Introduction
Children’s health-related quality of life (HRQoL) encompassing their perceptions of the impact of their physical, mental, social and emotional health status [1]. It is being increasingly utilized as a general health indicator in population-based epidemiological studies [2,3]. In particular, research has aimed to identify correlates of HRQoL, with the intention of informing targeted interventions and public health policies.

To date, studies of lifestyle and HRQoL have predominantly been conducted in developed nations (e.g., Australia [4,5], Canada [6], France [7]). Our recent cluster analysis among children from 12 nations was the first to examine the relationship between HRQoL and lifestyle behavior clusters among children from nations of low and medium human development index (HDI) [8]. We found that among most nations, HRQoL was highest among children with moderate MVPA and sedentary time in combination with low screen time and a healthy diet. However, cluster analysis simply identifies groups of children with common lifestyle behaviors, and subsequent post-hoc analyses are used to explore the relationship between cluster membership and HRQoL [9]. If a specific behavior is unimportant in defining cluster membership (as in Dumuid et al. [8] where sleep duration was consistent between the clusters) it is not possible to examine its influence on HRQoL. However, it is possible that behaviors unimportant to cluster definition are in fact important correlates of HRQoL.

Previous studies have investigated the relationship between HRQoL and individual movement behaviors [5,6,10,11,4], however these studies have neglected to analyze the data within their 24-h context, as parts of the human movement composition [i.e., daily time spent in sleep, sedentary time, light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA)]. One of these behaviors cannot change without compensatory changes in the remaining behaviors; therefore the behaviors are co-dependent and should not be considered in isolation from each other. As previous studies have not included all behaviors, the relationship between children’s HRQoL and their daily movement behaviors remains unclear [12,13]. It is also unknown
whether any relationship would be consistent among children of different nations. It is of particular interest whether a nation’s HDI influences this relationship as recent studies have suggested that developing nations are undergoing an epidemiological transition, specifically, as developing nations become increasingly westernized, children accumulate less MVPA and more sedentary behavior [14-16].

This study’s aim was to use compositional data analysis to investigate the relationship between children’s self-reported HRQoL and 24-h movement data and to explore whether this relationship was consistent across nations of differing HDI.

Patients and Methods
Study design and participants:
Data from the cross-sectional International Study of Childhood Obesity, Lifestyle and the Environment (ISCOLE) were used. A detailed description of the ISCOLE protocol can be found in Katzmaryzk et al [17].

Children aged 9-11 years were recruited from schools in study sites from Australia, Brazil, Canada, China, Colombia, England, Finland, India, Kenya, Portugal, South Africa and the United States. Each site contributed approximately 500 children, with a total sample of 7372. Data collection was carried out between September 2011 and December 2013. Participants were excluded if they were missing data for HRQoL (n=94), and/or valid accelerometry (n=1165) and/or sociodemographic covariates (child sex and body mass index (BMI) z-score, number of parents and number of siblings residing in the home and highest parental education level) (n=258). The final analytical sample was n=5855 (79% of all data analyzable).

Ethics:
The ISCOLE coordinators obtained ethical approval from the Institutional Review Board of the Pennington Biomedical Research Center in Baton Rouge, Louisiana, USA. Each site also gained site-specific ethical approval. Written informed parental consent and child assent were obtained from all individual participants included in the study.

Measurement:
Health-Related Quality of Life

The KIDSCREEN-10 [18] was completed by child participants. The KIDSCREEN-10 is the brief form of a European measure (KIDSCREEN-54) [1], however; it has been used and validated in many non-European nations [19] (e.g., Mexico [20], Chile [21], Iran [22], Kenya and Uganda [23]). The KIDSCREEN-10 consists of 10 questions about children’s physical activity, energy and fitness, moods and emotions, social and leisure participation, social and family relationships, cognitive capacity, and school experience. Responses are recorded on a 5-point scale, and reversed when appropriate to ensure that higher scores indicate better HRQoL. Each participant’s scores were summed, transformed to Rasch person-parameters, from which T-values with a mean of 50 and a standard deviation of approximately 10 [18] were calculated.

Daily 24-h movement behaviors: the composition

Daily time spent in sleep, sedentary behaviors, LPA and MVPA was determined from 24-h, 7-day hip-worn accelerometry (Actigraph GT3X+ [ActiGraph LLC, Pensacola, FL, USA]). The overall average daily wear-time was 22.8 h. Valid participants had ≥10 h/day waking wear time (at least 4 days, including at least one weekend day) and ≥160 min total sleep time for at least 3 nights (including one weekend night) [24]. Accelerometry data were sampled at 80 Hz, downloaded in 1-sec epochs, and subsequently aggregated into 60-s epochs for the application of a published algorithm to estimate nocturnal sleep duration [25]. Waking-wear time was re-processed in 15-s epochs and subjected to Evenson’s cut-points to determine duration of sedentary time, LPA and MVPA [26]. The weighted averages (weekdays:weekend days at 5:2) of each behavior (sleep, sedentary time, LPA and MVPA) were used as parts of the daily movement composition. Each participant’s daily composition was normalized to sum to 1440 minutes.

Sociodemographic covariates

Parents completed a questionnaire [17] regarding their child’s sex, family composition (number of siblings and number of parents) and highest level of education achieved by either parent (1=less high school or some high school; 2=completed high school and some post-secondary; 3=bachelor degree and post-graduate). Participants’ body mass index (BMI) was calculated [BMI=weight (kg)/height (m^2)] from measured weight (TANITA Corporation, Tokyo, Japan [27])
and height (Seca 213 portable stadiometer, Hamburg, Germany), and then expressed as z-scores using age- and sex-specific World Health Organization reference data [28].

**Data analysis:**

Data analysis consisted of (1) comparing the relationship between HRQoL and the daily movement behavior composition between study sites, (2) exploring the relationship between HRQoL and the movement composition, and changes to the movement composition, among children from nations of varying HDI.

Analyses were conducted in R [29] using the compositions [30], robCompositions [31] and lme4 [32] packages. Analyses performed at the site-level used mixed-effects multivariable linear regression, with HRQoL as the dependent variable. Daily movement behaviors (time spent in sleep, sedentary time, LPA and MVPA) were considered as the explanatory variables. However, these four behaviors are mutually exclusive and exhaustive parts of the daily movement behavior composition: altogether they must always sum to 24 hours each day. This means that time in one behavior cannot be changed without a compensatory equal but opposite change among the remaining behaviors. Consequently, these movement behaviors are relative data, and one should not be considered in isolation from the remaining behaviors. However, due to multi-collinearity, it is not usually possible to include all the behaviors in one model. This can be overcome by using compositional data analysis [33]. Compositional data analysis for daily movement behavior data is described in detail by Chastin et al. [33], and has been compared to traditional non-compositional methods of analysis elsewhere [13,34]. Briefly, compositional data analysis involves expressing the daily movement behaviors in relative terms, as a set of isometric log-ratio coordinates [35]. The log ratios cannot be created if there are zero values in any movement behavior, as the logarithm of zero is undefined. Procedures for dealing with zero values are presented elsewhere [36]. The behavior data were checked for zeros; none were present. In this analysis, a specific isometric log-ratio transformation was used so that the first coordinate had MVPA as its numerator and the geometric mean of the remaining behaviors (sleep, sedentary time and LPA) as its denominator. The first coordinate therefore contained all information regarding MVPA, relative to the remaining behaviors. This enabled interpretation of the first
regression coefficient from the model (beta1) as the HRQoL association of MVPA relative to the remaining behaviors [37,13,33]. Covariates (parental education, number of siblings, number of parents, BMIz and sex) were included in the models as fixed effects, and school was added as a random effect (random intercepts). Subsequently, Pearson's product moment correlation coefficient was calculated between HDI at all the sites and the strength of the relationship between HRQoL and MVPA (relative to the remaining behaviors— as quantified by the first regression coefficients (beta 1) obtained from each site’s mixed-effects multivariable linear regression model). The analysis was repeated for sleep, sedentary time and LPA. The models were checked for linearity, normality, homoscedasticity and outliers to ensure assumptions were not violated.

To explore the second aim, participants were stratified according to their country’s HDI into: very high HDI (Australia, United States, Canada, Finland, England and Portugal), high HDI (Brazil and Colombia) and medium-low HDI (China, South Africa, India and Kenya). Mixed-effects multivariable linear regression (random intercepts) was used as for Aim 1, however the multi-level nested nature of the sampling design (participants recruited from schools nested within countries) was accounted for in the models. The relationship between HRQoL and daily movement behaviors was explored using the models to estimate HRQoL from a range of different daily movement compositions. Daily movement behaviors were iteratively changed from the baseline daily composition (the compositional mean) to represent incremental 15-minute increase/decrease in one behavior (e.g., MVPA) while all remaining behaviors were relatively decreased/increased to maintain a total daily maximum of 24 hours (procedural detail and example R code can be found in Supplementary File 1). This process was repeated for each behavior. Subsequently, estimated HRQoL was calculated for each new daily movement composition, and plotted to aid interpretation. Effect-sizes (ES) for difference between estimates (conditional on country and school) were calculated as a ratio of the model residual standard deviation.

Results
Included participants were more likely to be female (p<0.001), have parents of higher education (p<0.001), and have fewer siblings (p<0.001) than excluded participants.
Included participants also had lower BMI z-scores \((p<0.001)\). However, effect-sizes of differences between included and excluded participants were small (Cramer’s \(V=0.00-0.28\) for nominal variables, and Cohen’s \(d=0.05-0.12\) for continuous variables) (Supplementary File 2, Tables e1 to e3). Participant characteristics are summarized in Table 1 and Table 2.