#Pop Health Lab

Research protocol

Worldwide trends in sodium and potassium intakes in children and adolescents: a systematic review and meta-analysis

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IMPRESSUM

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Background

Intakes of sodium (Na) and potassium (K) are key determinants of health and diseases from birth to adulthood (1,2). High Na intake is a cause of elevated blood pressure (3,4) and cardiovascular diseases (5,6), and is associated with other conditions such as osteoporosis, diabetes, and cancer (7,8). Low K intake is associated with elevated blood pressure and cardiovascular diseases (9), as well as with chronic kidney stone formation and low bone-mineral density (10,11). An adequate intake of Na and K starting in childhood has the potential to ensure an optimal life course trajectory and to prevent high blood pressure later in life (1).

The World Health Organization (WHO) recommends a maximum of 2 g Na per day and a minimum of 3.5 g K per day for adults, as well as a Na/K ratio of ≤0.6 (12). For children and adolescents, the target recommended levels are adjusted downwards to account for estimated energy intake requirements at that age (see **Table 1** and **Appendix**). Unfortunately, a large share of the world population does not meet these recommendations, with the majority of the population consuming too much Na and not enough K (5,13).

Table 1. Target recommended daily intakes in Na and K in adults and children, based on (12,14,15)

Age group	Na [g/d]	K [g/d]
Infants <1 year	<0.5	≥1.0
Children 1-3 years	<0.9	≥1.6
Children 4-9 years	<1.4	≥2.4
Children and adolescents 10-18 years	<2.3	≥3.9
Adults	<2	≥3.5

To adapt prevention strategies targeting these recommendations, data on Na and K intakes trends in different populations are needed. Global Na and K intakes and trends in adult populations have been investigated in several studies (5,13,16,17). One comprehensive, albeit not systematic, review found that Na intakes in children above 5 years old were above 2.3 g/d in more than 66% of the studies (16). One systematic review of studies in Sub-Saharan Africa found that 33% of the studies reported Na intakes in children above 2 g/d (18). However, to our knowledge, global estimates of trends of Na and K intakes in children and adolescents based on a systematic review of the literature are lacking.

Objective

The objective of this systematic review is to estimate global, regional, and national trends in Na and K intakes (primary outcome) and Na/K intake ratio (secondary outcome) in children and adolescents. We aim to produce worldwide maps of Na and K intakes in children in 1990, 2000, 2010 and 2020.

The specific research questions are:

- What are the trends in Na and K intakes in children 0-18 years old worldwide, in different regions and countries, from 1990 up to now?
- What are the Na and K intakes, and Na/K ratio, in different age groups of children?

Methods

This protocol is designed following the recommendations of PRISMA-P (19) and will not be edited after data extraction has started. It will be registered in PROSPERO and made available upon request.

Eligibility criteria

We will identify studies having assessed Na or K intake in apparently healthy children up to 18 years of age from 1990. The detailed eligibility criteria are listed in **Table 2**.

Table 2. Inclusion and exclusion criteria

Characteristic	Inclusion	Exclusion
Participants	Apparently healthy children and adolescents 0-18 years old	Children mean age >18 years old Children with health conditions
Exposure	Total Na, K, Na/K intake or urinary excretion	Only discretionary salt
Study design	Cross-sectional studies, longitudinal studies, baseline or control group of intervention studies	Case reports, case series, case-control studies, reviews, meta-analyses
Publication type	Full-text publications	Conference abstracts, commentaries, editorials Studies with unavailable full-text
Publication data	From 1/1/1990 up to date of search	Before 1/1/1990
Language	English, French, German, Spanish, Italian, and Portuguese	If possible, studies in other languages will be translated to allow inclusion
Location of study	No restriction	

Search strategy

A systematic search of the online databases Medline and Embase will be conducted. The search strategy will include the concepts “children” with “sodium”, “potassium”, or “sodium-to-potassium ratio” (see PubMed search strategy in **Table 3** and Embase search strategy in **Table 4**). To limit the number of records identified, the search will be limited to to human studies published from 1/1/1990 onwards.

In order to ensure studies from all over the world to be captured, the African Journals Online, the Latin American and Caribbean Health Sciences Literature (LILACS), and the Scientific Electronic Library Online (SciELO) databases will also be searched. In addition, the references list from other related reviews (13,16–18), reviews identified with the Medline and Embase searches and included publications will be screened.

Study selection

The identified records will be imported into Rayyan. Duplicates will be automatically removed. The selection of the records will be conducted by two reviewers. Any disagreement on the exclusion or inclusion of a record between the two reviewers will be resolved by discussion between the two reviewers.

Table 3. PubMed search strategy

ID	Query
#1	"baby"[tiab] OR "neonat*"[tiab] OR "newborn*"[tiab] OR "infant, newborn"[mh] OR "infan*"[tiab] OR "infant"[mh] OR “toddler*”[tiab] OR "child*"[tiab] OR "child"[mh] OR "preschool"[tiab] OR "child, preschool"[mh] OR "school"[tiab] OR "pupil*"[tiab] OR "pupil"[mh] OR "boy"[tiab] OR "boys"[tiab] OR "girl*"[tiab] OR "adolescen*"[tiab] OR "adolescent"[mh] OR "teenage*"[tiab]
#2	("salt"[tiab] OR "sodium"[tiab] OR "sodium, dietary"[mh] OR "sodium/urine*"[mh] OR "potassium"[tiab] OR "potassium, dietary"[mh] OR "potassium/urine*"[mh] OR "sodium to potassium ratio"[tiab] OR "sodium-to-potassium ratio"[tiab] OR "Na/K ratio"[tiab]) AND (“intake”[tiab] OR “excret*”[tiab] OR “consum*”[tiab] OR "urin*"[tiab])
#3	1990/01/01:2023/04/06[dp]
#4	humans[mh]
#5	#1 AND #2 AND #3 AND #4

Table 4. Embase search strategy

ID	Query
#1	'baby'/exp OR 'baby' OR 'neonat*' OR 'newborn*' OR 'newborn'/exp OR 'newborn' OR 'infan*' OR 'infant'/exp OR 'infant' OR 'child*' OR 'child'/exp OR 'child' OR 'preschool' OR 'preschool child'/exp OR 'preschool child' OR 'school'/exp OR 'school' OR 'school child'/exp OR 'school child' OR 'pupil*' OR 'boy*' OR 'boy'/exp OR 'boy' OR 'girl*' OR 'girl'/exp OR 'girl' OR 'adolescent'/exp OR 'adolescent' OR 'teenage*'
#2	('salt' OR 'sodium' OR 'potassium' OR 'sodium to potassium ratio' OR 'sodium-to-potassium ratio' OR 'na/k ratio') AND ('intake*' OR 'excret*’ OR ‘consum*’ OR ‘urin*')
#3	[1990-2023]/py
#4	NOT ([animals]/lim NOT [humans]/lim)
#5	[embase]/lim NOT [medline]/lim
#6	[article in press]/lim OR [article]/lim OR [letter]/lim OR [preprint]/lim OR [review]/lim
#7	#1 AND #2 AND #3 AND #4 AND #5 AND #6 AND #7

Data extraction

Data extraction will be conducted in a pre-piloted standardized Excel form. Data will be first extracted in duplicate by two reviewers for 10 studies at the beginning of the data extraction process. The data extracted by the two reviewers will be compared and the data extraction process will be improved. Thereafter the remainder of the data extraction will be done by one reviewer and every one out of 10 studies will be verified by a second reviewer.

Due to the large amount of records expected to be identified, a two-step data extraction approach will be used. In the first step, the following information will be extracted:

- Study ID (First author Publication Year)
- Country of the study
- Year(s) of the data collection (mid-point, range)
- Sampling representativeness (national, subnational, non-representative of the country’s population)
- Setting (population-based, community-based, school-based, hospital-based, health-care-provider-based, other)
- Sample size
- Participant age (mean, range)

- Sex (female/male/both)
- Which outcomes are reported (Na, K, and/or Na/K ratio)
- Measurement method (single or multiple, 24h urine, urinary spot, 24h recall, dietary record, or food frequency questionnaire)

The information extracted in this first step will be used to determine which studies are selected for further data extraction. We will aim to select at least one study for every combination of country, year and participant age group. For countries and for years and age groups, in which more than one study is available, we will select the study that is the most nationally representative, with the largest sample size, and the preferred measurement method. The preferred measurement methods will be (in decreasing order of preference): multiple 24h urine, single 24h urine, multiple urinary spot, single urinary spot, multiple 24h recall, single 24h recall, multiple dietary records, single dietary records, and food frequency questionnaire. If one study is reported in more than one publication, they will be merged into one record to avoid duplication.

In the second step, full data extraction from the selected set of studies will be conducted and will consist of:

- Name of study (if available)
- Study design (cross-sectional, longitudinal, trial)
- Area classification (urban, rural, both, not reported)
- Sex (if available percentage male)
- Na, K and Na/K estimates from the smallest group available (n, mean/median, SD/SE/95%CI/IQR/range, unit, percentage with low/high intake and definition of low/high intake)
- Body weight (if available, mean, unit)
- Energy intake (if available, mean, unit)
- Information on measurement method quality control (for 24h urine: PABA validation, exclusion based on total urinary creatinine or creatinine ratio, strict urine collection protocol; for spots: validation with 24h urine in sub-sample, use of reliable equation; for dietary methods: multiple days, corrections for underreporting)
- Funding source (government, industry, other)

Missing information will be requested from the study authors via e-mail.

Data analysis

The measures of interest will be, first, the average daily Na intake and the average daily K intake and, second, the average daily Na/K intake ratio.

Data transformations and imputations will be done according to the Cochrane Handbook for Systematic Reviews of Interventions (20) and following the recommendations of Borenstein et al (21). Na, K and Na/K intakes will be converted into common units (i.e. g/d and g/g), with the conversion factors of 1 mmol Na = 23 mg and 1 mmol K = 39 mg. If standard deviations were not available, they will be imputed from standard errors, medians, interquartile ranges, ranges, or from the weighed mean standard deviations of the other included studies (20). The distributions of Na, K, and Na/K intakes will be analysed with histograms, boxplots, and Baujat plots. Identified extreme values will be double-checked for correctness.

The values will be meta-analysed using a random effects multi-level model. Sub-group analyses will be conducted to compared differences in Na, K and Na/K intakes, by region, by country, by measurement method, and, if data allows it, by urban/rural areas. The effect of age

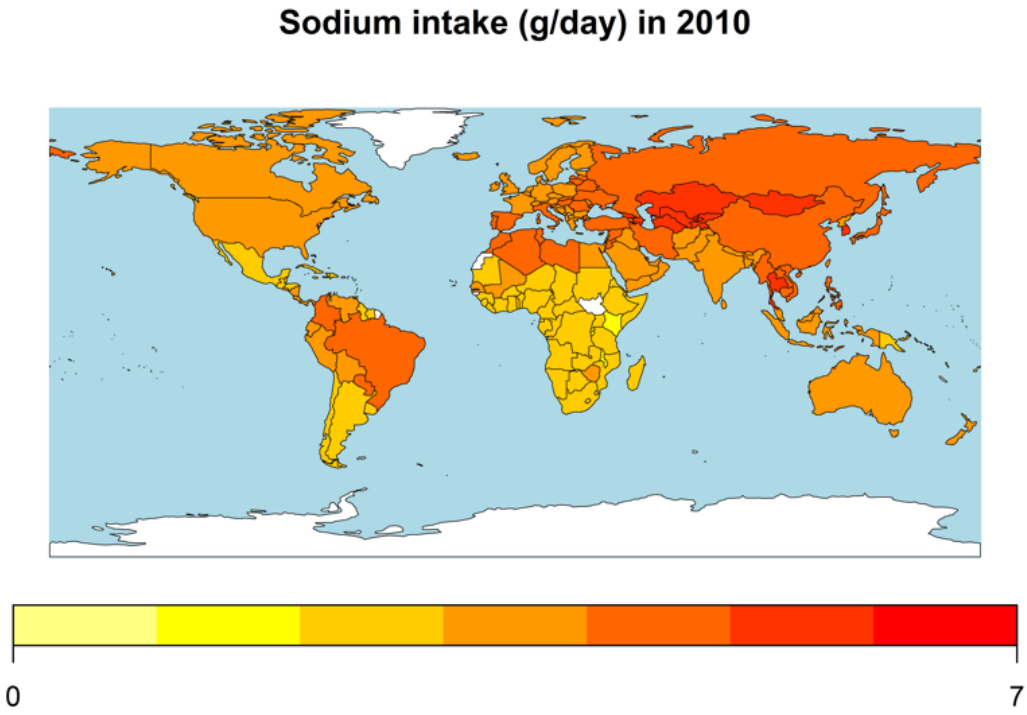
on Na, K and Na/K intakes will be investigated with sub-group meta-analyses and meta-regression. The time trends will be explored with meta-regression. Different meta-regressions models (linear, cubic, quadratic, logarithmic, exponential, polynomial, and restricted cubic splines) will be fitted and the best fitting model based on AIC will be selected. As body weight has a large influence on dietary intakes in very young children (<3 years old), the possibility of presenting Na and K intakes per day per body weight will explored. In adults, Na and K estimates have been standardized by energy intakes (13). This possibility will also be explored.

It is expected that in some regions, countries, and age groups, data will be scarce. To be able to overcome the data gaps, we will explore the feasibility of predicting intakes in countries where no data is available (e.g. using multi-level Bayesian meta-regression (22)). For example, we could possibly build a model that integrates geographical and time proximity and GDP to characterize countries (13) or use intake estimates from adults (e.g. from NCD portal, Global Burden of Disease database, or (13)) to extrapolate intakes in children and to predict the reality as close as possible. If this approach is not feasible, we will match and group countries with missing data with other countries with data who have similar characteristics (especially similar diets). We will aim to produce sodium intake estimates and 95% CI for all age groups, sexes, regions, countries and the years 1990, 2000, 2010 and 2020. Worldwide maps, graphs, and tables will be created (see example **Figure 1**). Sensitivity analyses will be conducted to investigate the effect of the extrapolated data on the results.

Moreover, the possibility of correcting the estimates based on their measurement with quantitative bias analyses will be explored. This correction would be conducted as a secondary sensitivity analysis.

The heterogeneity will be assessed by the I^2 statistic and between-study variance σ^2. Publication bias will be evaluated by enhanced funnel plots and Egger's test.
Data analyses will be conducted in R.

Figure 1. Example of worldwide map



Quality assessment

The quality of each included study will be assessed according to the tailored list of criteria described in **Table 5**.

Table 5. Criteria for assessing study quality

Criteria	Quality
Sample representativeness	
Nationally representative	High
Sub-national, non-representative or unclear	Low
Selection bias	
Population-based sample, school-based sample unlikely to be affected by selection bias	High
Hospital-based, convenience sample, likely affected by selection bias	Low
Measurement method	
24h urine, multiple urinary spots, or multiple 24h recall	High
Single 24h recall, dietary records, food frequency, other	Low
Measurement method quality control	
For 24h urine: PABA validation, exclusion based on total urinary creatinine or creatinine ratio, strict urine collection protocol; for spots: validation with 24h urine in sub-sample, use of reliable equation; for dietary methods: multiple days, corrections for underreporting	High
For 24h urine: no check of completeness of 24h urine collection; for spots: unclear use of equation; for dietary methods: single day measurement, no check of reliability of reporting	Low

Dissemination

The results of this review will be written up in one (or more) report(s) following the PRISMA checklist (23) and published in a peer-reviewed open access journal. To make the results more widely available and interactive, the possibility of creating on online interactive map with the results of this review could be explored (similar to https://ncdportal.org). The results of this review could be used for salt reduction programs and salt iodization programs.

Timeline

The planned timeline is shown in **Table 6**.

Table 6. Planned timeline 2023

Activity / Month	2	3	4	5	6	7	8	9	10	11	12
Finalization and registration of protocol	X	X	X								
Literature search			X								
Study selection				X	X						
Data extraction					X	X	X				
Data analysis							X	X			
Writing publication									X	X	
Submission											X

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Appendix – Recommended sodium and potassium intakes

Several different types of dietary reference intakes exist: 1) The recommended daily allowance (RDA), also called recommended nutrient intake (RNI) and population reference intake (PRI), is the daily intake that meets the nutrient requirements of almost all (97.5%) apparently healthy individuals; 2) the estimated average requirement (EAR), also called average requirement (AR) is the daily intake that meets the nutrient requirements of half (50%) of a population; 3) the adequate intake (AI) is calculated when the RDA and EAR cannot be calculated due to lack of data, and it corresponds to the average daily intake observed in apparently healthy individuals or an approximation of an adequate intake.

Such recommendations also exist for upper levels of intake: 1) a tolerable upper intake level (UL), is the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects; 2) the no-observed-adverse-effect level (NOAEL) is the highest daily nutrient intake at which no adverse effects have been observed; 3) the lowest-observed-adverse-effect level (LOAEL), is determined when the NOAEL cannot be set due to lack of data, and it corresponds to the highest daily nutrient intake at which no adverse effects have been observed.

In the case of lack of evidence where none of the above could be set, some organizations have also published recommended or target intakes. This is the case of the 2012 WHO recommendation mentioned in the background. None of the above dietary reference intakes could be set and instead a “strong recommended maximum intake” was set. The WHO is currently in the process of updating their requirements and, given the new evidence available, will probably set a RDA and EAR or AI for sodium and potassium in the future.

Nutrient requirements differ between authoritative bodies. The different recommendations are summarized below.

Authoritative body and year	Dietary reference intakes for sodium (g/d) by age group
EFSA 2019/2016	AI: 7-11 m: 0.2, 1-3 y: 1.1, 4-6 y: 1.3, 7-10 y: 1.7, 11-17 y: 2.0
NASEM 2019	AI: 0-6 m: 0.11, 7-12 m: 0.37, 1-3 y: 0.8, 4-8 y: 1.0, 9-13 y: 1.2, 14-18 y: 1.5
D-A-CH 2016	AI: 4-11 m: 0.2, 1-3 y: 0.4, 4-6 y: 0.5, 7-9 y: 0.75, 10-12 y: 1.1, 13-14 y: 1.4, 15-18 y: 1.5
Nordic Council of Ministers 2014	Target: 0-2 y: 0.2, 2-9 y: 1.2-1.6, 10-18 y: 2.4
SINU 2014	AI: 6-12 m: 0.4, 1-3 y: 0.7, 4-6 y: 0.9, 7-10 y: 1.1, 11-14 y: 1.5, 15-17 y: 1.5 Target: 1-3 y: 0.9, 4-6 y: 1.2, 7-10 y: 1.5, 11-17 y: 2.0
SACN 2003	Target: 0-6 m: 0.4, 7-12 m: 0.4, 1-3 y: 0.8, 4-6 y: 1.2, 7-10 y: 2.0, 11-18 y: 2.4
UK COMA 1991	AI: 4-6 m: 0.28, 7-9 m: 0.32, 10-12 m: 0.35, 1-3 y: 0.5, 4-6 y: 0.7, 7-10 y: 1.2, 11-14 y: 1.6, 15-18 y: 1.6
Authoritative body and year	**Dietary reference intakes for potassium (g/d) by age group**
EFSA 2016	AI: 7-11 m: 0.75, 1-3 y: 0.8, 4-5 y: 1.1, 7-10 y: 1.8, 11-14 y: 2.7, 15-18 y: 3.5
D-A-CH 2015	AI minimum: 4-11 m: 0.65, 1-3 y: 1.0, 4-6 y: 1.4, 7-9 y: 1.6, 10-12 y: 1.7, 13-14 y: 1.9, 15-18 y: 2.0
Nordic Council of Ministers 2014	RDA: 6-11 m: 1.1, 12-23 m: 1.4, 2-5 y: 1.8, 6-9 y: 2.0, 10-13 y: 2.9-3.3, 14-17 y: 3.1-3.5
IOM 2005	AI: 7-12 m: 0.7, 1-3 y: 3, 4-8 y: 3.8, 9-13 y: 4.5, 14-18 y: 4.7
SCF 1993	RDA: 6-11 m: 0.8, 1-3 y: 0.8, 4-6 y: 1.1, 7-10 y: 2.0, 11-17 y: 3.1 y
UK COMA 1991	RDA: 4-6 m: 0.85, 7-12 m: 0.7, 1-3 y: 0.8, 4-6 y: 1.1, 7-10 y: 2.0, 15-18 y: 3.5


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