Longitudinal associations between changes in sleep duration and blood pressure across school holiday in sleep-deprived teenagers

Introduction

Why do we study sleep deprivation?

With the emergence of "24/7 society (24 hours throughout 7 days of a week)" and the increasing complexity of modern life, reduced sleep duration has become a hallmark of contemporary society. The National Sleep Foundation recently published recommendations on optimal sleep duration for children and adolescents [1], but in real life, they are sleeping far less than the age-appropriate recommended amount. In Hong Kong, adolescents are typically sleeping for less than 7.5 hours during school term time and compensate at weekends and school holidays [2-4].

Lack of sleep has consistently been linked with an array of negative consequences to adolescents' daytime functioning and health [5-9]. There is also strong evidence to demonstrate that sleep duration impacts on BP, and acts as a risk factor for hypertension [10]. Results from cross-sectional studies on adolescents have been consistent in showing negative relationships between sleep duration and BP [11-14]. Our own cross-sectional study [14] demonstrates that an increase in sleep duration by one hour is associated with a decrease in wake/sleep systolic and diastolic BP by 2 mm Hg and 1 mm Hg respectively in a cohort of normal weight adolescents. In the same study, we are able to demonstrate that BP is sensitive to acute changes in sleep pattern, its level is influenced by sleep quantity and quality of the previous night [14].

Importance to maintain healthy cardiac status in adolescence

There is robust scientific data to support that essential hypertension in adulthood has its roots in childhood and adolescence [15,16]. Epidemiological evidence from various longitudinal cohorts such as the Young Finns study [17] and the Kangwha study [18] show that BP tracks from childhood to adulthood, which is also supported by a systematic review and meta-regression analysis of various paediatric cohorts [19].

Elevated BP is a well-known risk factor for cardiovascular diseases (CVDs) in children and adults [20]. Eight percent of children and adolescents with hypertension have already developed left ventricular mass index elevated to a level associated with a 4-fold increased risk of CVDs in adults with hypertension [20]. In the Muscatine Study, childhood diastolic BP is a significant predictor of carotid intima media thickness in adult males [21]. Similarly, individuals with consistently raised blood pressure in childhood are at significantly increased risk of developing carotid atherosclerosis [22]. The Young Finns Study finds that systolic BP measured in childhood and adolescence is inversely linked with adulthood brachial artery flow-mediated dilation (FMD), an indicator of endothelial-function [23]. All published findings underscore the clinical importance of blood pressure elevation / abnormalities in children and adolescents.

Are blood pressure abnormalities reversible with sleep extension?

Twenty-two adults with pre-hypertension or type 1 hypertension were randomly assigned to a sleep extension group that aimed to increase bedtime by 1 hr. per day over a 6-week period, or to a sleep maintenance group that maintained their usual sleep routines. Both groups received sleep hygiene education. Increasing average nighttime sleep duration by about 30 minutes over a period of 6 weeks resulted in a significant reduction of beat-to-beat systolic and diastolic BP. Control group who maintained their usual sleep duration have static BP levels. Though small sample size, findings suggest behavioural strategy designed to increase sleep duration can be effective in the management of BP abnormalities [24].

Evidence of benefits with sleep extension in children and adolescents

Delaying school start time is recognized as an effective countermeasure to chronic sleep deprivation. There is accumulating evidence to demonstrate significant improvements in markers of health and academic success in a variety of settings in association of later school start time [25]. On the other hand, the logistic considerations in initiating delayed school start times are important obstacles to overcome [26]. Indeed resistance from teachers, parents and school bus companies in our locality has prevented us from using delay school start time as a measure to increase sleep duration of students. In our experience and data obtained from our on-going research, adolescents tend to sleep compensate at weekends and school holidays. The amount of extra sleep they are able to obtain can be up to 2-3 hours during school holidays.

Objectives

To examine whether sleep extension during holidays would lead to reduction in BP in chronically sleep deprived adolescents.

Plan of Investigation

Subjects

Subjects will be recruited from local primary and secondary schools. We will send invitation letters to Principals to ask them for their help with screening questionnaire distribution and assessment arrangements in their school. The screening questionnaire asks about children sleep pattern during school terms and holidays, sleep-related symptoms (e.g. snoring), and medical history to see whether they are eligible to participate. Eligible subjects will receive the study factsheet and written informed consent form. Subjects with parental consent will be enrolled in our study.

Inclusion criteria

1. Adolescents aged between 10-18 years;
2. Written informed consent and assent obtained from parents and adolescents.

For sleep deprived group:

i. Self-reported time in bed (period from bedtime to get-up time) during school days of <8 hours per day
ii. Self-perceived insufficient sleep during school days

For normal sleep group:

i. Self-reported time in bed during school days of >=8 hours per day
ii. Self-perceived sufficient sleep during school days

Exclusion criteria

1. Obesity which is defined as a body mass index (BMI) ≥95th percentile (corresponding to a z score of 1.645) of the local reference. [27]
2. Subjects who are having sleep disorder for example insomnia and/or currently receiving treatment for sleep problems.
3. Known medical or psychiatric conditions or use of current medication that may affect sleep and BP.

The sleep deprived and normal sleep groups will be in 1:1 ratio and they have to be age- and gender-matched to minimize the effects of age and gender on both sleep duration and blood pressure.

The study protocol will be submitted to ethic committee of the New Territory East Cluster Board for approval. All subjects will participate on a voluntary basis. The protocol complies with the Declaration of Helsinki.

Study design

This is a cohort study that consists of 4 visits over a 3-week study period that includes two periods of 7-day school attendance and one period of 7-day school holiday (Study design flow chart). Subjects who have undergone physical examination and completed the screening questionnaire, and are found to meet all the inclusion and none of the exclusion criteria will be recruited. The first study week will be during school days, followed by a week of school holiday, and the final week is when the subject returns back to school after the holiday. The 3 periods need not to be consecutive so as to allow more flexibility to cater for the subjects' schedule. All assessments however have to be completed within 60 days to minimize the effects of growth on BP / sleep pattern.

Outcome measures

(a) Primary outcome: Ambulatory systolic BP during wakefulness.

(b) Secondary outcomes: Other ambulatory BP parameters; Actigraphy measured sleep quantity and quality, neurocognitive function.

Screening

During screening examination, participants will undergo a series of anthropometric measurements. The body build of the subject will be assessed using standard procedures. Standing height (in metres) will be measured without shoes using a Harpenden Stadiometer (Holtain, UK). Body weight will be measured by an electronic weighing scale (Tanita BF-522, Japan). Waist and hip circumference (in centimetres) will also be obtained.[28] Body mass index and waist circumference will be converted into z score using local reference.[27,28] Blood pressure will be taken using the Datascope Accutorr Plus. Two measurements are taken at 1-minute intervals, with a third reading taken 5 minutes later if the difference between the first two >4 mmHg. The average of two repeatable readings (difference ≤4 mmHg) will be used. Sexual maturity rating will be evaluated by a validated gender specific self-assessment questionnaire.[29] Subjects will have to fill in a sleep questionnaire asking about their sleep habits and symptoms, pediatric daytime sleepiness scale (PDSS),[30] Epworth sleepiness scale (ESS),[31] and strength and difficulties questionnaire (SDQ).[32] They will also have Information on parental medical history will be obtained from the parents using a medical history questionnaire. The school calendar of each participant will also be obtained.

Collection of Data
Sleep pattern will be monitored by actigraphy together with sleep diary throughout the whole study period. Twenty four-hour ambulatory BP monitoring and neurocognitive tests will be performed on the last day of each study week. All BP monitoring and neurocognitive tests will be performed during weekdays instead of weekends to avoid the possible weekend effect on sleep pattern and outcomes. Saliva samples will also be collected in the evening and the morning when the subjects are wearing the BP monitor for assessing cortisol awakening response.

Actigraphy
On day 1 of the first week of study, participants will attend our sleep laboratory to start actigraph recording (Actiwatch spectrum device; Phillips Respironics, Murrysville, PA; on their non-dominant wrist) and they will also be instructed on how to complete the sleep diary. Participants will have to wear the device until the end of the study period. Actigraphs will be configured to collect information in 1-minute epochs by using a medium sensitivity threshold, which has high sensitivity for detecting sleep compared with polysomnography.[33] Self-reported bedtimes and wake times will be used to score actigraph data using established procedures.[34,35] Variables of interest include actigraph-defined sleep period (ie, the period between scored sleep onset and scored final awakening), actigraph scored sleep (minutes of scored sleep within the actigraph-defined sleep period), wake after sleep onset (minutes of scored wake within the actigraph-defined sleep period), and sleep efficiency (actigraph scored sleep/actigraph-defined sleep period). The activity level during wakefulness will also be extracted as a covariate for statistical analysis, as it may affect both sleep pattern and BP.

Twenty four-hour ambulatory blood pressure monitoring
A validated oscillometric monitor (SpaceLabs 90217, SpaceLabs Medical, Redmond, Washington, USA) will be used.[36] Systolic, diastolic and mean arterial BP will be measured every 30 minutes. The exact cut-off time dividing wake and sleep BP will be defined individually according to actigraphy. Recordings are included in the analysis when they possessed a minimum of 40 successful readings for the 24-hour period with a minimum of 1 successful reading per hour.[37] Individual mean systolic, diastolic and mean arterial BP are calculated for wake and sleep periods. These BP data will be converted to z scores using the local “LMS” reference values (with reference to gender and height).[38] Subjects will be defined as hypertensive if their systolic or diastolic BP is ≥95th percentile (z score ≥1.645).

Neurocognitive tests
Conners’ Continuous Performance Test (CPT)
CPT-II (Ver. 5.2 for Windows®) is designed as a computer game-like test for the evaluation of sustained attention and response inhibition for respondents aged 6 or above.[39] Subjects are required to press the space bar or click the mouse whenever any letter except the letter ‘X’ appears on the computer screen. The test requires about 14 minutes to complete, and it will be administered in the morning in a quiet room.

Trail-making Test Part A & B (Executive function)
The Trail-making test is composed of two parts which assess test-takers in attention, visual scanning, speed of eye-hand coordination, information processing and set switching of executive functions [40,41]. Part A required subjects to connect sequentially 25 encircled numbers which are randomly scattered over the test sheet. Similarly, for Part B, they are asked connect encircled numbers (1-13) and alphabets (A-L) alternately in ascending patterns, i.e. 1-A-2-B-C. Any mistakes made throughout the test are pointed out by examiner immediately. Thus, the scores of the tests are the time taken to complete the task.

Stroop Test-Victoria Version (Executive function)
This test captures cognitive flexibility and inhibition of executive functioning by three successive tasks with increasing demands [42,43]. It consists of three sets of stimulus cards (1) colored dots, (2) common words printed in same colors as dots, and (3) color words printed in non-corresponding colors of ink. For the first task, subjects are asked to simply name the color of the dots in maximum speed as possible. For the second task, they are asked to identify the color of ink each word is printed in, not to identify the word itself. For the third task, they are asked to identify the color of ink each of the color words is printed in, not to read the color word presented. Number of errors and time to perform the task are recorded for each trial. The Chinese Victoria Version of the Stroop Test is translated and validated by Dr. Tatia Lee and Dr. Kai Wang from the Laboratory of Neuropsychology, the University of Hong Kong.

Raven’s Standard Progressive Matrices Test (Nonverbal reasoning)

The Test is a nonverbal measure of general ability that uses nonverbal stimuli including visual patterns and shapes to asses reasoning by analogy. It contains five sets with 12 problems in each set [44,45]. Each question is a puzzle with a missing part; subjects are asked to identify the most appropriate piece from six similar options. Children of age 5 years 6 months to 8 years 5 months can do a shortened version with only Set A, B, and C to allow better control of test administration. Each set starts with a problem and develops a theme that build on previous questions and become progressively more difficult. The test is administered in a paper and pen format. While it is an open-ended session, most people complete the test in less than 40 minutes.

Grooved Pegboard (Visual-motor coordination)
It is a manipulative dexterity test aim at assessing visual-motor coordination [46,47]. It consists of 25 holes with randomly positioned slots. Subjects are asked to place pegs, which have a key along one side, into the holes from left to right. The task is performed once with dominant hands and once with non-dominant hands. They are advice to complete the task as fast as possible. Subjects from 5 years old to 8 years 12 months will use a Kiddie version of the test in which they only need to complete the first two rows (10 pegs) of the pegboard. Time taken, number of pegs placed on the pegboard, and number of dropped pegs are recorded to assess the score of fine-motor coordination.

Symbol Digit Modality Test (Working memory)
It is a simple test assessing neurocognitive functions including attention, visual scanning, and motor speed.[48] It consists of a sheet of paper which showed paired symbols and digit at the top of the page. With 90 seconds, test-takers are required match up a series of symbols with numbers as showed. The test can be administered in both written and oral modalities.[49]

Digit Span Test (Working memory)
The test contains a forward and a backward element which assess working memory and attention of the test takers. Experimenters read an increasingly longer series of digits (spans 2 to 9) to the test-takers at a rate of 1digit/s. Test-takers are asked to recall the digits in the exact same (Forward Task) or in the reverse order (Backward Task). The score is the total of number of correct trials, prior to failing two consecutive trials at any one span size.[50]

Cortisol awakening response (CAR)
Saliva samples will be collected with Salivette tubes for assessing the level of cortisol and cortisone, as a reflection of stress which on its own can influence both sleep pattern and BP.
Participants will be asked to collect their saliva in the morning when they are wearing the BP monitor. Each subject will have to provide five saliva samples according to a fixed sampling protocol [51]: (1) one hour before bedtime, (2) immediately after awakening, (3) 15 min after awakening, (4) 30 min after awakening, and (5) 45 min after awakening. Salivary cortisol [51] and cortisone [52] concentrations in these samples will be measured by a liquid chromatography tandem mass spectrometry method at the Biomedical Mass Spectrometry Unit, Department of Chemical Pathology, Prince of Wales Hospital. Between-batch precision performance of the method has coefficients of variation of <5%. The lower limits of quantitation are <0.5 nmol/l.

Statistical analysis
Subjects who do not comply with the study protocol will be considered as dropouts and excluded from the final analysis. Two-way ANCOVA repeated measures will be performed to test the difference in change in BP across holidays between the sleep deprived and normal sleep groups, while adjusting for other covariates including activity level, cortisol level and holiday. Linear mixed model will be used to determine whether change in sleep duration is associated with change in BP over time. The fixed effects of the change in sleep duration, the change in cortisol level and time, and the random effect of different holiday periods on the change in BP will be assessed. Bonferroni adjustments will be made for multiple comparisons. Data analysis will be conducted by using IBM SPSS Statistics for Windows, Release 20.0.0 (©IBM Corp., 2011, Armonk, NY; www.ibm.com).

Estimated sample size and preliminary data
We have collected self-reported questionnaires on sleep pattern from 446 adolescents (age range: 10-18 years), of whom 143 slept <8 hours during school days (Sleep deprived group). These preliminary data revealed that adolescents who were sleep deprived during school days had a greater increase in sleep duration during holidays than the normal sleep group (2.6h ± 1.4 c.f. 0.9h ± 1.4, $p<0.001$). (Table 1) We expect similar findings can be obtained from this proposed prospective study.
According to our previous cross-sectional study [14], the addition of sleep duration into the linear regression model with wake systolic BP as the dependent variable increased the R^2 by 0.042. The effect size (f) was 0.204. For the current proposal, we expect a similar effect size for the association

between changes in wake systolic BP and sleep duration. Assuming that the repeated measures are independent of each other, a total of 102 subjects (51 per arm) will be required to detect such effect size with 90% power and 5% type I error probability. This calculation is performed using computer program (G*Power version 3.1.9.2). Assuming a dropout rate of approximately 50%, a total of 204 subjects have to be recruited.

Feasibility and timetable of project

The proposed study will require a total of 36 months to complete. There are 4 main holiday periods in the local school calendar, including Christmas, Lunar New Year, Easter and Summer vacation. The progress of the study will mainly depend on the number of actigraphy recorders we have. Assuming we have a total of 20 recorders, we will be able to assess at most 20 subjects for each holiday period. Assuming that we are able to arrange 16-20 subjects to participate for each holiday period, a total of 12 holiday periods will be required. The same number of sleep deprived and normal sleep subjects will be recruited for each holiday period so as to minimize the possible effect of seasonality on both sleep duration and BP outcomes. We proposed to start the project on Christmas 2016 and finish data collection by Summer 2019. The remaining time will be for data entry, analysis and report writing.

Purpose and Potential

The American Academy of Pediatrics recognizes sleep deprivation in adolescents as an important public health issue with far-fetching implications. Therefore our proposed research is timely and addresses a highly relevant problem. Our study will provide the much needed evidence-based data to determine whether sleep extension is beneficial for BP control in adolescents who are chronically sleep deprived. If this study shows that sleep deprivation-related BP abnormalities are reversible following natural sleep extension, this will be useful information for parents counseling, and will also lead to a change in current thinking and management approach for adolescents sleep needs. More importantly positive results from this project will provide background information on which government and local school policy can be based and altered for the betterment of our youths, and putting us in a stronger position to argue for a delay in school start time!

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