Title: A cross-sectional comparison of the prevalence of obstructive sleep apnea symptoms in adults with Down syndrome in Scotland and Japan

Running title: OSA and Down syndrome in Scotland/Japan

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Abstract

Small studies in Western populations report a high prevalence of obstructive sleep apnea (OSA) in adults with Down syndrome. To date, ethnic differences have not been explored. A questionnaire sent to 2,752 adults with Down syndrome aged ≥16 years in Scotland and Japan (789 valid responses) estimated OSA prevalence based on reported symptoms. Symptoms were common in both countries, with snoring (p=0.001) and arousals (p=0.04) more prevalent in Japan. Estimated OSA prevalence in adults with Down syndrome was similar in the two countries, and raised in comparison with the general adult population (19.6% in Scotland and 14.3% in Japan (p=0.08)), though BMI was a confounder. Identification and treatment of OSA is recommended in adults with Down syndrome, regardless of ethnicity.

Keywords

Obstructive sleep apnea; Down syndrome; Sleep-related breathing disorders; Epidemiology

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Abstract

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1. Introduction

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder, affecting 5-14% of Western and 4-12% of Japanese adults (Matsumoto et al., 2018; Mirrakhimov, Sooronbaev, & Mirrakhimov, 2013; Peppard et al., 2013). Untreated OSA is associated with a host of adverse effects, including excessive daytime sleepiness (EDS), impairment of cognitive function, cardiovascular and metabolic dysfunction and increased morbidity and mortality (Javaheri et al., 2017; Jennum & Riha, 2009; Sawatari, Chishaki, & Ando, 2016; Vgontzas, Bixler, & Chrousos, 2005).

Down syndrome is one of the most common causes of intellectual disability worldwide, affecting 1.1 per 1000 live births in Europe (Loane et al., 2013) and 0.6 per 1000 in Japan (Hoshi et al., 1999). Individuals with Down syndrome are predisposed to OSA due to overlap between risk factors for OSA and common characteristics of Down syndrome, including midface hypoplasia (reduced growth around the cheekbones and eye sockets), relative macroglossia (enlarged tongue), generalized hypotonia (systemic reduced muscle tone) and raised body mass index (BMI) (Roizen & Patterson, 2003). Previous small studies using polysomnography, the gold-standard diagnostic test for OSA, in Italy and the US have reported a high prevalence of OSA in adults with Down syndrome (Italy: 83%, US: 88%) (Resta et al., 2003; Trois et al., 2009). In Japan, the estimated prevalence of OSA in adults with Down syndrome has been unclear, though studies using questionnaires and pulse oximetry indicated a high prevalence of OSA (prevalence of witnessed apneas: 32.3%, 4% oxygen desaturation index: 6.1/hour respectively) (Rahmawati et al., 2015; Sawatari et al., 2015).

OSA has been the subject of inter-ethnic comparison in a number of studies in the general population. As differences in craniofacial anatomy can predispose to OSA (Cistulli, 1996;

Sutherland, Lee, & Cistulli, 2012), OSA can be further exacerbated by differing ethnicity (Sutherland et al., 2019; Sutherland et al., 2018; Villaneuva, Buchanan, Yee, & Grunstein, 2005). In addition, ethnical differences are observed between Caucasians and Asians in the general population, likely due to the increased risk of central and/or visceral obesity in Asians, increasing the risk of OSA (Chen et al., 2016; Kritikou et al., 2013; Lear et al., 2007; Mehra et al., 2007; Yamagishi et al., 2010) To our knowledge, there have been no studies comparing the effects of ethnicity on OSA prevalence in people with Down syndrome The aim of this study was to compare the prevalence of OSA in adults with Down syndrome in two nations with differing ethnicity - Scotland (primarily Caucasian) and Japan (primarily Japanese).

2. Methods

A comparative cross-sectional study was conducted using subsets of data from two cross-sectional studies conducted contemporaneously in Scotland (ISRCTN55685305) and Japan. Both studies received individual ethical approval from the relevant local research ethics body (Scotland A Research Ethics Committee; Ethics Committee of the Faculty of Medicine at Kyushu University, Japan and Japan Down Syndrome Society). Written informed consent was not required, as return of a completed questionnaire was considered as implicit consent to participate.

In Scotland, easy-read questionnaires were sent to adults aged 16 years and older with Down syndrome and their caregivers between February 2011 and June 2014. Participants were identified and contacted by national charitable organisations supporting adults with Down syndrome (Down's Syndrome Scotland; Sleep Scotland) on behalf of the researchers to preserve anonymity.

In Japan, questionnaires were sent to children and adults with Down syndrome and their caregivers between May 2011 and September 2013. All individuals were members of the national Japan Down Syndrome Society. All responders younger than 16 years were excluded from the current analysis.

Questionnaires were completed by either the individual with Down syndrome themselves or their caregiver, depending on their intellectual ability. BMI values were calculated from weights and heights provided in the questionnaires, and classified according to standard classifications for overweight and obesity (WHOExpertConsultation, 2004). Although alternative cut-off values have been proposed to control for differing body fat compositions between European and Asian populations (Wang et al., 1994), a World Health Organization (WHO) expert review recommended that the standard cut-offs should be retained as the international classification (WHOExpertConsultation, 2004). Therefore, in this study, the degree of obesity was classified into 5 categories, regardless of ethnicity: underweight (BMI: below 18.5 kg/m^2), normal weight (BMI: 18.5 to 24.9 kg/m^2), pre-obese (BMI: 25.0 to 29.9 kg/m^2), obese class I (BMI: 30.0 to 34.9 kg/m^2), obese class II (BMI: 35.0 to 39.9 kg/m^2) and obese class III (BMI: 40.0 kg/m^2 or above).

Subjective sleepiness was rated using the English-language pictorial Epworth Sleepiness Scale (Ghiassi, Murphy, Cummin, & Partridge, 2011), or the Japanese version of the Epworth Sleepiness Scale (Takegami et al., 2009) as appropriate (referred to henceforth as (p/J)ESS). A score of 11 to 24 points on either scale indicates EDS. Symptoms of OSA (snoring, witnessed apneas, nocturnal awakenings and daytime sleepiness) were classified as frequently (5 to 7 nights/week), sometimes (1 to 4 nights/week) or rarely/never (less than 1 night/week).

Likely diagnosis of OSA was determined using previously published algorithms which have been validated in a large, cross-sectional survey the general population in France (Fuhrman, Fleury, Nguyen, & Delmas, 2012):

– Definition 1: Frequent snoring + (witnessed apneas on 1 or more nights/week or (p/J)ESS of 11 to 24 points)

– Definition 2: Frequent snoring + (witnessed apneas on 1 or more nights /week or daytime sleepiness on 1 or more nights/week)

- Likely OSA: Meets Definition 1 and/or Definition 2

The third published definition (frequent snoring + [witnessed apneas or non-restorative sleep at least three nights a week]) was not assessed as this information was not captured by the questionnaire used in Japan.

2.1. Statistical analysis

Standard statistical analyses were undertaken using SPSS Statistics 19, (IBM Corp., USA). Significance was set at $p<0.05$ and all analyses were two-tailed. All variables were checked for normality using the Kolmogorov–Smirnov test. The Chi-square test was used for discrete variables. Student's t-test was used for continuous variables and Mann-Whitney-U test for non-parametric data. Binary logistic regression and multiple regression analysis were undertaken to explore associations between variables. The model was based on clinical findings which are well established by previous studies. (Young, Skatrud, & Peppard, 2004) For the purpose of logistic analysis, OSA symptoms were analysed as binary data (i.e. presence/absence of symptoms). Results are presented as mean ± standard deviation for parametric variables, as number and percentage, or as an odds ratio with 95% confidence interval (OR [95%CI]). We calculated magnitude of confounding to determine the confounding factors using the following formula;

$$\text{Magnitude of confounding} = \left| \frac{\text{RR}_{without\ exposure} - \text{RR}_{exposure}}{\text{RR}_{exposure}} \right|$$

When the calculated value was 10% or more, we regarded the factor as confounding. In order to minimize bias, we adopted propensity score matching in this study. We matched adults with Down syndrome in Scotland and Japan according to age, BMI, and sex which are well-known confounders for OSA (Young et al., 2004). We matched participants on propensity score using the nearest participant, matching with a maximum caliber of 0.02 of the score.

3. Results

A summary of questionnaires sent, responses received and questionnaires valid for analysis is shown in Figure 1. A total of 2,752 questionnaires were sent (752 in Scotland, 2,000 in Japan) and 1,549 responses were received (56%; see Figure 1). Of the 1,549 returned questionnaires, fifty questionnaires from people in Scotland were excluded. Reasons for exclusion include questionnaires returned to sender as undeliverable (n=7), duplicate questionnaires received (n=25), declined participation (n=7), recipient deceased (n=4), questionnaire returned uncompleted (n=5), and reply sent but lost in the post (n=2). In Japan, 697 questionnaires were excluded because the participant was less than 16 years old. In total, 13 responders had a prior diagnosis of OSA and were using continuous positive airway pressure (CPAP) therapy (Scotland: n=10, Japan: n=3); these individuals were excluded from further analysis since the symptoms of OSA such as snoring, apneas, and EDS would likely be ameliorated by CPAP. The remaining 789 (29% of the total sent) questionnaires were valid for analysis – 267 (34% of total analyzed) from participants in Scotland and 522 (66% of total analyzed) from participants in Japan.

The characteristics of valid responders in Scotland and Japan are summarised in Table 1. Responders were generally young adults, 56% of whom were male. Mean (p/J)ESS scores were broadly within the normal range (pESS 7±5/24 points; JESS 7±5/24 points). No significant differences were noted between the two populations in terms of gender, (p/J)ESS or proportion of individuals exhibiting EDS. However, the Scotland population was significantly older than the Japan population ($p<0.001$), and had a higher mean BMI ($p<0.001$). Three-quarters of the group in Scotland were pre-obese or obese, in comparison with 41.1% of the individuals in Japan. Fifty-six percent of the responders in Japan met the WHO criteria for increased or high risk BMI.

Symptoms of OSA were common in both populations (Table 2). The responders in Japan were more likely to report "ever snoring" and "ever nocturnal awakening" than responders in Scotland (snoring: 67.9% vs. 79.2%, $p=0.001$; awakenings: 50.0% vs. 58.5%, $p=0.04$), while responder in Scotland more often reported "frequent snoring" and "frequent nocturnal awakenings" ($p=0.001$, $p=0.04$; respectively). "Ever witnessed apneas" were reported by around a third of responders, with no significant differences between the two groups. However, the responders in Scotland were more likely to reported witnessed apneas as "frequent" than responders in Japan ($p=0.03$). Interestingly, daytime sleepiness *per se* was more frequently reported as "Ever" and "Frequent" in the population in Scotland (both $p<0.001$), despite no significant difference in (p/J)ESS between the two groups.

Likely diagnosis of OSA in adults with Down syndrome was estimated at 19.6% in Scotland and 14.3% in Japan. Prevalence did not significantly differ between the two populations ($p=0.08$; Table 3).

Ethnic differences were assessed using multivariate analysis to evaluate the possible effects of the two significantly different confounders, age and BMI, between the two cohorts.

Logistic regression analysis for OSA symptoms and values for magnitude of confounding are summarized in Table 4. Responders in Japan had more frequent snoring and nocturnal awakenings than their counterparts in Scotland, even after adjusting for age, BMI and sex. Responders in Scotland had more frequent daytime sleepiness than responders in Japan after adjusting for age, BMI (as continuous variable) and sex. There was no significant difference in prevalence of witnessed apneas and EDS between adults with Down syndrome in Scotland or Japan. Regarding evaluation of confounding factors between the two cohorts, age was a significant confounder for snoring, daytime sleepiness, and excessive daytime sleepiness (magnitude of confounder: 18.8%, 13.0%, and 15.2%; respectively). In addition, BMI was a significant confounder for snoring, daytime sleepiness, and excessive daytime sleepiness ([Continuous value] magnitude of confounder: 56.8%, 31.0%, and 39.4%; respectively [WHO category] 43.8%, 37.1%, and 43.8%; respectively).

Differences between Scotland and Japan in terms of likely OSA are summarised in Table 5. A difference in prevalence of estimated OSA by Definition 1 (i.e. frequent snoring + [witnessed apneas ≥1 night/week or (p/J)ESS>10]) between countries was not observed in any of the models. However, although a significant ethnic difference in prevalence of estimated OSA by Definition 2 (i.e. frequent snoring with witnessed apneas on 1 or more nights/week or daytime sleepiness on 1 or more nights/week) was observed in the unadjusted model and when adjusting for age only, no difference was observed when adjusting for age and BMI. This result indicates that BMI is a significant predictor for OSA using this definition. For likely OSA (i.e. meeting the criteria for Definition 1 and/or Definition 2), a significant ethnic difference was observed when adjusting for age only. When evaluating confounders between the two cohorts, BMI was a significant confounder for Definition 1, Definition 2 and likely OSA.

Symptoms and OSA prevalence in Scotland and Japan were compared with participants were matched for the confounders age, BMI and sex. The results are shown in Table 6. The frequency of snoring and nocturnal awakenings was higher in Japan than in Scotland (p=0.03 and p=0.04; respectively). However, no differences in frequency of witnessed apnea, daytime sleepiness and the estimated prevalence of OSA (i.e., Definition 1, Definition 2, and Likely OSA) between adults in Japan and in Scotland were observed.

4. Discussion

In this first international comparative cross-sectional study of subjectively-reported prevalence of OSA and its symptoms in adults with Down syndrome, the likely overall subjective prevalence of OSA was 16.6%. Subjective prevalence of OSA was much higher in adults with Down syndrome in both countries than is noted in the general population, supporting previous reports of increased risk of OSA in adults with Down syndrome. Although high BMI was a strong predictor of prevalence of OSA in adults with Down syndrome in both Scotland and Japan, prevalence did not differ significantly between the two countries after adjustment of confounding factors such as age, sex and BMI. Ethnicity itself does not appear to significantly affect the prevalence of OSA in the adults with Down syndrome populations.

Cephalometric x-ray data in Caucasian and Japanese populations have identified a number of craniofacial features which may predispose to OSA (Villaneuva et al., 2005), and cephalometric studies have found differences between adolescents with Down syndrome and typically-developing controls of the same ethnic background (Suri, Tompson, & Cornfoot, 2010). Given that the characteristic craniofacial features observed in individuals with Down syndrome are evident regardless of ethnicity, it appears that the Down syndrome craniofacial phenotype over-rides underlying ethnicity. In this study, ethnic differences in suspected OSA

were no longer significant after adjustment for confounding factors (Table 5), supporting these previous findings. However, this study shows the prevalence of snoring in people with Down syndrome was higher in Japan than that in Scotland. This may be a reporting bias due to differing social circumstances between countries; homes in Japan are generally smaller than in Scotland, with families often sleeping in shared rooms with paper partitions, rather than individual bedrooms as is commonplace in the UK. Many people with Down syndrome live independently in the UK, and so may not have someone at home to witness apneas or snoring.

Mean BMI was much lower in adults with Down syndrome in Japan than in Scotland. A previous study in the general population (Genta, Marcondes, Danzi, & Lorenzi-Filho, 2008), comparing OSA in males of Caucasian and Japanese descent in Brazil, found that ethnicity was not associated with severity of OSA when Asian-specific obesity cut-offs were used (WHOExpertConsultation, 2004). Using these thresholds in the current study, raised BMI was a risk factor for higher prevalence of snoring and sleepiness scores, but responders in Japan had higher frequency of snoring despite lower BMI, which may reflect the effect of differences in the underlying distribution of body fat with ethnicity in the aetiology of OSA (Wang et al., 1994). Information on living arrangements was not collected during this study; previous studies have noted variation in BMI with residential status (Prasher, 1995), which may contribute to the differences in BMI observed here.

Snoring and/or intermittent nocturnal hypoxia due to apneic events during sleep are known to affect cognitive function, emotion and behaviour both in the general population and in individuals with Down syndrome (Andreou, Galanopoulou, Gourgoulianis, Karapetsas, & Molyvdas, 2002; Engleman & Douglas, 2004). People with Down syndrome are predisposed to early-onset Alzheimer's-type dementia, with neuropathological changes in the brain, such as beta-amyloid plaques and neurofibrillary tangles, evident in nearly all adults with Down

syndrome by 40 years of age (Wisniewski, Wisniewski, & Wen, 1985). It has been proposed that untreated OSA may accelerate cognitive decline in adults with Down syndrome (Fernandez & Edgin, 2013), and so early recognition and treatment of OSA may not only improve diurnal behaviour and diminish sleepiness, but may also play a role in slowing cognitive decline and improving overall quality of life. Sleep fragmentation due to snoring, apnoeic events and consequent arousals may result in a paucity of stage N3 sleep, which in turn may disrupt functioning of the glymphatic system which is responsible for clearance of toxins, including beta-amyloid and tau, from the brain (Xie et al., 2013).

It is of note that only 2% of questionnaire responders had a prior diagnosis of OSA and were receiving treatment for this, despite a likely prevalence of 17%. This may be related to diagnostic overshadowing - the belief that sleep-related breathing problems are part of the Down syndrome condition and do not merit or will not respond to treatment - or a lack of recognition of OSA symptoms in the population as a whole.

4.1. Limitations and future research

This study has limitations which are inherent in self-reported questionnaire studies, including responder bias and lack of objective data. Though the response rate was reasonable (56%), responder bias cannot be ruled out.

It is well documented that increasing age is a risk factor for OSA (Malhotra & White, 2002). However, the majority of responders in both cohorts in this study were young adults, and, therefore, the true prevalence of OSA in adults with Down syndrome may be underestimated. As life expectancy in individuals with Down syndrome continues to rise, with many adults with Down syndrome living into their 60s and 70s (Wu & Morris, 2013), this may impact on the prevalence of OSA in this population and, in turn, on healthcare services.

Future large-scale studies using polygraphy or polysomnography to objectively assess prevalence of OSA would be beneficial. Although the current study did not collect objective data, large cohort studies such as the Sleep Heart Health Study (Peppard et al., 2013; Young et al., 2002) have previously demonstrated the relationship between BMI, self-reported symptoms and polysomnographic measures in the general population, as well as changes in prevalence over time. Previous studies using polysomnography in adults with Down syndrome have reported an OSA prevalence of >80% (Resta et al., 2003; Trois et al., 2009). However, the very limited participant numbers (24 adults in total across the two studies) may not be representative of the Down syndrome population as a whole, and larger objective studies in people with Down syndrome are required.

The pictorial and Japanese translation of the ESS were used to evaluate EDS. Although similar in content, further cross-validation of these questionnaires for consistency may be appropriate, in both adults with Down syndrome and the general population.

5. Conclusions

This study is the first to compare self-reported symptoms of OSA in two ethnically diverse populations of adults with Down syndrome. Although differences were noted in symptoms of OSA between countries, the overall subjective prevalence of OSA did not differ significantly after adjustment for age, BMI and sex, and was raised in comparison with that of the general population. Very few individuals reported an existing diagnosis of OSA, and this study highlights that the clinical diagnosis of OSA in adults with Down syndrome is limited relative to the high estimated prevalence. Given the elevated prevalence of estimated OSA in adults with Down syndrome in both countries, there is a real need for this to be

addressed; in doing so, the potential for improving the health, cognitive function and quality of life of adults with Down syndrome of all ethnicities and nationalities would be enhanced.

References

Andreou, G., Galanopoulou, C., Gourgoulianis, K., Karapetsas, A., & Molyvdas, P. (2002). Cognitive status in Down syndrome individuals with sleep disordered breathing deficits (SDB). *Brain Cogn, 50*(1), 145-149. doi: 10.1016/S0278-2626(02)00019-2

Chen, X., Wang, R., Lutsey, P. L., Zee, P. C., Javaheri, S., Alcantara, C., . . . Williams, M. A. (2016). Racial/ethnic differences in the associations between obesity measures and severity of sleep-disordered breathing: the Multi-Ethnic Study of Atherosclerosis. *Sleep medicine, 26*, 46-53. doi:10.1016/j.sleep.2015.06.003

Cistulli, P. A. (1996). Craniofacial abnormalities in obstructive sleep apnoea: implications for treatment. *Respirology, 1*(3), 167-174. doi: 10.1111/j.1440-1843.1996.tb00028.x

Engleman, H. M., & Douglas, N. J. (2004). Sleep. 4: Sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. *Thorax, 59*(7), 618-622. doi: 10.1136/thx.2003.015867

Fernandez, F., & Edgin, J. O. (2013). Poor Sleep as a Precursor to Cognitive Decline in Down Syndrome : A Hypothesis. *Journal of Alzheimer's disease & Parkinsonism, 3*(2), 124-124. doi:10.4172/2161-0460.1000124

Fuhrman, C., Fleury, B., Nguyen, X. L., & Delmas, M. C. (2012). Symptoms of sleep apnea syndrome: high prevalence and underdiagnosis in the French population. *Sleep medicine, 13*(7), 852-858. doi:10.1016/j.sleep.2012.04.005

Genta, P. R., Marcondes, B. F., Danzi, N. J., & Lorenzi-Filho, G. (2008). Ethnicity as a risk factor for obstructive sleep apnea: Comparison of Japanese descendants and white males in São Paulo, Brazil. *Brazilian Journal of Medical and Biological Research, 41*(8), 728-733. doi: 10.1590/s0100-879x2008000800015

Ghiassi, R., Murphy, K., Cummin, A. R., & Partridge, M. R. (2011). Developing a pictorial Epworth Sleepiness Scale. *Thorax, 66*(2), 97-100. doi:10.1136/thx.2010.136879

Hoshi, N., Hattori, R., Hanatani, K., Okuyama, K., Yamada, H., Kishida, T., . . . Fujimoto, S. (1999). Recent trends in the prevalence of Down syndrome in Japan, 1980-1997. *Am J Med Genet, 84*(4), 340-345. doi: 10.1002/(sici)1096-8628(19990604)84:4<340::aid-ajmg6>3.0.co;2-n

Javaheri, S., Barbe, F., Campos-Rodriguez, F., Dempsey, J. A., Khayat, R., Javaheri, S., . . . Somers, V. K. (2017). Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. *Journal of the American College of Cardiology, 69*(7), 841-858. doi: 10.1016/j.jacc.2016.11.069

Jennum, P., & Riha, R. L. (2009). Epidemiology of sleep apnoea/hypopnoea syndrome and sleep-disordered breathing. *The European respiratory journal, 33*(4), 907-914. doi:10.1183/09031936.00180108

Kritikou, I., Basta, M., Tappouni, R., Pejovic, S., Fernandez-Mendoza, J., Nazir, R., . . . Vgontzas, A. N. (2013). Sleep apnoea and visceral adiposity in middle-aged male and female subjects. *The European respiratory journal, 41*(3), 601-609. doi:10.1183/09031936.00183411

Lear, S. A., Humphries, K. H., Kohli, S., Chockalingam, A., Frohlich, J. J., & Birmingham, C. L. (2007). Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *Am J Clin Nutr, 86*(2), 353-359. doi:10.1093/ajcn/86.2.353

Loane, M., Morris, J. K., Addor, M. C., Arriola, L., Budd, J., Doray, B., . . . Dolk, H. (2013). Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening. *Eur J Hum Genet, 21*(1), 27-33. doi:10.1038/ejhg.2012.94

Malhotra, A., & White, D. P. (2002). Obstructive sleep apnoea. *Lancet, 360*(9328), 237-245. doi:10.1016/S0140-6736(02)09464-3

Matsumoto, T., Murase, K., Tabara, Y., Gozal, D., Smith, D., Minami, T., . . . Chin, K. (2018). Impact of sleep characteristics and obesity on diabetes and hypertension across genders and menopausal status: the Nagahama study. *Sleep, 41*(7). doi:10.1093/sleep/zsy071

Mehra, R., Stone, K. L., Blackwell, T., Ancoli Israel, S., Dam, T. T., Stefanick, M. L., . . . Osteoporotic Fractures in Men, S. (2007). Prevalence and correlates of sleep-disordered breathing in older men: osteoporotic fractures in men sleep study. *Journal of the American Geriatrics Society, 55*(9), 1356-1364. doi:10.1111/j.1532-5415.2007.01290.x

Mirrakhimov, A. E., Sooronbaev, T., & Mirrakhimov, E. M. (2013). Prevalence of obstructive sleep apnea in Asian adults: a systematic review of the literature. *BMC pulmonary medicine, 13*, 10. doi:10.1186/1471-2466-13-10

Peppard, P. E., Young, T., Barnet, J. H., Palta, M., Hagen, E. W., & Hla, K. M. (2013). Increased prevalence of sleep-disordered breathing in adults. *American journal of epidemiology, 177*(9), 1006-1014. doi:10.1093/aje/kws342

Prasher, V. P. (1995). Overweight and obesity amongst Down's syndrome adults. *Journal of intellectual disability research, 39 (5)*, 437-441. doi: 10.1111/j.1365-2788.1995.tb00548.x

Rahmawati, A., Chishaki, A., Ohkusa, T., Sawatari, H., Hashiguchi, N., Ono, J., . . . Ando, S. I. (2015). Relationship between sleep postures and sleep-disordered breathing parameters in people with Down syndrome in Japan. *Sleep and Biological Rhythms, 13*(4), 323-331. doi:10.1111/sbr.12122

Resta, O., Barbaro, M. P., Giliberti, T., Caratozzolo, G., Cagnazzo, M. G., Scarpelli, F., & Nocerino, M. C. (2003). Sleep related breathing disorders in adults with Down syndrome. *Down's syndrome, research and practice : the journal of the Sarah Duffen Centre / University of Portsmouth, 8*(3), 115-119. doi: 10.3104/reports.138

Roizen, N. J., & Patterson, D. (2003). Down's syndrome. *Lancet, 361*(9365), 1281-1289. doi: 10.1016/S0140-6736(03)12987-X

Sawatari, H., Chishaki, A., & Ando, S. I. (2016). The Epidemiology of Sleep Disordered Breathing and Hypertension in Various Populations. *Curr Hypertens Rev, 12*(1), 12-17. doi: 10.2174/1573402112666160114093307

Sawatari, H., Chishaki, A., Nishizaka, M., Matsuoka, F., Yoshimura, C., Kuroda, H., . . . Ando, S. (2015). A nationwide cross-sectional study on congenital heart

diseases and symptoms of sleep-disordered breathing among Japanese Down's syndrome people. *Internal medicine, 54*(9), 1003-1008. doi:10.2169/internalmedicine.54.3989

Suri, S., Tompson, B. D., & Cornfoot, L. (2010). Cranial base, maxillary and mandibular morphology in Down syndrome. *The Angle orthodontist, 80*(5), 861-869. doi:10.2319/111709-650.1

Sutherland, K., Keenan, B. T., Bittencourt, L., Chen, N. H., Gislason, T., Leinwand, S., . . . Cistulli, P. A. (2019). A Global Comparison of Anatomic Risk Factors and Their Relationship to Obstructive Sleep Apnea Severity in Clinical Samples. *Journal of clinical sleep medicine : JCSM, 15*(4), 629-639. doi:10.5664/jcsm.7730

Sutherland, K., Lee, R. W. W., Chan, T. O., Ng, S., Hui, D. S., & Cistulli, P. A. (2018). Craniofacial Phenotyping in Chinese and Caucasian Patients With Sleep Apnea: Influence of Ethnicity and Sex. *Journal of clinical sleep medicine : JCSM, 14*(7), 1143-1151. doi:10.5664/jcsm.7212

Sutherland, K., Lee, R. W. W., & Cistulli, P. A. (2012). Obesity and craniofacial structure as risk factors for obstructive sleep apnoea: Impact of ethnicity. *Respirology, 17*(2), 213-222. doi:DOI 10.1111/j.1440-1843.2011.02082.x

Takegami, M., Suzukamo, Y., Wakita, T., Noguchi, H., Chin, K., Kadotani, H., . . . Fukuhara, S. (2009). Development of a Japanese version of the Epworth Sleepiness Scale (JESS) based on item response theory. *Sleep medicine, 10*(5), 556-565. doi:10.1016/j.sleep.2008.04.015

Trois, M. S., Capone, G. T., Lutz, J. A., Melendres, M. C., Schwartz, A. R., Collop, N. A., & Marcus, C. L. (2009). Obstructive sleep apnea in adults with Down syndrome. *Journal of clinical sleep medicine : JCSM, 5*(4), 317-323.

Vgontzas, A. N., Bixler, E. O., & Chrousos, G. P. (2005). Sleep apnea is a manifestation of the metabolic syndrome. *Sleep medicine reviews, 9*(3), 211-224. doi:10.1016/j.smrv.2005.01.006

Villaneuva, A. T., Buchanan, P. R., Yee, B. J., & Grunstein, R. R. (2005). Ethnicity and obstructive sleep apnoea. *Sleep medicine reviews, 9*(6), 419-436. doi:10.1016/j.smrv.2005.04.005

Wang, J., Thornton, J. C., Russell, M., Burastero, S., Heymsfield, S., & Pierson Jr, R. N. (1994). Asians have lower body mass index (BMI) but higher percent body fat than do whites: Comparisons of anthropometric measurements. *American Journal of Clinical Nutrition, 60*(1), 23-28. doi:10.1093/ajcn/60.1.23

WHOExpertConsultation. (2004). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet, 363*(9403), 157-163. doi:10.1016/S0140-6736(03)15268-3

Wisniewski, K. E., Wisniewski, H. M., & Wen, G. Y. (1985). Occurrence of neuropathological changes and dementia of Alzheimer's disease in Down's syndrome. *Ann Neurol, 17*(3), 278-282. doi:10.1002/ana.410170310

Wu, J., & Morris, J. K. (2013). The population prevalence of Down's syndrome in England and Wales in 2011. *European Journal of Human Genetics, 21*(9), 1016-1019. doi:10.1038/ejhg.2012.294

Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., . . . Nedergaard, M. (2013). Sleep Drives Metabolite Clearance from the Adult Brain. *Science, 342*(6156), 373. doi:10.1126/science.1241224

Yamagishi, K., Ohira, T., Nakano, H., Bielinski, S. J., Sakurai, S., Imano, H., . . . Tanigawa, T. (2010). Cross-cultural comparison of the sleep-disordered

breathing prevalence among Americans and Japanese. *European Respiratory Journal, 36*(2), 379-384. doi:Doi 10.1183/09031936.00118609

Young, T., Shahar, E., Nieto, F. J., Redline, S., Newman, A. B., Gottlieb, D. J., . . . Samet, J. M. (2002). Predictors of sleep-disordered breathing in community-dwelling adults: The Sleep Heart Health Study. *Archives of internal medicine, 162*(8), 893-900. doi:10.1001/archinte.162.8.893

Young, T., Skatrud, J., & Peppard, P. E. (2004). Risk factors for obstructive sleep apnea in adults. *JAMA, 291*(16), 2013-2016. doi:10.1001/jama.291.16.2013

Figure Legends

Figure 1: Flow chart.

CPAP: Continuous positive airway pressure

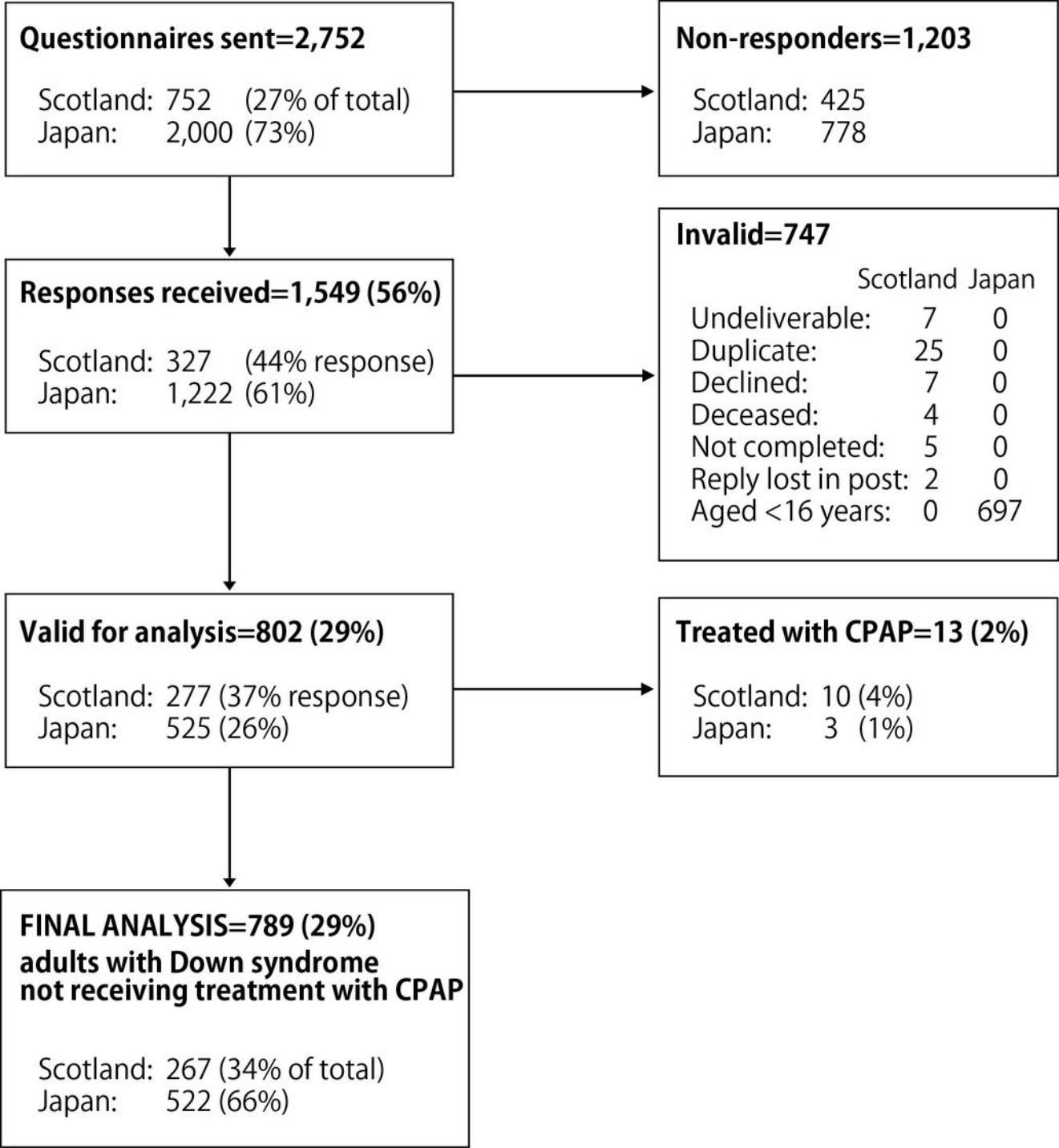
Questionnaires sent=2,752
Scotland: 752 (27% of total)
Japan: 2,000 (73%)
Non-responders=1,203
Scotland: 425
Japan: 778
Responses received=1,549 (56%)
Scotland: 327 (44% response)
Japan: 1,222 (61%)
Invalid=747
Scotland Japan
Undeliverable: 7 0
Duplicate: 25 0
Declined: 7 0
Deceased: 4 0
Not completed: 5 0
Reply lost in post: 2 0
Aged <16 years: 0 697
Valid for analysis=802 (29%)
Scotland: 277 (37% response)
Japan: 525 (26%)
Treated with CPAP=13 (2%)
Scotland: 10 (4%)
Japan: 3 (1%)
FINAL ANALYSIS=789 (29%)
adults with Down syndrome
not receiving treatment with CPAP
Scotland: 267 (34% of total)
Japan: 522 (66%)

Table 1: Anthropometric and sleep characteristics of responders in Scotland and Japan.

Characteristics	Total responses	Whole group	Scotland	Japan	p-value
Number	789	789	267	522	-
Male	780	434 (55.6)	149 (55.8)	285 (55.6)	1.00
Age, years	789	27±10	32±11	25±8	<0.001
Body mass index, kg/m^2	730	25.8±5.8	29.7±7.0	24.0±4.0	<0.001
*Underweight (<18.5 kg/m^2)	553	16 (2.9)	1 (0.5)	15 (4.3)	<0.001
*Normal weight (18.5-24.9 kg/m^2)		242 (43.8)	52 (25.4)	190 (54.6)	
*Pre-obese (25.0-29.9 kg/m^2)		177 (31.5)	63 (30.7)	111 (34.6)	
*Obese class I (30.0-34.9 kg/m^2)		76 (13.7)	47 (22.9)	29 (8.3)	
*Obese class II (35.0-39.9 kg/m^2)		29 (5.2)	26 (12.7)	3 (0.9)	
*Obese class III (40.0≤ kg/m^2)		16 (2.9)	16 (7.8)	0 (0.0)	
*Increasing but acceptable risk (18.5-22.9 kg/m^2)	348	-	-	136 (39.1)	-
*Increased risk (23.0-27.4 kg/m^2)		-	-	125 (35.3)	
*Higher risk (≥27.5 kg/m^2)		-	-	74 (21.3)	
Epworth Sleepiness Score, points	691	7±5	7±5	7±5	0.39
Excessive daytime sleepiness (ESS>10/24), n (%)	691	134 (19.4)	46 (20.0)	88 (19.1)	0.76

Results are shown as mean±SD or number (%) as appropriate.

*WHO BMI categories valid for individuals aged 20 years and older only.

Table 2: Prevalence of obstructive sleep apnea related symptoms in adults with Down syndrome in Scotland and Japan.

Characteristics	Total responses	Whole group	Scotland	Japan	p-value
Snoring, n (%)					
Ever	741	560 (75.6)	163 (67.9)	397 (79.2)	0.001
Frequently		154 (20.8)	57 (23.8)	97 (19.4)	
Sometimes		406 (54.8)	106 (44.2)	300 (59.9)	<0.001
Rarely/never		181 (24.4)	77 (32.1)	104 (20.8)	
Witnessed apneas, n (%)					
Ever	565	183 (32.4)	57 (34.8)	126 (31.4)	0.49
Frequently		48 (8.5)	22 (13.4)	26 (6.5)	
Sometimes		135 (23.9)	35 (21.3)	100 (24.9)	0.03
Rarely/never		382 (67.6)	107 (65.2)	275 (68.6)	
Nocturnal awakenings, n (%)					
Ever	727	405 (55.7)	118 (50.0)	287 (58.5)	0.04
Frequently		81 (11.1)	35 (14.8)	46 (9.4)	
Sometimes		324 (44.6)	83 (35.2)	241 (49.1)	0.001
Rarely/never		322 (44.3)	118 (50.0)	204 (41.5)	
Daytime sleepiness, n (%)					
Ever	771	308 (39.9)	136 (53.8)	172 (33.2)	<0.001
Frequently		49 (6.4)	38 (15.0)	11 (2.1)	
Sometimes		259 (33.6)	98 (38.7)	161 (31.1)	<0.001
Rarely/never		463 (60.1)	117 (46.2)	349 (66.8)	

Ever: 1 night or more/week; Rarely/never: less than 1 night/week; Sometimes: 1 to 4 nights/week; Frequently: 5 to 7 nights/week

Table 3: Subjective prevalence of obstructive sleep apnea.

Criteria for likely OSA	Total responses	Whole group	Scotland	Japan	p-value
Definition 1 *	717	95 (13.2)	36 (15.5)	59 (12.2)	0.13
Definition 2 **	726	112 (15.4)	46 (19.6)	66 (13.4)	0.04
Likely OSA ***	725	116 (16.6)	46 (19.6)	70 (14.3)	0.08

Results are shown as number (%)

* Definition 1: Frequent snoring with witnessed apneas on 1 or more nights/week or (p/J)ESS 11 to 24 points.

** Definition 2: Frequent snoring with witnessed apneas on 1 or more nights/week or daytime sleepiness on 1 or more nights/week.

*** Likely OSA: Meets criteria on one or both algorithms.

Table 4: Ethnic differences in symptoms of obstructive sleep apnea in adults with Down syndrome in Scotland and Japan.

(A) Snoring

	Model 1		Model 2		Model 3		Model 4	
	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value
BMI (continuous)								
Scotland	0.56 (0.39-0.78)	0.001	0.69 (0.48-1.00)	0.049	0.44 (0.28-0.68)	<0.001	0.42 (0.28-0.65)	<0.001
MC	-		18.8%		56.8%		4.8%	
BMI (WHO category)								
Scotland	0.56 (0.39-0.78)	0.001	0.69 (0.48-1.00)	0.049	0.48 (0.30-0.77)	0.002	0.44 (0.27-0.72)	0.001
MC	-		18.8%		43.8%		9.1%	

(B) Witnessed apneas

	Model 1		Model 2		Model 3		Model 4	
	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value
BMI (continuous)								
Scotland	1.16 (0.79-1.71)	0.44	1.26 (0.84-1.89)	0.26	1.14 (0.71-1.82)	0.58	1.12 (0.70-1.79)	0.64
MC	-		7.9%		10.5%		1.8%	
BMI (WHO category)								
Scotland	1.16 (0.79-1.71)	0.44	1.26 (0.84-1.89)	0.26	1.17 (0.70-1.96)	0.55	1.14 (0.68-1.92)	0.61
MC	-		7.9%		7.7%		2.6%	

(C) Nocturnal awakenings

	Model 1		Model 2		Model 3		Model 4	
	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value
BMI (continuous)								
Scotland	0.71 (0.52-0.97)	0.03	0.72 (0.51-1.00)	0.052	0.68 (0.46-1.00)	0.048	0.68 (0.46-1.00)	0.0496
MC	-		1.4%		5.9%		0.0%	
BMI (WHO category								
Scotland	0.71 (0.52-0.97)	0.03	0.72 (0.51-1.00)	0.052	0.60 (0.40-0.92)	0.02	0.61 (0.40-0.93)	0.02
MC	-		1.4%		20.0%		1.6%	

(D) Daytime sleepiness

	Model 1		Model 2		Model 3		Model 4	
	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value
BMI (continuous)								
Scotland	2.34 (1.72-3.18)	<0.001	2.07 (1.49-2.87)	<0.001	1.58 (1.08-2.31)	0.02	1.55 (1.05-2.28)	0.03
MC	-		13.0%		31.0%		1.9%	
BMI (WHO category								
Scotland	2.34 (1.72-3.18)	<0.001	2.07 (1.49-2.87)	<0.001	1.51 (1.01-2.28)	0.046	1.46 (0.96-2.22)	0.08
MC	-		13.0%		37.1%		3.4%	

(F) Excessive daytime sleepiness (ESS>10/24)

	Model 1		Model 2		Model 3		Model 4	
	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value
BMI (continuous)								
Scotland	1.06 (0.71-1.58)	0.78	0.92 (0.60-1.42)	0.72	0.66 (0.39-1.10)	0.11	0.64 (0.38-1.07)	0.09
MC	-		15.2%		39.4%		3.1%	
BMI (WHO category								
Scotland	1.06 (0.71-1.58)	0.78	0.92 (0.60-1.42)	0.72	0.64 (0.36-1.13)	0.12	0.59 (0.33-1.06)	0.08
MC	-		15.2%		43.8%		8.5%	

Model 1: unadjusted; Model 2: adjusted for age; Model 3: adjusted for age and BMI; Model 4: adjusted for age, BMI, and sex.

For analysis using WHO BMI categories, adults who were under 20 years old were excluded since these categories do not apply to this age group.

MC: Magnitude of confounding

Table 5 Ethnic differences in subjective prevalence of obstructive sleep apnea in adults with Down syndrome in Scotland and Japan

(A) Definition 1

	Model 1		Model 2		Model 3		Model 4	
	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value
BMI (continuous)								
Scotland	1.33 (0.85-2.08)	0.22	1.39 (0.86-2.24)	0.18	0.92 (0.52-1.62)	0.76	0.88 (0.50-1.56)	0.67
MC	-		4.3%		51.1%		4.5%	
BMI (WHO category								
Scotland	1.33 (0.85-2.08)	0.22	1.39 (0.86-2.24)	0.18	1.01 (0.54-1.88)	0.98	0.95 (0.51-1.77)	0.87
MC	-		4.3%		37.6%		6.3%	

(B) Definition 2

	Model 1		Model 2		Model 3		Model 4	
	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value
BMI (continuous)								
Scotland	1.57 (1.04-2.37)	0.03	1.69 (1.09-2.63)	0.02	1.08 (0.64-1.82)	0.78	1.03 (0.61-1.74)	0.90
MC	-		7.1%		56.5%		4.9%	
BMI (WHO category								
Scotland	1.57 (1.04-2.37)	0.03	1.69 (1.09-2.63)	0.02	1.16 (0.65-2.07)	0.61	1.09 (0.61-1.95)	0.76
MC	-		7.1%		45.7%		6.4%	

(C) Likely OSA

	Model 1		Model 2		Model 3		Model 4	
	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value	OR (95% Cl)	p-value
BMI (continuous)								
Scotland	1.46 (0.97-2.20)	0.07	1.57 (1.02-2.42)	0.04	1.01 (0.60-1.69)	0.97	0.97 (0.58-1.63)	0.91
MC	-		7.0%		55.4%		4.1%	
BMI (WHO category								
Scotland	1.46 (0.97-2.20)	0.07	1.57 (1.02-2.42)	0.04	1.07 (0.61-1.89)	0.81	1.01 (0.57-1.78)	0.98
MC	-		7.0%		46.7%		5.9%	

Definition 1: Frequent snoring with witnessed apneas on 1 or more nights/week or (p/J)ESS 11 to 24 points.

Definition 2: Frequent snoring with witnessed apneas on 1 or more nights/week or daytime sleepiness on 1 or more nights/week.

Likely OSA: Meets criteria on one or both algorithms.

Model 1: unadjusted; Model 2: adjusted for age; Model 3: adjusted for age and BMI; Model 4: adjusted for age, BMI, and sex.

For analysis using WHO BMI categories, adults who were under 20 years old were excluded since these categories do not apply to this age group.

MC: Magnitude of confounder

Table 6. Ethnic differences in symptoms and prevalence of obstructive sleep apnea in the matched adults with Down syndrome in Scotland and Japan.

	Total responses	Scotland	Japan	p-value
Number	327	164	163	-
Snoring, n (%)	313	105 (68.6)	128 (80.0)	0.03
Apnea, n (%)	233	41 (38.7)	41 (32.3)	0.34
Nocturnal awakenings, n (%)	301	72 (49.3)	95 (61.3)	0.04
Daytime sleepiness, n (%)	317	72 (46.8)	63 (38.7)	0.17
Definition 1, n (%)	303	23 (15.6)	23 (14.7)	0.87
Definition 2, n (%)	308	28 (18.7)	24 (15.2)	0.45
Likely OSA, n (%)	308	28 (18.7)	26 (16.5)	0.65

Matched for age, BMI as continuous variable and sex

Definition 1: Frequent snoring with witnessed apneas on 1 or more nights/week or (p/J)ESS 11 to 24 points.

Definition 2: Frequent snoring with witnessed apneas on 1 or more nights/week or daytime sleepiness on 1 or more nights/week.

Likely OSA: Meets criteria on one or both algorithms.