse population groups.^{2–4}

Representing one of the most recognized sources of healthcare guidance, the World Health Organization (WHO) issued recommendations about the ideal amount of physical activity (PA), sedentary behaviour (SB) and sleep in infants, toddlers and preschool children.⁵ These guidelines represent important tools for healthcare providers, educators, parents and policymakers in fostering optimal physical, cognitive and socio-emotional development during early childhood.⁵

The development of lifestyle guidelines is typically challenging due to the complexity of the exposure evaluation and the high prevalence of observational evidence,⁶ which carries a high risk of information bias, reverse causality and confounding.⁷ Thus, lifestyle behaviours guidelines, including those issued by the WHO on PA, SB and sleep,^{8,9} are frequently based on low-quality evidence,^{1,5,10} which poses some challenges on their interpretation and translation into public health policies.

We analysed for the first time the quantity and the quality of the evidence that supported the development of each recommendation of the WHO ‘Guidelines on physical activity, sedentary behaviour and sleep for children under 5 years of age’,⁵ in order to help identifying which policies could be prioritized, based upon the strength of the evidence of each specific recommendation.¹¹

2 | METHODS

The WHO ‘Guidelines on physical activity, sedentary behaviour and sleep for children under 5 years of age’ (GLs) were published in 2019⁵ and developed starting from the systematic reviews^{12–15} that were conducted to inform the Canadian and Australian guidelines.^{16,17} These systematic reviews were revised and updated by the WHO Guideline Development Group purposely gathered. As reported in the GLs,⁵ the final recommendations were formulated using the GRADE Evidence-to-Decision framework.¹⁸

We retrieved and extracted the data from the studies used to inform the WHO guidelines.¹⁹ When data were unavailable, the authors were contacted. We included

studies evaluating the associations between PA, SB or sleep and health outcomes. We extracted the following information for each exposure-outcome pair analysed in each study: (a) study design (experimental/cohort/case-control/cross-sectional); (b) target age group (<1 years/1–2 years/3–4 years); (c) age of the participants (congruent/partially congruent with the GLs target age groups); (d) exposure category (PA/SB/Sleep); (e) exposure variable (e.g. hours/day spent watching TV); (f) type of exposure variable (continuous/categorical using recommendations cut-off/categorical not using recommendations cut-off); (g) outcome category (derived from the outcome categories considered for the WHO GLs development, as reported in the GRADE tables of the GLs appendix¹⁹); (h) outcome variable (e.g. bone mineral density); (i) type of outcome (surrogate/relevant); (l) results (null, protective/harmful, based on statistical significance and on the assumption that there are causal links directed from exposures to health outcomes). The age of the participants was considered ‘congruent’ if all the participants of the study could be fitted in one of the GLs three target age groups, and ‘partially congruent’ if a fraction of the participants of a study could be fitted in one of the three target age groups (e.g. studies including children aged 3–6 years were labelled as ‘partially congruent’ for the age group ‘3–4 years’). Moreover, ‘relevant’ outcomes were defined as clinically relevant, patient-important outcomes (e.g. obesity status), while ‘surrogate’ outcomes were defined as substitute variables of a relevant outcome (e.g. Body Mass Index, BMI, as a continuous variable), following the methodology recommended by the GRADE system.²⁰ In specific, the term ‘relevant’ was used to label the outcome variables that indicate a confirmed pathological condition, such as, in the case of adiposity, a diagnosis of obesity. Instead, ‘surrogate’ outcomes refer to proxy outcome variables that, if associated with an exposure, may suggest a link between the exposure and a ‘relevant’ outcome. For example, an exposure negatively associated with BMI, used as a continuous variable, may represent a protective factor for obesity, but this association indicates only indirect evidence of an association between the exposure and obesity. If an exposure-outcome association was analysed through more than one statistical model in the same study, only the results of the model reported as ‘complete’, or ‘final’, were extracted. If a study reported stratified group analyses only and mixed results emerged (e.g. null association in males and protective association in females), the statistically significant results were extracted.

If a study reported both total score and per-domain partial scores of a test or a questionnaire as outcomes, only the total score was extracted. Finally, if a study analysed the same exposure-outcome association both with a cross-sectional and with a longitudinal design, only the results of the longitudinal analysis were extracted. Two authors (A.B. and M.F.) independently and blindly extracted data from the included studies, and disagreements were solved through consensus.

Descriptive statistics were reported as absolute and relative frequencies (%) for categorical variables and as mean and standard deviation, or median and interquartile range, for continuous variables. Descriptive analyses were also stratified by recommendation, matching each exposure-outcome association to a recommendation based on the 'age group' and 'exposure category' variables. A further subgroup descriptive analyses was performed selecting only exposure-outcome pairs that were analysed using the GLs thresholds values as exposure of interest. All analyses were performed using R-Studio Software, R version 4.3.2.²¹

The full database resulting from the data extraction process is available on Open Science Framework (link: <https://osf.io/xg5sd/files/osfstorage/6654956d65e1de43c6893eaa>).

3 | RESULTS

Of the 251 articles informing the WHO 'Guidelines on physical activity, sedentary behaviour and sleep for children under 5 years of age' (GLs), 14 were excluded: six were not pertinent with (GLs) research question, three studies assessed only the association between two exposures (sleep and SB), two were mismatched between the content of the study and what was reported in the GRADE table, two were not accessible in full text and one reported

no primary data (review). The complete list of the excluded articles is available in [Table S1](#), and the 237 included articles are listed in [Table S2](#).

Overall, 37 studies (16%) were experimental (20 randomized trials and 17 non-randomized trials), and 200 (84%) were observational (129 cross-sectional, 66 cohort and 5 case-control studies). From all studies, we extracted the data of 920 analyses on the association between a relevant exposure (PA, SB, sleep, or a mix) and a health outcome ([Figure 1](#)).

As reported in [Table 1](#), the majority of the analyses used a surrogate outcome (93.3%), led to non-significant results (65.7%), focused on the 3–4 years age group (63.4%). Most of the analyses evaluated the association between PA (38.0%), sleep (32.2%) or SB (25.7%) and outcomes related to 12 health contexts, including cardiometabolic health (23.6%), emotional regulation (15.8%), adiposity (13.0%) and cognitive development (11.6%). The exposure and outcome variables of the 920 extracted analyses are reported in [Table S3](#).

The evidence available for each of the 10 WHO GLs recommendations has been reported in [Table 2](#). All recommendations were based upon a large number of samples with a congruent age, and nine were informed by at least 10 analyses with significant results, although most of these analyses used surrogate outcomes.

The 62 analyses that used a relevant outcome, with or without significant results, for each of the 10 WHO GLs have been summarised in [Table 3](#). The recommendations 1, 2, 4 and 10 were based upon zero analyses with significant results on a relevant health outcome. Recommendations 3, 5 and 6 were supported by a single analysis with significant results, while the recommendations on the age group 3–4 years were based upon five or more analyses with significant results, most of which evaluated obesity-related outcomes. Only four analyses provided evidence on outcomes that were not related to obesity: one evaluated

Characteristics of the 920 evaluations of an association between a lifestyle exposure and a health outcome included in the WHO Guidelines on physical activity, sedentary behavior and sleep for children under 5 years of age

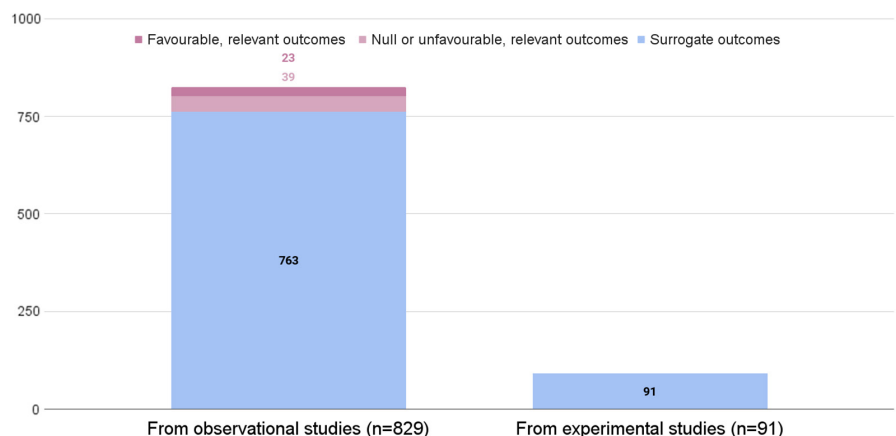


FIGURE 1 Characteristics of the 920 evaluations of an association between a lifestyle exposure and a health outcome included in the WHO Guidelines on physical activity, sedentary behaviour and sleep for children under 5 years of age, by study design and relevancy of outcomes.

TABLE 1 Overall characteristics of the 920 evaluations of an association between a lifestyle exposure and a health outcome included in the WHO Guidelines on physical activity, sedentary behaviour and sleep for children under 5 years of age.

	<i>n</i> (%)
Study exposure category	
Physical activity	350 (38.0)
Sedentary behaviour	236 (25.7)
Sleep	296 (32.2)
Physical activity + Sedentary behaviour	26 (2.8)
Sedentary Behaviour + Sleep	12 (1.3)
Study outcome category	
Adiposity	120 (13.0)
Cardiometabolic health	217 (23.6)
Cognitive development	107 (11.6)
Emotional regulation	145 (15.8)
Fitness	36 (3.9)
Growth	1 (.1)
Injuries	3 (.3)
Motor development	77 (8.4)
Other	6 (.7)
Psychosocial health	49 (5.3)
Risks	4 (.4)
Skeletal health	39 (4.2)
Age of the study sample	
Congruent with the guidelines	555 (60.3)
Partially congruent	365 (39.7)
Target age group	
<1 years	120 (13.0)
1–2 years	217 (23.6)
3–4 years	583 (63.4)
Type of outcome	
Relevant	62 (6.7)
Surrogate	858 (93.3)
Overall results	
Statistically significant	316 (34.3)
Non-significant	604 (65.7)

the association between PA and motor difficulty, and the other three evaluated the relationship between sleep and Attention Deficit and Hyperactivity Disorder (ADHD), accidental falls, or injury risk.

The quantity of the evidence informing the recommended thresholds for the ideal amounts of PA, SB and sleep is summarized in Table 4. All the studies were observational, and the recommended thresholds for sleep in infants and for PA and SB for toddlers aged 1–2 were not informed by any evidence. The other thresholds were based on a very scarce number of mixed-results associations.

Only two of the GLs thresholds (SB and sleep in the 3–4 age group) were informed by analyses that used a clinically relevant outcome. Of these, only two were statistically significant and supported the threshold value.

4 | DISCUSSION

The WHO guidelines on PA, SB and sleep in early childhood have been developed using a rigorous and validated methodology, and the working groups made every effort to find all the existing evidence.^{5,12–15} However, for all guidelines, as advocated by the GRADE system,¹⁸ the strength of the recommendations is inevitably related to the robustness of the underlying evidence. Therefore, when applying a guideline into practice and public health programmes, it is crucial to understand which policy should be prioritized based upon the strength of the evidence supporting each specific recommendation.¹¹

Overall, from this in-depth revision of the studies that formed the basis of the WHO GLs, a very scarce quantity of high-quality evidence was available to support the recommendations. Most of the results derived from observational studies (mainly with a cross-sectional design), several recommendations were not supported by any study with significant results on relevant health outcomes, and most of the available evidence focused on a single health condition (childhood obesity) for one age class (3–4 years). It should also be noted that all the 23 statistically significant associations using relevant outcomes were derived from studies with a very low certainty on the effect estimates, due to the observational design and the risk of information and confounding biases, as reported by the authors of the GLs.¹⁹ Moreover, while the GLs recommendations included desirable thresholds of PA, sedentary screen time and sleep time based on previously published expert opinions,⁵ only two of these targets actually had a study showing a significant, favourable effect on a clinically relevant outcome of the compliance with those targets versus the non-compliance, while the thresholds contained in eight of the 10 recommendations were not supported by evidence based on relevant outcomes. These thresholds were recommended for years in multiple national guidelines,^{16,17} which explains why some of the included studies were testing them. However, due to the relative novelty of these national recommendations, the first of which was published in 2012,¹⁷ it could be expected that most previous studies did not evaluate specific cut-offs that were not formulated yet.

These findings are certainly not surprising, given the challenges of lifestyle research,^{7,22–24} especially on infants,^{25,26} and because the same authors of the WHO guidelines correctly reported that all of the recommendations

TABLE 2 Characteristics of the 920 evaluations of an association between a lifestyle exposure and a health outcome included in the WHO Guidelines on physical activity, sedentary behaviour and sleep for children under 5 years of age, by WHO recommendation category.

Recommendation category	Congruent age ^a	Statistically significant results ^b	Clinically relevant outcome ^c
Infants—age <1 year	(120/120)	(36/120)	(2/120)
1. Be physically active several times a day in a variety of ways, at least 30 min in tummy time	30/30	14/30	0/30
2. Not be restrained more than 1 h at a time. Screen time is not recommended	13/13	4/13	0/13
3. Sleep 14–17 h daily (first 3 months), 12–16 h (4–11 months), including naps	77/77	18/77	2/77
Children—age 1–2 years	(173/204)	(70/204)	(14/204)
4. Spend at least 180 min in a variety of types of physical activities	21/28	14/28	5/28
5. Not be restrained for more than 1 h at a time. For 1-year-olds, sedentary screen time is not recommended. For those aged 2 years, sedentary screen time should be no more than 1 h; less is better	53/63	27/63	3/63
6. Sleep 11–14 h daily, including naps	99/113	29/113	6/113
Children—age 3–4 years	(251/558)	(198/558)	(45/558)
7. Spend at least 180 min in a variety of physical activities, of which at least 60 min moderate to vigorous	137/292	111/292	16/292
8. Not be restrained more than 1 h at a time, sedentary screen time should be no more than 1 h	53/160	36/160	13/160
9. Sleep 10–13 h daily, including naps	61/106	51/106	16/106
Integrated recommendations			
10. For the greatest health benefits, infants and young children should meet all the recommendations for physical activity, sedentary behaviour and sleep in a 24-h period	11/38	12/38	1/38
Total	555/920	316/920	62/920

^aAge was labelled as 'congruent' if all the participants of the study could be fitted in one of the three Guidelines' target age groups/Overall (congruent + partially congruent age).

^bResults were labelled as 'significant' based on statistical significance/Overall (significant + non-significant results).

^cAn outcome was labelled as 'relevant' when a clinically relevant, patient-important, outcome was used (e.g. obesity status)/Overall (relevant + surrogate outcomes).

were based upon 'very low quality evidence'.⁵ However, all indications were labelled as 'strong recommendations' in the GLs.¹⁹ The need of panellists to provide effective guidelines in fields with uncertain quality of evidence sometimes lead to strong recommendations stemming from evidence with low levels of certainty, usually referred as 'discordant recommendations'.^{27–30} Importantly, however, discordant recommendations have been described as potentially harmful, since they may encourage campaigns promoting interventions with high uncertainty on benefits, harms and costs.³¹ In this specific case, as well as in other guidelines on the same topic,^{25–31} the GLs also provided strong recommendations on the precise amount of time that infants, toddlers and young children should spend in physical activity, sedentary behaviour and

sleeping. Although a rationale for each decision of issuing discordant recommendations was provided in the GLs,¹⁹ none of the cases fits within the situations in which discordant recommendations are appropriate according to GRADE.²⁷

This is not a secondary issue, as the guidelines' recommended thresholds generally play a central role in the surveillance of lifestyle exposures and behaviours, both at local and at national or international levels.^{19,32–35} In particular, the use of thresholds implies that interventions should be needed for non-compliant groups.¹⁹ This process may lead to public health policies focused on groups of children not achieving recommended targets that are not supported by strong evidence. If these targets are proven imprecise by further research, the allocation of families and healthcare

TABLE 3 Clinically relevant outcomes informing each recommendation category of the WHO Guidelines on physical activity, sedentary behaviour and sleep for children under 5 years of age.

Recommendation category	Accidental Fall (n/N)^b	ADHD^a (n/N)^b	Injury risk (n/N)^b	Injury severity (n/N)^b	Motor difficulty (n/N)^b	Obesity (n/N)^b
Infants—age <1 year	(0/0)	(1/2)	(0/0)	(0/0)	(0/0)	(0/0)
1. Be physically active several times a day in a variety of ways, at least 30 min in tummy time.	0/0	0/0	0/0	0/0	0/0	0/0
2. Not be restrained more than 1 h at a time. Screen time is not recommended.	0/0	0/0	0/0	0/0	0/0	0/0
3. Sleep 14–17 h daily (first 3 months), 12–16 h (4–11 months), including naps.	0/0	1/2	0/0	0/0	0/0	0/0
Children—age 1–2 years	(0)	(0/2)	(0/1)	(0/1)	(0)	(2/10)
4. Spend at least 180 min in a variety of types of physical activities.	0/0	0/0	0/1	0/1	0/0	0/3
5. Not be restrained for more than 1 h at a time. For 1-year-olds, sedentary screen time is not recommended. For those aged 2 years, sedentary screen time should be no more than 1 h; less is better.	0/0	0/0	0/0	0/0	0/0	1/3
6. Sleep 11–14 h daily, including naps.	0/0	0/2	0/0	0/0	0/0	1/4
Children—age 3–4 years	(1/1)	(0/2)	(1/2)	(0)	(1/1)	(17/39)
7. Spend at least 180 min in a variety of physical activities, of which at least 60 min moderate to vigorous.	0/0	0/0	0/0	0/0	1/1	6/15
8. Not be restrained more than 1 h at a time, sedentary screen time should be no more than 1 h.	0/0	0/0	0/0	0/0	0/0	5/13
9. Sleep 10–13 h daily, including naps.	1/1	0/2	1/2	0/0	0/0	6/11
Integrated recommendations						
10. For the greatest health benefits, infants, and young children should meet all the recommendations for physical activity, sedentary behaviour and sleep in a 24-h period.	0/0	0/0	0/0	0/0	0/0	0/1
Total	1/1	1/6	1/3	0/1	1/1	19/50

^aAttention deficit hyperactivity disorder.

^bNumber of statistically significant results favourable to the lifestyle group (e.g. physically active, non sedentary, adequate sleep, etc.)/All results.

financial and human resources would be incorrect. As an example, a recent systematic review found no significant relationships between compliance with the Canadian 24-h movement guidelines and the odds of being overweight or obese in toddlers and preschoolers.³⁶ Furthermore, the use of thresholds may emphasise the attention on quantity over quality and type of PA, SB and sleep. Finally, since the measurement of the amount of PA, SB and sleep is generally exposed to instrumental errors and bias, the risk of false-positive and false-negative non-compliance to these recommendations may be high.^{25,26,37} Despite these

downsides, it should also be acknowledged that the use of precise thresholds may provide practical advantages, since otherwise vague recommendations would be difficult to translate in public health practice, for example, guiding the choice of surveillance targets.

Although the efforts by WHO and other agencies to produce some rigorous guidelines should be commended, additional high-quality studies are clearly needed to validate or define the ideal targets of PA, SB and sleep in early childhood. Further RCTs on clinically relevant outcomes are necessary, as well as more reliable and valid

TABLE 4 Characteristics of the 25 evaluations of an association between a lifestyle exposure and a health outcome, informing on the choice of threshold values, included in the WHO Guidelines on physical activity, sedentary behaviour and sleep for children under 5 years of age.

Recommendation	Congruent age ^a	Statistically significant results ^b	Relevant outcome ^c	Relevant outcome and significant results ^d
Infants—age <1 year				
1. Be physically active several times a day in a variety of ways, at least 30 min in tummy time.	1/1	1/1	0/1	0/0
2. Not be restrained more than 1 h at a time. Screen time is not recommended.	3/3	2*/3	0/3	0/0
3. Sleep 14–17 h daily (first 3 months), 12–16 h (4–11 months), including naps.	0/0	0/0	0/0	0/0
Children—age 1–2 years				
4. Spend at least 180 min in a variety of types of physical activities.	0/0	0/0	0/0	0/0
5. Not be restrained for more than 1 h at a time. For 1-year-olds, sedentary screen time is not recommended. For those aged 2 years, sedentary screen time should be no more than 1 h; less is better.	0/0	0/0	0/0	0/0
6. Sleep 11–14 h daily, including naps.	6/6	3/6	0/6	0/0
Children—age 3–4 years				
7. Spend at least 180 min in a variety of physical activities, of which at least 60 min moderate to vigorous.	4/4	4/4	0/4	0/0
8. Not be restrained more than 1 h at a time, sedentary screen time should be no more than 1 h.	2/4	1/4	1/4	1/1
9. Sleep 10–13 h daily, including naps.	3/7	4/7	3/7	1/3
Integrated recommendations				
10. For the greatest health benefits, infants and young children should meet all the recommendations for physical activity, sedentary behaviour and sleep in a 24-h period.	0/0	0/0	0/0	0/0
Total	19/25	15/25	4/25	2/4

*One of the two analyses provided statistically significant results that were unfavourable to the compliance with the recommended threshold.

^aAge was labelled as 'congruent' if all the participants of the study could be fitted in one of the GLs three target age groups/Overall (congruent + partially congruent age).

^bResults were labelled as 'significant' based on statistical significance/Overall (significant + non-significant results).

^cAn outcome was labelled as 'relevant' when a clinically relevant, patient-important, outcome was used (e.g. obesity status)/Overall (relevant + surrogate outcomes).

^dSignificant results/Overall (significant + non-significant results); only relevant outcomes subset.

instruments for the measurement of PA, SB and sleep in early childhood.^{25,26,37}

Our findings also highlighted a lack of studies that considered the compositional nature of the 24-h day. The studies supporting the GLs focused primarily on the independent effects of PA, SB and sleep on health. However, the time allocated to each activity inherently affects the

distribution of the remaining hours within the finite 24-h period.³⁸ For instance, increasing time spent on PA would necessarily reduce the time available for SB and sleep, given the fixed nature of the 24-h timeframe. Therefore, further research using compositional data analyses would be useful to inform the feasibility of the GL's recommendations on the combined 24-h movement behaviours.³⁸

Finally, at the current stage of knowledge, due to the high uncertainty on benefit, harms and costs derived by the quantity and quality of evidence informing the GLs, it is hard to interpret how to translate the recommendations into public health practice. Educational campaigns and policies should balance whether to focus on the achievement of specific targets that are still not supported by high-quality evidence or on a general increase of the quantity and quality of physical activity and sleep.

This study has some limitations that must be considered. First, we chose to use within-study exposure-outcome associations as statistical units. While this choice permits a superior description of the quantity of evidence informing each recommendation, it also exposes the findings to the risk of an over-representation of results deriving from studies that tested more hypotheses. Additionally, although we set predefined criteria to classify outcomes and sample age relevancy, the interpretation of these criteria on single studies is inevitably subjective and may lead to misclassification bias.

In conclusion, while the findings of this study should not be interpreted as an attempt to disprove the benefits of healthy lifestyle habits in early childhood, neither to minimise the outstanding work of the experts committed in distilling the evidence from this extremely difficult research field, and while promoting an active lifestyle, reducing sedentary behaviours and ensuring an adequate sleep in early childhood is certainly a core element of primary prevention, a very limited evidence currently supports the adoption of the recommended thresholds as behavioural surveillance and public health interventions targets. Further high-quality research is obviously needed to shed light on the amount and types of physical activity, sedentary behaviours and sleep required to promote health in infants, toddlers and young children. Based on the present knowledge, the strict implementation of these recommendations may result in the mismatch between expected and actual effects of interventions, and educational campaigns and policies should balance whether to focus on the achievement of specific targets that are still not supported by high-quality evidence, or on a general increase of the quantity and quality of physical activity and sleep.

AUTHOR CONTRIBUTIONS

L.M. and M.E.F. conceptualised the study; L.M., M.E.F., C.A.M., A.R., E.Z., M.F. and A.B. designed the research; A.B., M.F. and A.R. acquired the data; A.B., M.F. and L.M. analysed the data; L.M. and M.E.F. provided the resources needed for the study; A.B. and M.F. wrote the original draft of the manuscript; A.R., C.A.M., E.Z., M.E.F. and L.M. reviewed and edited the manuscript; M.E.F. and L.M. supervised the research project; L.M. administered

the project. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have declared that no conflict of interest exists.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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