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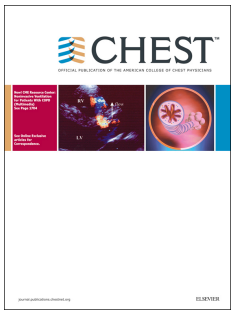

Genetic Ancestry for Sleep Research: Leveraging Health Inequalities to Identify Causal Genetic Variants

Bharati Prasad, MD, MS, Richa Saxena, PhD, Namni Goel, PhD, Sanjay R. Patel, MD, MS

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Bharati Prasad MD, MS[1], Richa Saxena PhD[2,3], Namni Goel PhD[4], Sanjay R. Patel MD, MS[5]

1 Department of Medicine, University of Illinois at Chicago and Jesse Brown VA Medical Center, Chicago, IL

2. Center for Genomic Medicine and Department of Anesthesia, Pain, and Critical Care Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA

3. Program in Medical and Population Genetics, Broad Institute, Cambridge, MA

4. Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

5. Department of Medicine, University of Pittsburgh, Pittsburgh PA

Corresponding Author:
Bharati Prasad, MD, MS
840 S Wood Street, MC 719
Chicago, IL 606012
bpradsad@uic.edu

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Abbreviations: OSA = obstructive sleep apnea, AA= African American, HA = Hispanic American, EA= European American, REM= rapid eye movement, OR = odds ratio, AHI = apnea-hypopnea index, SES = socioeconomic status, HLA = human leukocyte antigen, MSLT = multiple sleep latency test, CRSD = circadian rhythm sleep disorders, GWAS = genome-wide association study

Abstract:

Recent evidence has highlighted the health inequalities in sleep behaviors and sleep disorders that adversely impact outcomes in select populations, including African Americans and Hispanic Americans. Race-related sleep health inequalities are ascribed to differences in multilevel and interlinked health determinants, such as sociodemographic factors, health behaviors and biology. African Americans and Hispanic Americans are admixed populations whose genetic inheritance combines two or more ancestral populations originating from different continents. Racial inequalities in admixed populations can be parsed into relevant groups of mediating factors (environmental versus genetic) with the use of measures of genetic ancestry, the proportion of an individual's genetic make-up that comes from each of the major ancestral continental populations. This review describes sleep health inequalities in African Americans and Hispanic Americans and considers the potential utility of ancestry studies to exploit these differences to gain insight into the genetic underpinnings of these phenotypes. The inclusion of genetic approaches in future studies of admixed populations will allow greater understanding of the potential biological basis of race-related sleep health inequalities.

Sleep Health Inequalities: Introduction and Current Relevance

Sleep science has evolved rapidly in the recent decades, from refining methods to measure sleep in humans to gaining understanding of the pathophysiology and significant health impact of sleep disorders. This knowledge has led to the realization that remarkable health inequalities exist in sleep behaviors and sleep disorders. The World Health Organization (WHO) defines health inequalities "as differences in health status or in the distribution of health determinants between different populations" that is attributable to biological or sociocultural (voluntary) variations[1]. A multitude of important health determinants exist in all populations with complex interrelationships, including socioeconomic status, literacy, geographic location, age, gender, race, individual behavior and biology[2]. Accumulating evidence highlights the association of self-identified race with sleep health inequalities[3-5]. Racial differences in health outcomes are often due to cultural, social, economic, and environmental inequalities that have persisted for generations. For example, neighborhood disadvantage has been found to be a risk factor for pediatric obstructive sleep apnea (OSA),[6] and acculturation has important effects on sleep duration[7]. However, in certain cases, racial inequalities can also be due to heritable biological differences in risk that have a genetic underpinning. If the frequency of a genetic risk factor varies substantially across ancestral populations originating from different continents (e.g., Africans, Europeans, Native Americans), this variability can be exploited through the study of admixed populations whose genetic inheritance combines two or more ancestral populations. By correlating phenotype with genetic inheritance from the high-risk ancestral population, the location of the predisposing genetic alleles can be more readily identified. Thus, genetic studies of admixed populations (those who have descended from more than one ancestral population) can be a powerful tool for understanding the genetic underpinnings of biological traits including sleep-related phenotypes. To the extent that biology (rather than social, cultural, environmental,

and economic differences) underlies racial inequalities, genetic studies of admixed populations may also provide insights into the causes of racial health inequalities.

In this review, we discuss the current evidence on racial health inequalities in common sleep disorders focusing on reports in admixed populations in particular: African Americans, (AAs) who have a mixture of African and European ancestry, and Hispanic Americans (HAs), who have a mixture of African, European, and Native American ancestry compared to European Americans (EAs). Further, we outline how inclusion of genetic ancestry and techniques such as admixture mapping in association studies can improve scientific inference and identify novel genetic susceptibility loci contributing to variability in sleep phenotypes.

Inequalities in Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a chronic disease with a rising prevalence and considerable attendant morbidity[8,9]. Similar to other chronic diseases such as hypertension, there is significant heterogeneity among individuals with OSA in terms of pathophysiology and health outcomes[10,11]. An underlying factor that contributes to this heterogeneity is racial inequalities in prevalence, risk, and outcomes of OSA (summarized in Table 1). Epidemiological studies in the United States report the prevalence of OSA is greater among AAs and HAs compared to EAs. The relative risk of OSA in AAs is moderated by age, with the highest risk being noted in children and a resurgence of risk after the age of 65 years[4,12-15]. The conflicting data regarding higher prevalence in middle-aged AAs may be due to the underrepresentation of minorities in larger prospective cohorts and the use of different methods to define OSA, from questionnaires to different quantitative measures[16,17]. An important replicated finding is that AAs have more severe OSA, based on quantitative metrics such as apnea hypopnea index (AHI) and oximetry, after adjustment for obesity[18-21]. However, these studies were performed in clinical populations where bias related to access to care and delays in diagnosis may have confounded

the results[22]. While this inequality has not been specifically examined in population-based cohorts, a similar trend is suggested by the Multi-Ethnic Study of Atherosclerosis (MESA), in which the odds ratios (ORs) for mild, moderate and severe OSA in AAs compared to EAs showed a linear trend towards increasing risk from 1.03 to 1.35[4]. In fact, a statistically significant increase in risk was observed only for symptomatic OSA regardless of severity, suggesting a higher burden of disease[4]. An older meta-analysis indicates that the independent effect of AA race on OSA risk and severity is small (effect sizes 0.13 and 0.10, respectively) but AAs with OSA have significantly shorter sleep duration (effect size -0.30)[23]. Considering the chronic complex nature of OSA, with multiple fixed (age, sex, craniofacial anatomy) and modifiable (obesity) risk factors, this effect size is likely to be clinically significant[24,25].

There are fewer comparative studies on OSA prevalence between HAs and EAs. A previous report from a community cohort indicated a three-fold higher prevalence of moderate to severe OSA in HAs[16]. In the MESA cohort, HAs had higher risk of mild, moderate and severe OSA (OR 1.6, 1.9, and 2.1, respectively). In contrast with observations in AAs, the prevalence of symptomatic OSA was not significantly higher in HAs[4]. A recent report from the large Hispanic Community Health Study found the prevalence of OSA (approximately 26%, 10% and 4% for mild, moderate and severe disease, respectively) to be at least as high as studies from predominantly EA cohorts[8,26]. This study used home sleep apnea testing to assess OSA and included participants of seven Hispanic/Latino backgrounds, and significant differences in the prevalence of moderate to severe OSA were found in men across diverse Hispanic backgrounds even after adjustment for age and obesity. Elderly and post-stroke HAs are at higher risk for OSA compared to their EA counterparts[27,28]. In contrast, data from a community pediatric cohort found no difference in the prevalence of OSA between HA and EA children[29].

Consistent with the inequalities in OSA discussed above, poorer health outcomes have been reported in AAs and HAs compared to EAs with OSA. AAs with OSA symptoms report higher rates of excessive daytime sleepiness as well as poorer sleep quality and physical health[30-32]. Elderly AAs have higher rates of abnormal 24-hour blood pressure profiles (nocturnal non-dipping blood pressure), independent of obesity and severity of OSA[33]. Observational data from a clinical cohort and a general population survey suggest the risk of hypertension is higher in AAs[34,35]. In contrast, the risk of hypertension in OSA was not found to vary significantly by race in the Sleep Heart Health Study, a younger community-based predominantly EA cohort[36]. Severe OSA is associated with risk of peripheral arterial disease only in AAs[37]. Within AAs, OSA is independently associated with higher prevalence of hypertension, diabetes and in women with cellular senescence (telomere shortening)[38,39]. Moderate to severe OSA has been associated with abnormal fasting glucose levels in AAs and EAs but not HAs[40]. However, HAs with moderate to severe OSA report poorer mental health and are at increased risk for diabetes[26,31,41].

The mechanisms underlying these racial inequalities in OSA are not well understood. Obesity is the strongest risk factor for OSA and is rooted in both environmental and genetic factors, varying significantly by race[42,43]. Although the association of genetic risk loci for obesity with OSA traits remain to be described, it is plausible that racial inequalities in OSA are mediated in part by genetic and environmental factors that drive higher rates of obesity in AAs and HAs. The majority of studies in OSA adjust for BMI, but while the heritability estimates for BMI in AAs are similar to EAs, the role of fat distribution (parapharyngeal and abdominal fat) remains unclear[44,45]. There are two recent reports identifying novel OSA genetic risk loci with genome-wide significance in HAs[46] and another quantitative trait locus for non-rapid eye movement sleep AHI in men of diverse racial backgrounds[47]. In contrast, genome-wide association studies (GWAS) in EAs and AAs have not yet identified any OSA genetic loci

meeting genome-wide significance criteria though the sample sizes used have been smaller and this remains an area of active investigation. Linkage analyses and candidate gene studies have reported differences in OSA risk loci between AAs and EAs, but the sample sizes for replication have been underpowered[44,45,48,49]. There are few studies examining the role of craniofacial characteristics as an explanatory factor in racial OSA inequalities. While brachycephaly is an important mediator of OSA risk in EA, enlarged tongue and soft tissue are reported to mediate the propensity for OSA in AAs[50-52]. Although AAs have smaller upper airway dimensions, the heritability of this trait in AAs is similar to EAs[24]. There is little data regarding racial differences in OSA phenotypes with respect to respiratory control, upper airway collapsibility and arousal threshold or racial differences in the physiological responses to perturbations in OSA (chronic intermittent hypoxia, sleep fragmentation and sympathetic activation). AAs have lower vital capacity and more hypoxemic attenuation of baroresponse in sleep than EAs[12,53], but these results have not been replicated, so the implications of these findings remain unclear.

In summary, the prevalence and severity of OSA is higher in AA's and likely in HA's, independent of obesity. Thus far, limited data indicate that the risk of adverse health outcomes such as daytime sleepiness and cardiometabolic outcomes may also be higher in these populations. It is important to note that socioeconomic status (SES), neighborhood disadvantage, and poverty have been shown to mediate the elevated risk of OSA in AAs, underscoring the importance of considering and controlling for psychosocial factors in future studies of racial inequalities[54-56].

Inequalities in Insomnia

Overall, minorities are at a higher risk for insomnia compared to EAs[57,58]. When self-reported insomnia is examined specifically in AA (and in HAs in some studies), the prevalence is either lower than in EAs or largely explained by SES and psychosocial stressors[23,59-65]. The

importance of SES as a mediator of sleep quality can also be gleaned from two studies done on college students, in which education and health between racial groups should be comparable. These studies used validated questionnaires and found equivalent or lower prevalence of insomnia in AAs[66,67]. On the other hand, physician-diagnosed insomnia rates, sleep quality by validated questionnaires and quantitative measures indicate poorer sleep quality, particularly in urban AAs[60,68-71]. Thus, racial inequalities related to insomnia reveal paradoxical findings, which highlight the role complex mediators and cultural beliefs may play on self-reported symptoms (Table 2). In addition to the consideration of the multilevel factors noted above and their interactions, future use of high throughput wearable technologies and genetic ancestry to add quantitative measures of sleep quality, bio-geographical ancestry to population surveillance and clinical association studies will advance our understanding of racial inequalities in insomnia.

Inequalities in Narcolepsy

Narcolepsy is a rare, central disorder of hypersomnolence characterized by excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis, and abnormal rapid eye movement (REM) sleep, and is caused by a lack of hypocretin/orexin[72]. Genetic studies of narcolepsy reveal certain commonalities and differences across racial populations including AAs and EAs (Table 3). In most, but not all studies[73], AAs are more frequently DRB1*15 (DR2) negative than EAs[74-76]. A number of studies have shown the human leukocyte antigen (HLA) DQB1*0602 rather than DRB1*15 (DR2) is the unifying, most strongly associated susceptibility allele across racial groups including AAs and EAs[75-79]. In AAs, the association is stronger with DQB1*06:02 since linkage disequilibrium, the nonrandom pattern of association between alleles at different loci within a population, is not as high between DQB1*0602 and DRB1*1501, indicating greater independence of these alleles [76,78]. Significant effects of other HLA-DQ alleles also have been reported across racial groups. In AAs, narcolepsy is associated with

DQB1*0602 haplotypes bearing distinct DRB1 alleles, most commonly DRB1*1503, DRB1*1501, DRB1* 1101, and DRB1*0806[80]. In addition, the DRB1*13, DQA1*0103, and DQB1*0603 haplotypes confer moderate protection in EAs and AAs[78].

Beyond the HLA genes, other risk genes have also been implicated in the development of narcolepsy in various racial/ethnic groups (Table 3). Associations between narcolepsy and polymorphisms in the *TCRA* locus[81], in the *P2RY11* gene[82], and in the *EIF3G* gene[83] have been found in AAs and EAs.

A few studies conducted to date have investigated the prevalence and clinical phenotypic expression of narcolepsy by race. The prevalence of DQB1*0602 in narcolepsy was much higher in AAs than in EAs[72,80], although in normal healthy adult sleepers, the prevalence of this risk allele did not differ significantly between these racial groups[84]. Notably, heterozygous or homozygous DQB1*0602 allele status influenced risk and disease expression in AAs and EAs[79,85]. Thus, frequency differences of the DQB1*0602 risk haplotype in racial groups indicate environmental factors contribute to the development of narcolepsy and thus may explain differences in narcolepsy prevalence. Indeed, two studies found a higher prevalence of diagnosed narcolepsy with cataplexy in AAs compared with EAs[86,87]. In narcoleptics with cataplexy, AAs and EAs showed similar symptomatology, age of onset, and symptom severity, but had minor differences in severe sleep paralysis, reports of cataplexy affecting the jaw and arms and being triggered by negative emotions, and reports of going blank due to sleep attacks[88]. In general clinic and hypersomnia groups, AAs, compared to EAs were 2.8-4.0 times as likely to have a sleep-onset REM period on polysomnography, after controlling for other significant variables[89]. Another study found that sex ratio, polysomnographic and multiple sleep latency test (MSLT) measures did not differ between AAs and EAs, although AAs with narcolepsy had higher DQB1*0602 positivity, earlier symptom onset and more severe daytime

sleepiness[72]. AAs also had lower cerebrospinal fluid hypocretin-1 levels and lower rates of cataplexy[72,90].

Beyond racial differences, there is a paucity of research for other health inequalities in narcolepsy. One study found a higher prevalence of diagnosed narcolepsy with cataplexy in households with lower educational attainment and lower annual income[87]. Another study found students with a history of adverse childhood experiences had higher mean scores on subjective sleep disorder measures of narcolepsy than those without such experiences[91]. Longitudinal studies among diverse populations are needed to understand this association and to investigate potential racial inequalities in the strength of this association[92].

In summary, there are well established racial differences in narcolepsy, with genetic underpinnings. Since both environmental and genetic factors underlie racial inequalities, genetic ancestry is an ideal method for future studies in AAs and other admixed groups with narcolepsy to parse the genetic aspects of race from the cultural, behavioral, and social aspects that may underlie observed phenotypic differences. Such parsing could facilitate symptom identification and diagnosis of narcolepsy.

Inequalities in Chronotype, Circadian Parameters and Circadian Rhythm Sleep Disorders

Chronotype (also referred to as morningness-eveningness or diurnal preference), which shows considerable inter-individual variation, is the tendency to be an early “lark” (alert and preferring to be active early in the day) or a late “owl” (alert and preferring to be active later in the day). Several studies have found racial differences in chronotype and associated circadian parameters (Table 4). Further, chronotype differences have been found between HA subgroups[93] and between Europeans and Africans[94,95]. Using experimental studies, Eastman and colleagues found robust differences between AAs and EAs in basic properties of the circadian clock, including endogenous or free-running circadian period and the magnitude of

phase advances and delays, which can contribute to morningness-eveningness, with self-identification techniques[96,97]. Using genetic ancestry, differences in circadian period, chronotype and responses to shifts in the sleep-wake cycle, between these two racial groups have been reported[98-100]. Of interest, circadian period correlated with percentage of African and European genetic ancestry, whereby longer circadian periods were associated with a greater percentage of European ancestry and a smaller percentage of African ancestry. There was also sex by ancestry differences: EA women had a shorter circadian period than men, but there was no sex difference in circadian period between AA men and women. The aforementioned racial differences suggest there could be racial inequalities in disease risk, in response to jet lag or shiftwork and/or in the development of circadian rhythm based sleep disorders (CRSDs)[94,95,97,100]. In contrast to chronotype or circadian parameters, however, there are no published studies of racial inequalities in CRSDs, which are extreme clinical variants of chronotype, and include advanced and delayed sleep phase disorders.

The genetic underpinnings of chronotype and CRSDs have been well studied, although only a few studies have examined racial differences in core circadian clock genes. Three GWASs have identified genetic components of chronotype, although all used European ancestry populations[101,102], and nearly all candidate gene studies of chronotype or advanced and delayed sleep phase disorders have used individuals of European or Asian ancestry, with little investigation of admixed groups such as AAs or HAs[102,103]. Of note, two studies have found racial differences in the frequencies of polymorphisms of core clock genes associated with chronotype and with CRSDs[104,105].

In summary, despite extensive knowledge of the genetics of chronotype and CRSDs, studies examining racial differences are limited but promising. Given such findings, a better understanding of the prevalence of circadian rhythm perturbations by race and the extent to

which genetic differences underlie racial differences in phenotypes such as chronotype and circadian period are critical areas of health inequalities research.

Genetic Ancestry and Admixture Mapping: Application in Understanding Sleep Health Inequality

Although outside the scope of this review, the importance of social determinants of health in mediation of racial health inequalities must be emphasized. With respect to inequalities in health behaviors, polygenic traits and chronic diseases, social determinants of health such as education, lifestyle, living and work situations, income, environmental pollution, public policy, discrimination, and psychosocial stress can have a profound impact and should be considered in research and in practice[106]. As an overview, a schematic conceptual model is presented (Figure 1) outlining the multilevel genesis of racial sleep health inequalities.

DNA sequence is identical across more than 99.4% of sites across the human genome, and genetic diversity ranges widely across human populations, being greatest among populations with recent African ancestry [107]. The genomes of continental populations since the migration of humans out of Africa have diverged primarily because of genetic drift or natural random fluctuations of allele frequencies, with some contribution from natural selection acting differentially across continental populations and from the emergence of new population-specific mutations[108]. Admixed populations such as AAs and HAs, with recent ancestry from two or three continental populations, bring together combinations of these diverse genomes, and therefore carry substantial genetic variation that can contribute to phenotypic traits and health inequalities[109,110]. Genetic ancestry in admixed AAs and HAs can be measured reliably using as few as 400 Ancestry Informative Markers (AIMs)[111], which are single nucleotide polymorphisms that vary widely in allele frequency across ancestral populations from different continents. Analysis of these markers in combination provides estimates of the proportion of ancestry from

each contributing ancestral population, or average 'global ancestry' across the genome[112,113]. For example, AAs typically have ~80% recent African and ~20% recent European ancestry, whereas African, European and Amerindian ancestry proportions vary widely in HAs based on different admixture events and the number of generations since the admixture event[107,114]. As genome-wide genotypes become more readily available, global genetic ancestry is increasingly calculated using genome-wide data, which provides improved accuracy to differentiate between closely-related populations compared to specifically selected AIMs[111].

Genetic ancestry is a powerful tool to search for biological contributions to health inequalities in admixed populations[110]. Association of global ancestry estimates with sleep disorder prevalence and severity, or with differential response to sleep medications, signals that ancestry-specific risk or protective genetic factors are present. Importantly, ancestry-directed studies searching for genetic factors need to adequately control for other risk and social factors such as socioeconomic status[115]. Further, statistical power will depend on heritability of the trait, strength of ancestry-specific effects and sample size. For example, African genetic ancestry estimated by ~1700 AIMs in 70 AAs was found to be associated with highly heritable indices of sleep depth (slow-wave sleep and delta power) but this study may have been underpowered to detect genetic ancestry effects in less heritable sleep duration and sleep efficiency traits[116].

If prevalence and severity of a sleep trait vary by ancestry, admixture mapping can identify genomic regions that track with disease in one ancestral population[117]. Admixture mapping relies on the concept of 'local ancestry', where the ancestral origin of each chromosomal segment in the mosaic genome of an individual can be quantified on the basis of polymorphisms with highly differentiated allele frequencies in the ancestral populations[118]. In a case only admixture mapping study design, affected individuals from an admixed population are scanned for regions of the genome that deviate in local ancestry from genome-wide averages.

In a case-control study design or for quantitative traits, regression models are used to test the association of local ancestry with disease status or trait levels[117]. Admixture mapping has been used successfully to identify genetic associations for several traits, e.g. multiple sclerosis[119], chronic kidney disease[120] and pharmacogenetics of relapse of acute lymphocytic leukemia[121]. Advantages of admixture mapping include: 1) the requirement of low-density genomic coverage to identify genetic signals, leading to a lower multiple testing burden relative to GWAS; 2) the ability to aggregate evidence from multiple independently associated variants in a region of local ancestry, even if these variants are not directly genotyped; and 3) the opportunity to detect regions with functional variants that have undergone selection in one of the ancestral populations. However, admixture mapping requires follow-up genotyping and association testing to identify specific contributing genetic variants in the identified regions. Further, analysis for some HA groups remain challenging, because computational methods that detect three-way admixture are rare, and ancestral populations for HAs are often not well known or represented in public sequence datasets[122,123].

Newer methods combine independent association evidence from admixture mapping with single variant association tests in admixture-informed GWAS to enhance the power to detect novel genetic signals in admixed populations[124,125], or can identify new gene-gene or gene-environment interactions that arise based on the new combination of genomes or environmental contexts in admixed populations[126], and these could be useful tools in the effort to identify biological contributors to sleep inequalities in AA and HA populations.

Beyond gene discovery, follow up studies of newly discovered sleep disorder loci in AA and HA populations are expected to be useful to: 1) test if genetic effects for sleep disorders generalize or are consistent across different US populations[127]; 2) fine-map or narrow the genomic interval in which causal variants lie[128]; 3) estimate polygenic risk for sleep disorders or pharmacogenetic response to medications that may have implications for personalized

screening, prevention or therapy in AA and HA populations[129]; and 4) investigate the impact of sleep genetic factors on related comorbidities that contribute to health inequality.

Conclusions

Substantial inequalities exist in a wide range of sleep phenotypes and sleep disorders that may contribute to overall health inequalities given the impact of poor sleep on a wide range of psychiatric, neurocognitive, metabolic and cardiovascular health outcomes. Exploiting these inequalities in admixed populations such as AAs and HAs may prove to be a powerful tool to identify underlying genetic variants predisposing to sleep disorders, thereby providing important insights into the molecular pathogenesis of these diseases. For admixture studies to be statistically robust in identifying causal genetic variants, the studies must control for cultural, socioeconomic, or other environmental differences and be adequately powered to detect differences in risk between ancestral populations due to differences in the prevalence of the causal genetic variants. Our current understanding of OSA and insomnia both in terms of the magnitude of health inequalities and the extent to which these inequalities are due to genetic variants suggest that very large sample sizes will be required for ancestry studies to be helpful. In contrast, ancestry studies in narcolepsy and circadian rhythm sleep disorders/chronotype, because they putatively have a much larger genetic underpinning, may be more fruitful. Future studies using admixture-informed approaches hold great promise in identifying and ultimately addressing biological contributions to sleep health inequalities in these settings. Furthermore, because sleep health inequalities result in a disproportional impact on health in minority populations, it is vital that future genetic studies include these racial groups so that subsequent knowledge gained from such research can be applied directly to those populations who would derive the greatest benefit.

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Table 1. Health Inequalities in Sleep Apnea					
Risk and Severity of Sleep Apnea					
Author/Ref #	**Year**	**Study Design**	**Sample**	**Measurements**	**Results**
Ancoli-Israel[13]	1995	Cross-sectional, n= 400	>65 years old, population based cohort	HSAT	AA race was associated with two fold increased risk of severe OSA.
Kripke[16]	1997	Cross-sectional, n= 355	40-64 years, population based cohort	Home oximetry	Prevalence of OSA was three times higher in HA, AA and Other (mostly Asian) race.
Redline[12]	1997	Cross-sectional, n= 847	2-86 years, genetic-epidemiology cohort	HSAT	Prevalence of OSA was higher in younger AAs (< 25 years, adjusted OR 1.8).
Redline[15]	1999	Cross-sectional, n= 399	2-18 years, genetic-epidemiology cohort	HSAT	AA children had higher adjusted prevalence of OSA (OR 3.5).
Stepansky[18]	1999	Case-control OSA, n= 128 No OSA, n = 62	<17 years	PSG	AA children with similar BMI had more severe oxygen desaturation.
Meetze[19]	2002	Retrospective cross-sectional, n = 280	Age > 18 years, Single center, clinical cohort	PSG	AA women with OSA were younger and had higher BMI and prevalence of hypertension, AA men had more severe oxygen desaturation.
Young[17]	2002	Cross-sectional, n= 5615	>40 years old, Sleep Heart Health Study	Home PSG	Race was not associated with risk of OSA
Rosen[14]	2003	Cross-sectional, n= 850	8-11 years, population based cohort	HSAT	AA children had 3.5 fold increased adjusted risk of moderate OSA.
Goodwin[29]	2003	Cross-sectional n = 239	Age 6-11 years, Community based cohort	Home PSG	HA or EA race was not associated OSA risk or severity.
Scharf[56]	2004	Cross-sectional, n = 233	Retrospective clinical cohort	PSG	AAs had more severe OSA; this risk was mediated by income and BMI.
Ruiter[23]	2010	Meta-analysis	Prevalence from pooled sample, n = 2,534,882 Severity from pooled sample, n = 6182	Mixed methods	Higher prevalence (effect size 0.13) and greater severity (effect size 0.10) of OSA in AAs.
Ramos[27]	2011	Prospective cohort study, n = 1,964	Elderly, age 75 ± 9 years	Questionnaires	HAs had higher risk for snoring (OR 3.6) and daytime sleepiness (OR 2.8), but no difference for AAs.
Pranathiages waran[20]	2013	Prospective, observational study, n = 512	Adults, Single center, clinical cohort	PSG	Young and middle aged AA men had higher AHI after adjustment for BMI.
Weinstock[21]	2014	Cross-sectional, n= 464	5 to 10 years, with OSA	PSG	20% increase in AHI in AA children; adjusted for BMI.
Ramos[28]	2014	Prospective, observational study, n = 176	Adults, Single center, hospitalized patients with acute stroke	Berlin Questionnaire	HAs were at higher risk (OR 2.6), AAs had equivalent risk for OSA.
Chen[4]	2015	Cross-sectional,	Age 54-93 years,	Home PSG	AAs had higher odds of OSA; OR = 1.78, short sleep; OR =

		n = 2,230	population based cohort		4.95, poor sleep quality; OR = 1.57, and daytime sleepiness OR = 1.89 after adjustment for sex and age. HAs had higher odds of OSA and short sleep.
Mediators and Outcomes of Inequalities Sleep Apnea					
Cakirer[52]	2001	Cross-sectional, n = 364 EA and 165 AA	Adults, Cleveland Family Study	HSAT	Brachycephaly, measured by anthropometric calipers, was associated with AHI in EAs but not in AAs.
Ancoli-Israel[33]	2002	Prospective clinical cohort, n = 70 each of AA and EA	Age 65 to 93 years	Home actigraphy plus respiratory test	AAs had higher blood pressure dipping ratios (“non-dipping”) after adjustment for AHI and BMI.
Nieto[36]	2002	Cross-sectional, n= 6,132	>40 years old Sleep Heart Health Study	Home PSG	Risk of hypertension was associated with severity of OSA, but not race. ** 77% of the cohort was EA, with <10% in other racial categories.
Spilsbury[55]	2006	Cross-sectional n = 843	Age 8-11 years	HSAT	AAs were more likely to have OSA (OR 3.9) which was reduced to OR of 1.9 (0.8-4.6) with adjustment for neighborhood disadvantage.
Surani[41]	2009	Cross-sectional, n = 172	Single center clinical cohort	PSG	HAs with OSA had twofold increased prevalence of diabetes.
Baldwin[31]	2010	Cross-sectional, n = 5,237	Age >40 years, Sleep Heart Health Study	Home PSG	AAs with frequent snoring, insomnia symptoms or EDS had poorer physical health. HAs with frequent snoring, insomnia symptoms or EDS had poorer mental health.
Baron[30]	2010	Cross-sectional, n = 5,173	Mean age 66 years	ESS	Risk of EDS was higher in AAs (OR 1.8-2.0) with OSA.
Alkhazna[34]	2011	Cross-sectional, n= 280	Adult, Single center clinical cohort	PSG	OSA severity did not vary by race, but AA had higher prevalence of hypertension.
Fulop[38]	2012	Cross-sectional, n = 5,301	AA cohort	Modified Berlin Questionnaire	Risk of OSA in AA men and women was associated with co-morbid hypertension and diabetes after adjustment for BMI, neck and waist circumference.
Sands-Lincoln[35]	2013	Cross-sectional, n = 4,418	Adults, 2007-2008 NHANES survey data	Questionnaire	OSA symptoms were associated with risk of hypertension in overweight AA (OR 4.7), overweight EA (OR 1.6) and obese HA (OR 2).
Redline[26]	2014	Cross-sectional n = 14,440	Age 45-74 years, Hispanic Community Health Study	HSAT	Overall prevalence in HA was 25.8% for mild OSA; 9.8% for moderate OSA; 3.9% for severe OSA. Moderate-severe OSA were at higher risk for hypertension (OR 1.4) and diabetes (OR 1.9).
Bakker[40]	2015	Cross-sectional, n = 2,151	Mean age 68.5 ± 9.2 years, population based cohort	Home PSG	Moderate-to-severe OSA was associated with abnormal fasting glucose in AAs (OR 2.14) and EAs (OR 2.85), but not among HAs, after adjusting for age, sex, waist circumference, and sleep duration.

Turner[32]	2016	Two cohorts, n = 943 AA, n=452 EA, n=491	Mean age 80 ± 7.8 years, population based cohort	Berlin Questionnaire	OSA risk was not different but sleep quality was poorer in AA elderly.
Nagayoshi[37]	2016	Cross-sectional, n = 1,844	Mean age 68 years, population based cohort	Home PSG	Severe OSA was associated with higher prevalence of peripheral arterial disease in AA.
Wang[54]	2017	Cross-sectional, n = 774	Mean age 7 ± 1.4 years, Clinical cohort	PSG	Association between race and AHI was mediated by socioeconomic variables including poverty.
KEY: Ref #= In text reference number, African American= AA, Hispanic American= HA, European American= EA, Obstructive Sleep Apnea= OSA, Apnea-Hypopnea Index= AHI, Body Mass Index= BMI, Polysomnography= PSG, Home Sleep Apnea Test= HSAT, Odds Ratio= OR, Epworth Sleepiness Scale= ESS, Excessive Daytime Sleepiness= EDS. *Comparison group European Americans (EAs) unless otherwise specified.*					

Table 2. Health Inequalities in Insomnia					
Author/Ref #	**Year**	**Study Design**	**Sample**	**Measurements**	**Results**
Bixler[57]	2002	Cross-sectional, n=1,741	Age > 20 years, population based cohort	Self-reported symptoms	Non-EAs (OR 2.0) was significantly associated with risk of Insomnia.
Allen[68]	2008	Survey, n=1,910	Age >65 years, rural population based cohort	Adapted validated questionnaire	AAs reported similar frequency of insomnia.
Mezick[69]	2008	Cross-sectional, n=187	Age 45-75 years, population based cohort	PSQI, home PSG and Actigraphy	AAs had less SE, SWS, and poorer sleep quality. This effect was mediated by SES.
Ruiter[23]	2010	Meta-analysis	Pooled sample of >8000	Mixed methods	AAs were less likely to report Insomnia symptoms (ES -0.19 for WASO and -0.23 for sleep complaints).
Patel[65]	2010	Cross-sectional, n=9,714	Age > 18 years, population based sample	Self-reported symptoms	AAs and HAs reported poor sleep quality (OR 1.59, and 1.65, respectively) and this was mediated by SES.
Grandner[59]	2010	Survey, n=159,856	Age >18 years, population based sample	Self-reported symptoms	AA and HA women were less likely to report Insomnia symptoms (OR 0.74 for each).
Ram[60]	2010	Cross sectional, n=6,139	2005-2006 NHANES	Physician diagnosed and self-reported symptoms	AAs and HAs (≥1.5% vs. 0.8%) had higher rates of physician diagnosed Insomnia, but less self-reported WASO.
Gaultney[66]	2010	Survey, n=1,845	College students	Validated questionnaire	AA students reported less risk for insomnia and poor sleep practices.
Pigeon[70]	2011	Cross sectional clinical cohort, n=92	Mean age 52 years	PSQI	AAs were more likely to experience sleep disturbance (OR 2.4) after adjustment for education, depression and chronic illness.
Grandner[61]	2012	Cross sectional, n=7,148	Age >18 years, population based sample	Self-reported symptoms	Perceived racial discrimination in healthcare setting was associated with increased risk of sleep disturbance (OR 1.60, p = .04) in AAs.
Singareddy[58]	2012	Prospective with follow up of 7.5 years, n=1,246	Age ≥ 20 years, population based cohort	Self-reported symptoms	Non-EAs were more likely (OR 2.8) to develop incident insomnia independent of SES, physical and mental health.
Grandner[62]	2013	Cross sectional, n=4,081	2007-2008 NHANES	Self-reported symptoms	AAs were more likely to report prolonged sleep latency (adjusted OR 1.6). AAs and HAs were less likely to report insomnia symptoms (adjusted OR 0.56 to 0.82).
Hicken[63]	2013	Cross-sectional survey, n=3,105	Age > 18 years, Urban population based sample	Self-reported symptoms	AAs reported more insomnia symptoms. This was mediated by SES and racism-related vigilance. Similar trends were observed in HAs.
Petrov[67]	2014	Survey, n=1,684	College students	Validated questionnaire	Prevalence of Insomnia was not different in AAs.
Slopen[64]	2014	Cross-sectional, n=2,983	Age > 18 years, Urban population based sample	Self-reported symptoms	Discrimination mediates sleep duration and sleep difficulty in AAs and HAs, independent of SES and other psychosocial stressors.
Carnethon[71]	2016	Observational,	Age 35-64 years, urban	Actigraphy, PSQI	AAs had significantly lower SE, greater sleep fragmentation

		n=496	population		and poorer self-reported sleep quality adjusted for SES and health indicators.

KEY: Ref #= In text reference number, African American= AA, Hispanic American= HA, European American= EA, Socioeconomic Status= SES, Total Sleep Time= TST, Sleep Efficiency= SE, Slow Wave Sleep= SWS, Wake After Sleep Onset= WASO, National Health and Nutrition Examination Survey= NHANES, Obstructive Sleep Apnea= OSA, Polysomnography= PSG, Pittsburgh Sleep Quality Index= PSQI, Odds Ratio= OR, Effect Size= ES. *Comparison group European Americans (EAs) unless otherwise specified.*

Table 3. Health Inequalities in Narcolepsy					
Author/Ref#	**Year**	**Study Design**	**Sample**	**Measurements**	**Results**
Kramer[73]	1987	Cross-sectional, n = 14	36-74 years old, narcoleptic patients	Genotyping	100% of EAs and AAs were positive for DRB1*15 (DR2) indicating association between DRB1*15 (DR2) and narcolepsy. No differences between races.
Neely[74]	1987	Cross-sectional, n = 18 AA with narcolepsy; n = 99 AA controls	Adults, narcoleptic patients from Sleep Clinic in Chicago	Genotyping	33% AA narcoleptics did not have DRB1*15 (DR2), which was lower than historic EAs. 100% AAs and EAs had DQw1. 22% AAs had DQw1 but without DR2. 100% of historic EAs, had both DR2 and DQw1.
Mignot[75]	1994	Retrospective, n = 47	Adults, narcolepsy patients with cataplexy, from U.S. and international university-based sleep clinics and laboratories	Genotyping	95% EAs, but only 11% AAs, were DRB1*1501 (DR2) positive, 68% AAs, 0% EAs carried DRB1*1503. DQB1*0602 was found in 96% AAs and 95% EAs. DQB1*0602 was more sensitive marker for narcolepsy than DRB1*15 (DR2) in AAs and EAs.
Rogers[76]	1997	Retrospective, n = 188	Adults, narcolepsy patients with cataplexy, from Stanford database	Genotyping	67.2% AAs were positive for DRB1*15, compared with 84.5% EAs. In AAs, association was stronger with DQB1*06:02. DQB 1*0602 was more sensitive marker for narcolepsy with cataplexy than DRB1*15 (DR2) in AAs and EAs.
Mignot[77]	1997	Cross-sectional, n = 509	18-68 years old, narcolepsy patients enrolled in clinical trial for modafinil	Genotyping	DQB1*0602 positivity was significantly higher in AAs. DQB1*0602 was more sensitive marker for narcolepsy than DRB1*15 (DR2) in AAs and EAs.
Mignot[78]	2001	Retrospective population-based case-control study, n = 420 narcolepsy with cataplexy, n = 1087 controls	Adults, narcolepsy patients with cataplexy, from U.S. and international university-based sleep clinics and laboratories	Genotyping	DQB1*0602 positivity was significantly higher in AAs. In AAs, association was stronger with DQB1*0602. DRB1*13, DQA1*0103, DQB1*0603 haplotypes conferred moderate protection in EAs and AAs.
Pelin[79]	1998	Cross-sectional, n = 669	Adults, narcoleptic patients from Stanford database and multi-center clinical trial for modafinil	Genotyping	Both EAs and AAs with or without cataplexy who were homozygous for HLA-DQB1*0602 had relative risks 2-4 times higher compared with HLA-DQB1*0602 heterozygotes. No differences in severity with increasing allelic dosage in EAs or AAs.
Mignot[80]	1997	Retrospective, n = 58	Adults, non-DRB1*15 narcolepsy patients with cataplexy, from Stanford database	Genotyping	In AAs, narcolepsy was associated with rare DQB1*0602 haplotypes bearing distinct DRB1 alleles, most commonly DRB1*1503, DRB1*1501, DRB1* 1101, and DRB1*0806.
Hallmayer[81]	2009	Case-control GWAS, n = 807 cases, n = 1074 controls; replication: n = 1057 cases, n = 1104 controls	Adults, clinical cohorts from various national and international sleep clinics and laboratories	Genotyping	Association of narcolepsy within the *TCRA* locus polymorphisms in three ethnic groups, including EAs and AAs.
Kornum[82]	2011	Case-control GWAS, n = 807	Adults, clinical cohorts	Genotyping	Association of narcolepsy with a SNP in the *P2RY11* gene in

		cases and n = 1074 controls; n = 1858 cases and n = 2384 controls	from various national and international sleep clinics and laboratories		three ethnic groups, including EAs and AAs.
Holm[83]	2015	Case-control GWAS, EA: n = 807 cases, n = 1074 controls; Chinese: n = 1078 cases, n = 1903 controls; AA: n = 249 cases, n = 1048 controls	Adults, clinical cohorts from various national and international sleep clinics and laboratories	Genotyping	Association of narcolepsy with a SNP in the *EIF3G* gene in three ethnic groups, including EAs and AAs.
Longstreth[86]	2009	Retrospective population-based study, n = 425 narcolepsy	>18 years old, positive for DQB1*0602 allele, King County, Washington	Questionnaires, interviews, genotyping	Higher prevalence of narcolepsy with cataplexy in AAs .
Koepsell[87]	2010	Retrospective population-based case-control study, n = 45 narcolepsy with cataplexy, n = 95 controls	Ages 18-50 years, positive for the DQB1*0602 allele, King County, Washington	Questionnaires, interviews, genotyping	Higher prevalence of diagnosed narcolepsy cases in AAs than EAs (OR = 8.1). Higher prevalence of diagnosed narcolepsy in households with lower educational attainment and lower annual income.
Okun[88]	2002	Retrospective cross-sectional, n = 484	Mean age, 43.1 years old, diagnosis of narcolepsy-cataplexy	ESS, MSLT, PSG, genotyping, hypocretin-1 level	AAs and EAs showed similar symptomatology, age of onset, and disease severity. Minor differences in other variables: EA had less severe sleep paralysis and more reports of cataplexy affecting jaw and arms than AAs. AAs had more reports of negative emotions triggering cataplexy and going blank due to sleep attacks.
Cairns[89]	2015	Retrospective cross-sectional, n = 3,059 suspected hypersomnia, n = 79,651 general sleep clinic sample	>18 years old, repository of scored and physician interpreted records	MSLT, PSG	AAs were 2.8-4 times as likely to have a PSG SOREMP, controlling for other significant variables.
Kawai[72]	2015	Retrospective cross-sectional, n = 1097	Children and adults, diagnosed with narcolepsy, Stanford Center for Narcolepsy Research database	ESS, MSLT, PSG, genotyping, hypocretin-1 level	Sex ratio, PSG, and MSLT measures did not differ between AAs and EAs. ESS score was higher and age of onset of sleepiness was earlier in AAs.HLA-DQB1*0602 positivity was higher in AAs but. CSF hypocretin-1 level was more frequently low (≤110 pg/ml) in AAs. In patients with low CSF hypocretin-1, AAs were 4.5 fold more likely to be without cataplexy.
Andlauer[90]	2012	Retrospective population-based case-control study, n = 171 narcolepsy with cataplexy, n = 170 control narcolepsy without cataplexy	>18 years old, University-based sleep clinics and laboratories	ESS, MSLT, PSG, genotyping, hypocretin-1 level	Patients with low CSF hypocretin-1 level (≤110 pg/ml) were more likely to be AAs vs. EAs: 1% of normal-CSF-hypocretin-1 vs. 20% of low-CSF-hypocretin-1 cases were AAs, OR = 28.
Chambers[91]	1988	Cross-sectional, n = 97	Mean age, 21.6 years old, Canadian university students	Sleep Disorders Questionnaire	Abuse/trauma group scored more negatively than controls for narcolepsy (mean, 25.8 vs. 21.1; p <.01).
KEY: Ref #= In text reference number, African American= AA, European American= EA, Genome-Wide Association Study= GWAS, Odds Ratio= OR, Epworth Sleepiness Scale= ESS, Multiple Sleep Latency Test= MSLT, Polysomnography= PSG, Single Nucleotide Polymorphism= SNP, Sleep Onset Rapid Eye Movement Period= SOREMP,					

Cerebrospinal Fluid= CSF. *Comparison group European Americans (EAs) unless otherwise specified.*

Table 4. Health Inequalities in Chronotype and Circadian Parameters

Author/Ref#	Year	Study Design	Sample	Measurements	Results
Knutson[93]	2017	Cross-sectional, n = 113,429	Ages 18-74 years, self-identified Hispanic/Latino	Self-reported bedtimes and wake times. Chronotype defined as midpoint of sleep on weekends adjusted for sleep duration on	Significant differences between various HA groups, with Mexican Americans having earliest chronotype, bedtimes and waketimes.

			background	weekdays.	
Malone[94]	2016	Cross sectional, n = 439,933	Ages 40-69 years, UK Biobank study	Chronotype via single item in which participants rated themselves as definitely a morning person, more a morning than an evening person, more an evening than a morning person, definitely an evening person.	Morning vs. intermediate chronotype was 1.4 times more prevalent in self-identified Africans than Whites in the UK.
Malone[95]	2017	Cross sectional, n = 2044	Ages 40-69 years, UK Biobank study	Chronotype via single item in which participants rated themselves as definitely a morning person, more a morning than an evening person, more an evening than a morning person, definitely an evening person.	Africans had a 62% greater odds of being morning chronotype than Whites in the UK .
Smith[96]	2009	Experimental, n = 60	29 males, ages 18-45 years	Circadian period, circadian phase advances and delays via DLMO measurements.	AAs had significantly shorter circadian periods. AAs had larger phase advances and smaller phase delays,.
Eastman[97]	2012	Experimental, n = 94	45 males, ages 18-42 years	Circadian period via DLMO measurements. Chronotype via MEQ.	AAs had significantly shorter circadian periods. MEQ scores did not differ between races.
Eastman[98]	2015	Experimental, n = 36	19 males, ages 21-43 years	Circadian period, circadian phase shifts via DLMO measurements. Chronotype via MEQ.	AAs defined by genetic ancestry had significantly shorter circadian periods. Longer circadian periods were associated with greater percentage of European ancestry and smaller percentage of African ancestry. EAs had larger phase shifts after 9-h advance than AAs, but were more likely to phase delay. MEQ scores did not differ between races.
Eastman[99]	2016	Experimental, n = 45	22 males, ages 18-44 years	Circadian period, circadian phase shifts via DLMO measurements. Chronotype via MEQ.	AAs defined by genetic ancestry had significantly shorter circadian periods and an earlier chronotype (more morningness). EAs had larger phase delays than AAs after 9-h delay.
Eastman[100]	2017	Experimental, n = 63	31 males, ages 18-44 years	Circadian period, circadian phase shifts via DLMO measurements.	AAs defined by genetic ancestry had significantly shorter circadian periods. EA women had shorter circadian periods than men, but there was no sex difference in AAs.
KEY: Ref #= In text reference number, African American= AA, Hispanic American= HA, European American= EA, UK= United Kingdom, Dim Light Melatonin Onset= DLMO, Morningness-Eveningness Questionnaire= MEQ. *Comparison group European Americans (EAs) unless otherwise specified.*					

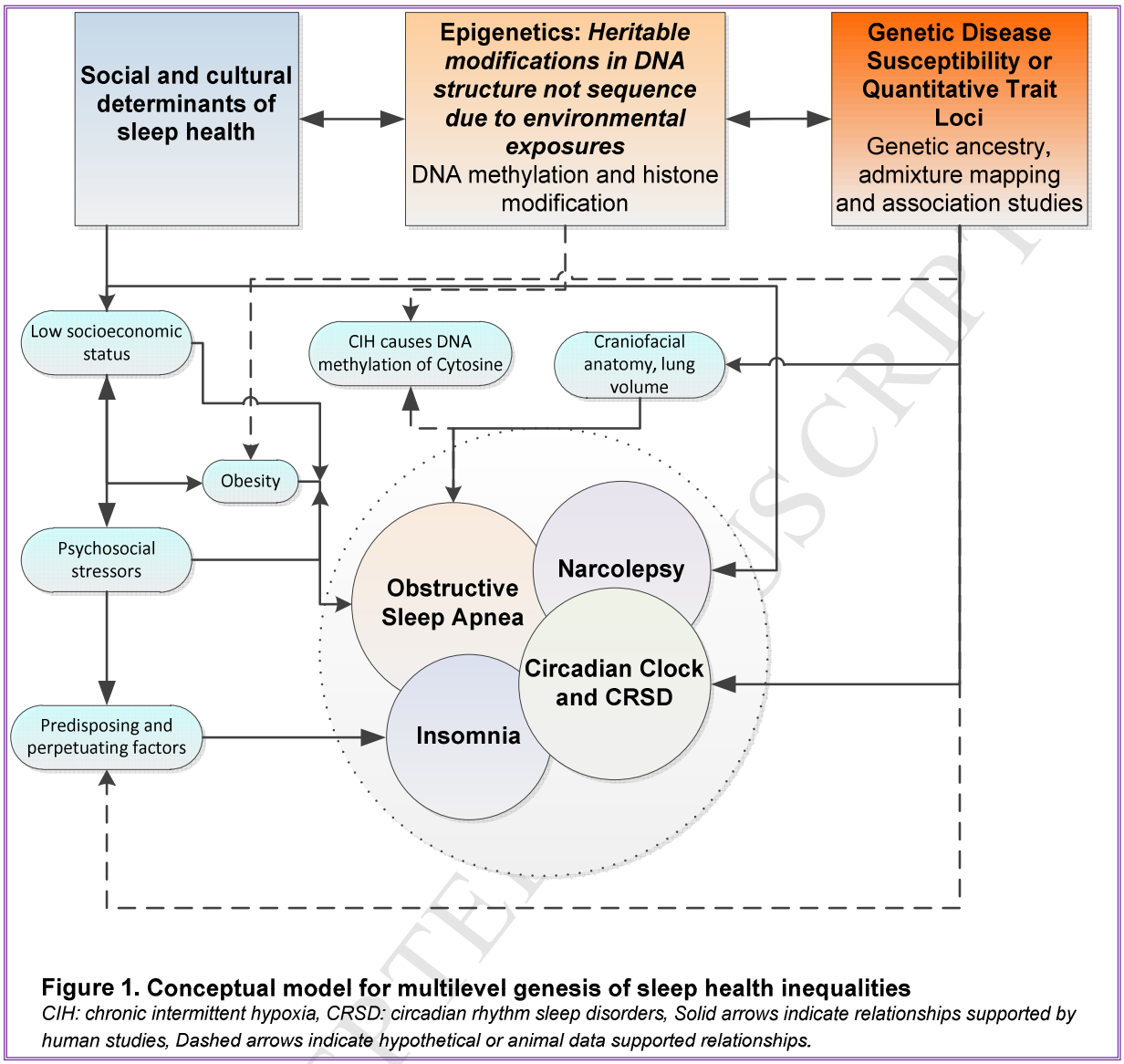

Figure 1. Conceptual model for multilevel genesis of sleep health inequalities

CIH: chronic intermittent hypoxia, CRSD: circadian rhythm sleep disorders, Solid arrows indicate relationships supported by human studies, Dashed arrows indicate hypothetical or animal data supported relationships.