Prevalence of obstructive sleep apnoea among adolescents in the general population

Study protocol

Abstract

Obstructive sleep apnoea (OSA) is associated with a variety of important complications, namely cardiovascular, neurocognitive and metabolic disturbances. The prevalence of OSA is well studied in children and adults. However, adolescence – an interface between childhood and adulthood, and a period of developmental changes known to affect sleep is largely unexplored in relation to OSA. The only published prevalence study on adolescents is limited by its small sample size, not a true representation of the general population and primarily focused on Caucasians. In this proposed study, we aim to determine the prevalence of OSA and associated clinical features in a large population-based sample of adolescents aged between 12 and 16 years.

The sample selection will be based on a stratified (by districts) and clustered (subjects within randomly selected schools) randomised sampling frame. We will stratify all secondary schools registered under the Education Bureau according to the four geographic regions in Hong Kong. In order to avoid sampling bias towards the region that has less population, the final number of schools to be recruited from each of the 4 geographical regions will be in proportion to the adolescent population that resides in that region. Students in each year grade from the chosen school will be randomly selected and invited to take part. Each participant will fill in a sleep habit questionnaire, undergo anthropometric measurements, complete polysomnographic recordings at home and will also have phenotyping for cardiovascular and metabolic risk. The primary outcome is prevalence of OSA, assessed by the obstructive apnoea hypopnoea index. Secondary outcomes include use of logistic regression models to assess association between different severities of OSA and various demographic and clinical variables, and risk of diabetes, hypertension and metabolic syndrome.

The obtained result will provide the much needed OSA prevalence in adolescents which is essential for estimating the true burden of disease within this population. This information is also vital when considering population-based health policies and interventional strategies. Globally, the findings from currently evidence-sparse region of the world allow future international comparison of disease burden. Our study will also form a platform from which repeated measurements can be made to assess time trends and to answer the important question of whether adulthood OSA takes its origin from adolescence.

Hypothesis

We hypothesize that the prevalence of obstructive sleep apnoea among adolescents is different from that reported for children.

Key Issues

(1) Our research group has demonstrated that childhood OSA is common in Hong Kong. We found OSA prevalence for boys and girls aged between 5 and 13 years being 5.8% and 3.8% respectively. [1] However, the prevalence of OSA in adolescents remains unknown. It is inaccurate to extrapolate prevalence of childhood OSA to adolescents as they go through a period of critical transition. In fact adolescence is associated with various developmental changes,

namely somatic growth, cerebral remodeling [2] and hormonal changes that can affect upper airway dynamics [3] and ventilator control. [4] These changes are expected to influence upper airway patency during sleep.
The only published study that examined OSA prevalence among adolescents involved a small sample size of 101 subjects. [5] After completion of an 82-item questionnaire, all participants underwent overnight cardiorespiratory monitoring at home. Twenty-nine percent of the subjects were snorers. Polygraphy showed a respiratory disturbance index ≥10 in 18 subjects (17.8%), but concurrent symptoms suggestive of OSA were found in only 2 subjects (1.9%). Further studies with sound methodology and a representative sample of the studied population are required to provide a reliable estimation of OSA in adolescents.

(2) Obstructive sleep apnoea in children and adolescents is an important clinically relevant condition because of its association with a number of significant short and long term consequences. [6] Specifically for adolescents, both metabolic disturbances (dyslipidaemia and insulin resistance) and cardiac complications (hypertension, left ventricular diastolic dysfunction and increased left ventricular mass) are well established OSA sequelae. [7-9]

(3) There is accumulating evidence of 2 types of childhood OSA, namely one associated with lymphoid enlargement in the absence of obesity, and the other being primarily associated with obesity. [10] This classification of childhood OSA allows better distinction between patients. Evidence also suggests that genetic susceptibility of OSA has both obesity-dependent and obesity-independent components, thus emphasizing the importance of segregating obese and non-obese subjects in OSA research. [11] The OSA subtypes are distinct entities. Former is the classical childhood OSA and the latter being more akin to adulthood OSA where obesity plays an important role. As obesity is becoming more common among adolescents, [12] we can expect to see an increasing prevalence of OSA in this age group. Furthermore, research in this area may provide the important answer as to whether adulthood OSA begins from adolescence.

Relevance, significance and value of the study
With the obesity epidemic, the prevalence of OSA in adolescents will be expected to increase further. Taking into account the association between OSA and clinically important short and long term complications, our proposed study is highly relevant and will yield vital information on disease burden. Our study will also form a platform from which repeated measurements can be made to assess time trends and to answer the important question of whether adulthood OSA takes its origin from adolescence. This study, with both significant academic and clinical value will invariably enrich the scanty scientific literature on adolescent OSA. It will also build on our internationally recognised track record on OSA research.

(a) Background of research
Why study OSA?
The prevalence of childhood OSA is quoted to be around 1 to 5%. [13] However in studies that utilized parental report with additional diagnostic testing, the prevalence is as high as 12-24%. [13] The variation in reported prevalence can be explained by the use of different methodologies and diagnostic cut-offs. In Hong Kong, our research group has completed an OSA prevalence study in community-based children aged 5 to 13 years. We used a two-phase strategy, namely questionnaire screening followed by overnight sleep study and we found a prevalence rate of 3-

5% using ICSD-II diagnostic criteria. [1] Obstructive sleep apnoea in adolescents is largely unexplored, and the only publication on its prevalence has quite a few methodological flaws, namely small sample size and failure to represent the general population. [5]
It is well documented that childhood / adolescent OSA can lead to a variety of important sequelae which include cardiovascular, growth, neurocognitive and behavioural deficits together with metabolic disturbances. [6-9] Individuals with OSA have higher morbidity, mostly related to respiratory diseases and health care use starting from a young age. [14] They are also found to have poorer quality of life scores than healthy controls. [15] Therefore this proposal deals with an important condition that is currently insufficiently researched.

Two types of childhood OSA

Recent research has emphasized the "newer" type of childhood OSA, namely primarily obese subjects with only mildly enlarged lymphoid tissue. These obese children with OSA present differently and have distinct clinical phenotypic characteristics from non-obese children with OSA. [10] Different metabolic and immunological changes are present in obese children with OSA, and obesity can induce health changes that are independent from an isolated upper airway problem. Therefore the distinction between obese children with OSA from those of normal weight is very crucial. This newer type of childhood OSA is more akin to adulthood OSA as obesity is the major component in both. There is accumulating evidence that this type of childhood OSA begins in adolescence. [16]
Obstructive sleep apnoea in childhood usually remit by adolescence, and a large proportion of adolescents OSA cases are incident cases. Distinct risk factors for OSA are at play at each time point across paediatric ages, underscore the need to separate OSA research for children and adolescents. [16,17]

Why study adolescents?

Adolescence is a rapid and critical transitional stage of physical and psychological development that generally occurs at the onset of puberty. Major biological changes take place during this period and they include changes to the sex organs, physical parameters, muscle mass, as well as vital developmental changes in brain structure and organization. It is well known that some of these changes will affect various aspects of sleep, predisposing adolescents to the development of OSA. [2-4] This period of growth and maturation is very distinct and should not be seen as a continuum of childhood, and it further emphasizes the importance not to extrapolate childhood OSA information to adolescents.

Research by our research group

We have successfully conducted clinical research on various aspects of childhood OSA. These include determining risk factors and prevalence, [1] establishment of screening methods, [18] examination of neurocognitive, metabolic and cardiovascular complications using cross-sectional and longitudinal study design. [19-27] Our group has also published work on the natural progression of mild OSA and primary snoring in children. [28,29] We have also recently completed a 10-year follow-up study on an OSA cohort and we document that moderate-to-severe OSA in childhood may be associated with higher blood pressure in early adulthood. [30] Thus our proposed study builds on our established track record in childhood OSA research.

(b) Research plan and methodology

Study Subjects

Adolescents will be recruited from local secondary schools which will be randomly selected from the 4 geographic regions of Hong Kong. Inclusion and exclusion criteria are as follows:

Inclusion criteria:

1. adolescents aged 12-16 years.
2. written informed consent from parents and assent from participants available.

Exclusion criteria:

1. subjects who have previously undergone upper airway surgery or currently receiving treatment for OSA.
2. craniofacial anomalies.
3. subjects who are unable to speak or read Chinese.

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 study will be conducted in compliance with the Declaration of Helsinki.

Study Design

It is a cross-sectional, population-based study. Subjects who are found to meet all the inclusion and none of the exclusion criteria will be recruited. They will complete a set of sleep-related questionnaires, undergo anthropometric measurements, home polysomnographic (PSG) monitoring, attention assessment and phenotyping of their metabolic and cardiovascular risk.

Pilot Data and Sample Size Estimation

We have previously established a school-based cohort in 2003-2005 which included children aged between 6 and 13 years to determine the prevalence of OSA. [1] We then conducted a 4-year follow-up for a subgroup of the cohort was carried out. [25] At follow-up, the subjects were aged between 10 and 17 years. A total of 243 teenagers returned for the follow-up visit. The prevalence of OSA defined by different cut-offs and the minimum sample size required to detect corresponding prevalence with various levels of precision are presented in table 1. On further analysis those who returned for the 4-year follow-up had higher baseline OSA severity compared to the rest of the cohort [OAHI: 1.0 (0.1–2.5) c.f. 0.6 (0–2.0), p=0.007], therefore the calculated prevalence is likely an over-estimation. Nonetheless, using the proposed sample size would provide adequate power should the genuine population prevalence is lower than the calculated one.

Table 1. Minimum sample size required to detect the prevalence of OSA defined by various cut-offs with different levels of precision.

	OAHI ≥5/h	OAHI ≥1/h	OAHI ≥1/h + habitual snoring (ICSD criteria)
No. of cases	34/243	120/243	31/243
Prevalence / Precision	0.140	0.494	0.128

	Minimum sample size required		
0.01	4623	9603	4276
0.015	2055	4268	1900
0.02	1156	2401	1069
0.025	740	1536	684
0.03	514	1067	475
0.04	289	600	267
0.05	185	384	171

In the current settings with limited budget allocation, our research team is capable of recruiting 740 adolescents to detect a prevalence of 14.0% with a precision of 2.5% (i.e. 95%CI: 11.5–16.5%) for the OAHI ≥5/h cutoff. The sample size can also ensure a precision of <4% for the OAHI ≥1/h cut-off and a precision of <2.5% for the ICSD criteria. [31] The sample size would also provide >99% power to detect the differences between the estimated prevalence of OSA in adolescents and the published prevalence of OSA in primary school children [1] no matter which cut-off is being used.

Sampling Frame

The sample selection will be based on a stratified (by districts) and clustered (subjects within randomly selected schools) randomised sampling frame. We stratify all secondary schools registered under the Education Bureau according to the four geographic regions in Hong Kong (i.e. Hong Kong Island, Kowloon, New Territories East and New Territories West). The student numbers in all secondary schools are available in the Bureau's website. Ten students in each school year grade will be randomly selected from the chosen schools. There are on average 50 children to be recruited per schools therefore we will need to randomly select 15 secondary schools from the whole of Hong Kong. In order to avoid sampling bias towards the region that has less population, the final number of schools to be recruited from each of the four geographical regions would be in proportion to the adolescent population that reside in that region. According to the 2016 population by-census statistics (available from the website of Census & Statistics Department, HKSAR), the proportions of adolescents residing in Hong Kong Island, Kowloon, New Territories East and New Territories West were 16.1%, 30.7%, 25.3% and 27.9% respectively. Thus, this study will recruit proportionally 2, 5, 4 and 4 secondary schools from the 4 regions. This sampling method ensures that our subjects are representative of the local school population. Lastly, this study will recruit and survey the subjects from the four regions in parallel throughout the study period in order to minimise the possible influences of different seasons on study outcomes.

Outcome Measures

(a) Primary outcome: prevalence of obstructive sleep apnoea as defined by obstructive apnoea hypopnoea index.
(b) Secondary outcomes: correlation between severity of OSA with clinical, laboratory parameters and cognitive function as measured by Conners' Continuous Performance Test (CPT).

Collection of Data

The subjects will attend our unit for assessment and explanation of home PSG monitoring. After a 15-minute rest, systolic (SBP) and diastolic (DBP) 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. Anthropometric parameters including standing height (in metres) without shoes and body weight (in kilograms) will be recorded using Harpenden Stadiometer (Holtain, UK) and an electronic weighing scale (Tanita BF-522, Japan) respectively according to standard recommendations. [12,32] Waist and hip circumference (in centimetres) will also be obtained. Neck circumference will be measured at the level of the most prominent portion of the thyroid cartilage with the head held erect and the eyes facing forward. Z scores of body mass index and waist circumference will be calculated using local references. [33,34]
If the participating school is agreeable and logistically feasible, our research team can carry out the above at school. However, in our experience schools close to our unit prefer to send their students to us to undergo the various assessments.
All assessments will be carried out during the week to avoid weekday-weekend difference in adolescents' sleep pattern. The students will also complete a chronotype preference questionnaire, result from which can provide guidance regarding effects of sleep phase. The reduced version of Horne and Östberg Morningness−Eveningness Questionnaire (rMEQ) will be used to measure chronotype preference [35]. It consists of five items designed to assess one's preferred bedtime and rise time, the degree of tiredness in the morning, peak time for optimal performance, and self-perceived circadian preference. The rMEQ has been validated in ethnic Chinese individuals, with good psychometric properties [36], and has been used in previous research conducted in adolescents.[37, 38] Participants scored higher than 17 and lower than 12 will be classified as morning-type and evening-type, respectively. Participants with total rMEQ scores between 12 and 17 will be classified as intermediate-type [36].

Sleep study

Level III sleep study will be conducted at home for every subject. A model of NOX-T3 sleep monitor will be used to record the following parameters: respiratory movements of the chest and abdomen by inductance plethysmography, oxygen saturation and derived heart rate by oximetry, respiratory airflow by pressure transducer, snoring, body movement and body position. We define an adequate overnight sleep study as one with total sleep time >6 hours.

A random sample of subjects will also be invited to undergo overnight full polysomnography (PSG) in our sleep laboratory to validate the level III study (please see below for details). In our laboratory, a model SiestaTM ProFusion III PSG monitor (Compumedics Telemed, Victoria, Australia) will be used to record the following parameters: electroencephalogram from three channels (F4/A1, C4/A1, O2/A1), bilateral electrooculogram, electromyogram of mentalis activity and bilateral anterior tibialis. Inductance plethysmography will be used to record respiratory movements of the chest and abdomen. Heart rate and electrocardiogram will be obtained from 2 chest leads. Oxygen saturation (SaO2) will be measured by an oximeter (Ohmeda Biox 3900 Pulse Oximeter) with finger probe. Respiratory airflow pressure signals and end tidal CO2 will be recorded simultaneously via a triple-port nasal catheter placed at the anterior nares and connected to a pressure transducer and a capnograph (BCI Capnocheck Plus)

respectively. An oronasal thermal sensor will also be used to detect absence of airflow. Snoring will be measured by a snoring microphone placed near the throat. Body position is monitored via a body position sensor.

Respiratory events including obstructive apnoeas, mixed apnoeas, central apnoeas and hypopnoeas will be scored based on the recommendations from The AASM Manual for the Scoring of Sleep and Associated Events. [39] Respiratory effort-related arousals (RERAs) will be scored when there is a fall of <50% from baseline in the amplitude of nasal pressure signal with flattening of the nasal pressure waveform, accompanied by snoring, noisy breathing, or evidence of increased effort of breathing. A respiratory event is only scored when it lasts ≥2 breaths irrespective of its duration. [39]
Obstructive apnoea hypopnoea index (OAHI), respiratory disturbance index (RDI), oxygen desaturation index (ODI), arousal index (ArI) and respiratory arousal index (RAI) are defined according to standard recommendations. [39]

We have carried out a pilot study to validate the proposed home sleep monitor (NOX-T3). Eleven subjects aged between 12-16 years were recruited from various sources, namely attendants to the sleep disorder clinic, healthy subjects who participated in our sleep duration and blood pressure study and relatives of patients who attend our respiratory clinic. They underwent an overnight in-laboratory polysomnography (PSG) with simultaneous NOX-T3 portable monitor recording, followed by unattended home recording with NOX-T3. The mean±SD OAHI was 5.8 ± 6.6 events/h on PSG, 6.0 ± 6.9 events/h on in-laboratory NOX-T3 recording, and 4.3 ± 4.8 events/h on home NOX-T3 recording (p=0.6). The intra-class correlation between OAHI obtained from in-laboratory PSG and in-laboratory NOX-T3 recording is 0.982 (95% CI: 0.937-0.995), indicating an excellent agreement. On the other hand, the intra-class correlation between OAHI obtained from in-laboratory PSG and home recording with NOX-T3 is 0.656 (95% CI: 0.155-0.893), indicating a moderate reliability of the home testing. Moreover, based on a cutoff of OAHI ≥1 or 5 events/h, the Cohen's Kappa agreement between in-laboratory PSG and home testing with NOX-T3 are both high at 0.814 (SE: 0.175).

We plan to further validate this degree of agreement (Cohen's Kappa = 0.814) of the home sleep testing by recruitment more subjects during the study period to undergo both home testing and in-laboratory PSG. A sample size of 23 will provide an 80% power with a type I error of 0.05 to validate a Cohen's Kappa of 0.814 of the home sleep testing against the null hypothesis that the Cohen's Kappa is less than 0.3, i.e. a poor agreement. In other words, we will recruit another 12 random subjects during the study period, making it a total of 23 subjects for validating the home monitor.

<u>7-day sleep pattern monitoring</u>
Sleep will be objectively measured using actigraphs. Actigraph is a wristwatch-like device that uses a piezo-electric beam to detect movements which are translated into digital counts accumulated across predesigned epoch intervals (for example, 1 minute) and stored in internal memory. Data can then be downloaded for further analysis.
The device will be worn on the non-dominant wrist for 7 consecutive days and nights. We will instruct the parents / caregiver to keep a sleep log on bedtimes and waking times, temporary pauses in actigraph registration (for example, while taking a bath), and significant events that

might affect sleep quantity or quality (for example, illness, injury etc). The child with help of parents / caregiver will be instructed to press a button (event marker) in the actigraph at bedtime and waking times. A completed sleep log will be obtained from all participants, including both parent-reported sleep log and event markers on bedtimes and waking times reported by the child. The activity data will be visually inspected to detect significant discrepancies among the sleep log, event markers, and the activity pattern. If there were discrepancies between event markers and sleep log recording, the latter will be used to define bedtime and waking times.
We will exclude nights for further sleep analysis if (a) the actigraph was not in use, (b) information on bedtime / waking times was missing, (c) there was a change in usual life routines due to, for example, illness.
The data will be scored using the Actiwatch Activity & Sleep Analysis software. The scored sleep data will be averaged for each study subject over the valid registration nights and separately for weekday and weekend nights. Sleep duration is defined as the actual sleeping time. Sleep start is defined as 10 minutes of consecutively recorded inactive data. Sleep efficiency is defined as the actual sleep time divided by the time in bed. Sleep duration and efficiency will be analysed as both continuous and dichotomous variables.

Upper Airway Size Examination
Tonsillar size will be examined and recorded using a validated grading system.[40] Modified Mallampati score [41] will also be obtained.

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.[42] 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. It will be administered in the morning in a quiet room.

Determination of Levels of Biomarkers
Blood sample will be taken from the subjects for fasting (at least 8 hours) glucose level, lipid profile, high sensitivity C-reactive protein (hs-CRP), appetite-regulating hormones and pro-inflammatory cytokines determination. Plasma and serum samples will be stored at −80 °C until measurement. Plasma glucose is measured by hexokinase method (Cobas C8000 Clinical Chemistry Analyser, Roche Diagnostics Corp, Indianapolis, IN). The inter-assay coefficient of variation is 3% or less at all concentrations up to 41.6 mmol/L. The lipid profile includes total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) concentrations, which are measured by appropriate enzymatic assays (Cobas C8000 Clinical Chemistry Analyser, Roche Diagnostics Corp, Indianapolis, IN, USA) with inter-assay coefficients of variation of ≤3%. Serum hs-CRP will be measured by chemiluminescence immunoassay using the IMMULITE Analyzer (Diagnostic Products Corporation, Los Angeles, CA). Our reference range for hs-CRP is<11.0 mg/L and the sensitivity and inter-assay coefficients of variation are 0.1 mg/L, 6.6% at 1.7 mg/L, 6.5% at 4.8 mg/L and 5.7% at 7.1 mg/L. Ghrelin, leptin, adiponectin and proinflammatory cytokines TNF-α and IL-6 will also be measured using Enzyme-Linked Immunosorbent Assay.

Statistical Analysis

The prevalence of OSA of each geographic region will be calculated individually. The overall prevalence will be calculated using the following formula:

$$Overall\ prevalence = \frac{\sum_{i=1}^{e} N_i \times P_i}{N}$$

where e is the number of strata, N_i is the number of eligible individuals from the population that form part of strata i, P_i is the prevalence of strata i, and N is the number of eligible individuals in the population.

The resultant prevalence will be compared to published prevalence of OSA in children. Logistic regression analysis will be used to identify possible risk factors of OSA in adolescents. Potential factors associated with a higher risk of OSA may include male sex, body weight, waist circumference, neck circumference, tonsil size, modified Mallampati score and chronotype. All these factors will be first assessed in univariate analysis. Those found to be significantly associated with OSA in univariate analysis will be assessed in multivariate model. The association between OSA and cardiovascular, metabolic and cognitive outcomes will be investigated. Comparisons will be made between subjects with and without OSA. Linear regression analysis will be conducted to assess the association between these outcomes and OAHI. Multiple linear regression analysis will be performed to see if OAHI is independently associated with these outcome measures while adjusting for possible confounders such as body mass index. The significant level will be set as $p < 0.05$. All analyses will be performed using SPSS version 20.0.

Feasibility and Timetable of Project

The proposed study will require a total of 30 months (130 weeks) to complete. We will be able to assess 8 subjects per week. For a sample size of 740, we will need 93 weeks for data collection. The first 12 weeks will be used for document preparation and school recruitment. The last 15 weeks will be used for data cleaning and analysis. The remaining 10 weeks should be allowed for clashes with schooling, missed appointments and public holidays.

Education plan

The principal investigator and the collaborator are all experienced teachers and supervisors. This project can further strengthen the educational activities and exchanges of the respective departments It will also provide a good opportunity to train undergraduate and postgraduate students, especially for someone who is interested in the field of sleep medicine. The student will be provided with the required theoretical and practical training, and will work under close supervision of the principal investigator and related research personnel. This will allow the student to learn the knowledge and skills as a scientist, an ideal opportunity to advance himself / herself.

Part of this project will be opened to undergraduate medical students to join as their elective or summer projects. This project will be an ideal learning opportunity for them to learn about one of the most common and important conditions within sleep medicine, namely obstructive sleep apnoea. They can have hands-on experience in carrying out home sleep monitoring under supervision and after appropriate guidance. These skills are of suitable levels to undergraduate

medical students and they can also be inspired and learn how to conduct clinical research and especially in the field of epidemiology.

The research findings from the proposed study will form 2-3 papers for publication in peer-reviewed journals and a few work-in progress reports to be presented in local and international meetings. The results are expected to enrich our understanding of OSA epidemiology in adolescents, and the associations between OSA severity and clinical parameters and risk of cardiovascular and metabolic disturbances. Such information will not only be useful for parents and practicing clinicians to delineate disease burden but also for government officials in relation to resource allocation. Dissemination via the media will also be considered as a mean to educate the public regarding adolescents' sleep needs and problems.

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