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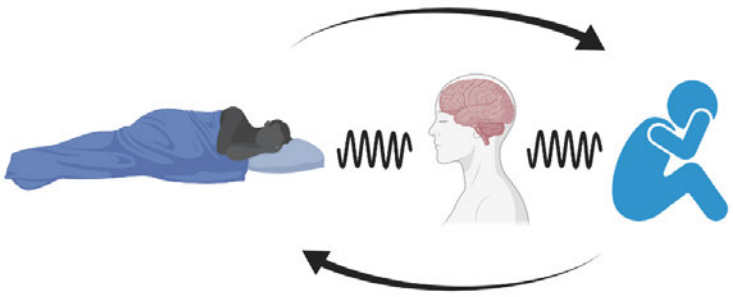
Structural brain changes in sleep disturbed children and adolescents and its relation to suicidality



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I declare that this thesis presented for the degree of Master of Science by Research in Psychiatry has:

1. Been composed entirely by myself
2. Been solely the result of my own work, except where explicitly stated otherwise
3. Not been submitted for any other degree or professional qualification

Signed

Nikolaj Kjær Høier

Table of content

1. Introduction

1.1 General overview

During the past decade the youth suicide rate has nearly tripled[1], and suicide remains one of the most frequent causes of death amongst young people.[2,3] Suicide itself is responsible for around 700,000 deaths every year[4] resulting in substantial suffering for those bereaved by it. Little is known about the emergence and development of suicidal behavior in children/young people and how this relates to other biological factors and behaviors. Tracing the roots of suicidal behavior in young people offers a unique opportunity for understanding risk factors and intervention early in life, to prevent the propagation of more significant mental health difficulties in adulthood. To address this knowledge gap, we examined participants in the Adolescent Brain Cognitive Development (ABCD) Study® of 11,886 children aged 9-10 years. Although this is a relatively young cohort, prevalence rates of suicidal ideation have been reported as 6.4% [5], providing the opportunity for studying the early development of such behaviors amongst young adolescents.

To date, studies of the Adolescent Brain Cognitive Development Study® (ABCD) cohort have identified childhood psychopathology and family conflicts as the most robust risk factors for suicidal outcomes.[6] Sleep disturbances have consistently been linked with increased suicidal behavior and suicide risk i.e. death by suicide amongst different adult populations[7,8], and evidence points towards clear associations between poor sleep and negative mental health outcomes such as suicidal ideation amongst adolescents.[9]

Suicidal ideation is defined as a situation wherein an individual frequently thinks of ending their own life actively by self-inflicted and self-directed acts of violence. These thoughts may be constant and can range from vague to severe and involving actual plans of action. This is different from the term suicidal behavior which in this thesis will be used to describe the two phenomena of self-harm and suicide attempt. Self-harm and suicide attempt refers to situations where an individual acts and engages in harmful behaviors directed towards themselves, with the overall goal of hurting themselves. Differences between self-harming and a suicide attempt do exist; primarily these complex behaviors are separated by the underlying intent of the individual carrying out the act.[10] Both suicidal ideation and suicidal behaviors (are independently linked to an increased risk of suicide, although only 10% of all suicide attempts result in death.[11]

Structural brain changes such as gray matter volume changes associated with sleep disturbances have been observed in previous studies amongst adolescents,[12] providing a biological conduit through which sleep could impact mental health. Indicating that more research in this area is needed. However, small sample sizes restricted to specific clinical populations mean that if we are to get closer to understanding what is happing in the developing brain, we need to utilize large data that allows for proper adjustment of relevant confounders and long term follow up of early adolescent's brain development with regard to both sleep disorders and suicidal behavior.

Early adolescence is a period of significant neurodevelopment where children undergo reductions in grey matter volume and cortical thickness, while surface areas tend to increase during early adolescence and slows down in mid adolescence.[13-15] Furthermore, individuals in early adolescence undergo chronobiological modulation and are influenced by different environmental factors, that have adverse outcomes.[16] Considering that an increased risk for psychopathologies, along with significant changes to sleep patterns and brain changes emerge in early adolescence, it is important to assess the relationship between these and their potential links to suicidal behaviors. This is in part because sleep offers a unique opportunity to implement lifestyle changes that could potentially mitigate risks within this relationship.

1.1.1. Sleep disturbance and the general adult population

It is estimated that sleep disturbances such as insomnia affect between 10-30% of the adult population.[17] Furthermore, there is evidence to suggest a decrease in recent years in both quantity and quality of sleep among adults.[18] Current measures of sleep disturbances in the general population are derived from a wide variety of sources, meaning that it can be hard to disentangle the true size and impact of sleep disturbances and disorders present in society. Even shorter durations of intermittent disruptions to sleep, although not chronic, are reported to have consequences.[18,19] As such, there is evidence to suggest that regardless of the nature of the specific sleep disturbance and the length of it, it is likely to have a variety of negative impacts on adults .[18,19] Sleep disturbance or disorder remain hard to assess; nonetheless it is clear that disruption of the typical 7-9 hours of sleep required for most adults can lead to acute challenges such as reduced cognitive capabilities.[20,21] Over time these disturbances can result in chronic issues such as the development of psychiatric disorders.[22-24]

In the adult population sleep disorders are associated with a host of mental disorders[24]. On numerous occasions sleep disorders and disturbances such as sleep apnea[25], nightmares[26], insomnia[7] and hypersomnia[27] have been related to outcomes of suicidality, depression and dementia. As such, it is well established that sleep disturbances serve as a pathway towards increased suicide risk in adults; however it is also a modifiable risk were certain treatments such as CBT for insomnia and hypnotics may mitigate certain risks presented by the sleep disorder.[28-30]

1.1.2 Sleep disturbance in children and adolescents

Sleep disturbance and sleep pattern changes occur frequently during adolescence,[9,31] as the brain rapidly develops in these years, sleep disturbances could be a normal part of adolescence. However, several studies point to the fact that identified sleep disturbances can lead to acute and chronic deterioration of day to day life in adolescents as well as in adults.[9]

Adolescents can further develop social jetlag[32] and distinct chronotypes. These can inflict certain challenges, as day to day activities might not match the current chronotype an adolescent fits into, affecting overall health such as BMI[33]. Thus, sleep disturbance may also be a result of a clash between the chrono-typical challenges often observed in teenagers.

Studies conducted in the ABCD cohort have previously identified that sleep disturbance are associated with differences in developing brain networks and cognitive abilities,[34,35] and that short sleep duration is associated with depression.[36] Depression is known as one of the biggest predictors for suicidal outcomes so underlying depression may be the main cause of suicidal behavior in this young cohort. Previous studies of sleep disturbance in adolescents have primarily been carried out within the populations of college or school students or other subpopulation samples, often not giving a thorough view of a nationwide representative sample. In the Adolescent Brain and Cognitive Development study results have emerged with regards to childhood insomnia and reduced brain structure in early adolescence[37] Other studies from the ABCD study also identify that low quality sleep and short sleep duration have detrimental effects on more than just brain morphology - it also affects connectivity,[38] thus highlighting that disturbed sleep in early adolescents affects the brain in both structural and functional terms.

Since little is known about the associations of poor sleep and brain structure in early adolescents it was decided as a part of this thesis to conduct a Scoping Review on poor sleep's relationship with

brain structural changes. This was to inform and highlight the known research on the subject. For the purposes of this thesis, a scoping review is defined as a research synthesis that aims to identify key concepts & gaps in the research. The Scoping Review will be presented in below in chapter 2.

1.1.3 Suicidality in early adolescents

Suicide is one of the leading causes of death amongst adolescents and young adults, but it is excessively rare in children and pre-adolescents. Suicide rates tend to increase with age in the population. Rates have risen in younger people over the last 50 years.[11] Recent assessment from the United States found a 56% increase in death by suicide amongst 10–19-year-olds and a 44% rise in the suicide rate between 2007-2016, implying a drastic increase. Even more worrying, in the span of 2010-2016 a 70% increase in the suicide rate amongst females was observed.[39] As death by suicide is fairly rare, suicidal ideations and suicide attempt are often more measurable in children and adolescents as a sign of deterioration in existing mental health conditions, or as a potential marker for future suicidal risk in its own right.[11]

As adolescents go through a vast variety of changes in a short period of time, a vast host of reasons can be the cause of increased suicidal thoughts and behaviors. It is thus important to identify certain types of exposures that influence early adolescent development towards increased suicidality. The ABCD study with its large and thorough data presents an important opportunity that can contribute in mapping out early risk predictors developing in early adolescence.
The large sample of ABCD covering early adolescence has in previous studies reported estimated lifetime prevalence of suicidal thoughts as high as 14.33% and 1.26% for suicide attempts.[40] This further indicates that this is a suitable sample in which to explore the aims of the current thesis.

1.1.4 Sleep disturbance as a risk factor for suicide

To date, sleep disturbances and disorders of all kinds have been associated with suicidality.[7] This includes suicidal ideation, self-harm, suicide attempts and death by suicide.[7,8] It should however be noted that variation exists within these results with regards to the specific outcomes and their

associations with specific exposures. In general, low-quality sleep, insomnia and short sleep duration are the most studied, as potential risk factors for suicidal thoughts and behaviors.[7] Specific disorders such as sleep apnea and narcolepsy have also previously been associated with suicidal outcomes[25,41] as well as more diffuse disturbances such as parasomnias with regard to nightmares[26], even when assessing for comorbid psychiatric conditions such as depression. Considering how sleep disturbance play a role in mental health disorders one could speculate that much of the associations could be driven by underlying or developing mental health disorders.
However, associations of sleep disorders and suicidality have been found to exist independently of mental disorders, however the complexities of the relationship between sleep and suicidal thoughts and behaviors are vast, especially with regards to brain changes. This current study aims to explore these neurobiological complexities that exists between sleep and suicide.

1.1.5 Structural brain changes and sleep disturbance

In order to establish prudent knowledge of the field a scoping review was carried out on the subject of sleep disturbances and its associations with brain structural changes. In the following the scoping review, prepared for publication (not yet submitted) will be presented:

2. Scoping Reivew (SR):

2.1 Introduction (SR)

As humans we spend approximately one third of our lives asleep. Sleep plays an important role in supporting cognitive processes such as memory consolidation and in restoration of energy and metabolic reserves necessary for regular daily activities and function[42,43]. The importance of sleep for human wellbeing is further illustrated by recent evidence which shows it is important for toxin clearance in the brain[44].

Sleep disturbances, defined as either sleep disorders or as insufficient quality or quantity of sleep, often serve as early prodromal or comorbid indications of other underlying conditions such as Parkinson's disease or other age-related cognitive decline[45-47]. Problems with sleep are also common in poor mental health outcomes like depression[48,49] and suicide[8]. Bidirectional relationship between sleep disorders and psychiatric disorders has previously also been shown in adolescents and children[50,51]. Insomnia, as one example of a sleep disorder, is known to be associated with greatly reduced quality of life amongst adolescents[49]. Despite the vast knowledge on the associations between sleep disturbances with poor physical and mental health outcomes, the relationships between disturbed sleep and brain structure remain to be uncovered in full.

From a mechanistic perspective, disturbed sleep may lead to changes in brain structure through the reduction in clearance of neurotoxins[44]. One study, for example, has shown that disturbed sleep is associated with increased volumes of perivascular Virchow Robin spaces, tentatively linked to poorer drainage of interstitial fluid[52]. Other studies have found reduced beta amyloid clearance in individuals who have suffered as little as one day of sleep deprivation[53], likely due to reduced function of the glymphatic system[54]. Notably, buildup of amyloid beta is considered to lead to the occurrence of plaques in Alzheimer's dementia and thus contribute to substantial cognitive deficits. Other mechanism by which sleep deprivation might alter brain structure is through reduction in neurogenesis[55]. For example, hampered neurogenesis due to sleep disruption has been shown to lead to reduced hippocampal volumes in some rodent studies[56,57]. Finally, the synaptic homeostasis hypothesis (SHY) theory suggests that sleep is necessary for re-normalization of synaptic connections, strengthened during learning in day-today activities[58]. Disturbed sleep could thus result in altered brain structure due to decreased pruning of new synaptic connections. On a macroscopic

level, disturbed sleep has been shown to be associated with brain atrophy, although the causal relationship and mechanisms have not been established[59,60].

Adolescence is a period of vast neurodevelopment and synaptic pruning. It is also a period of significant changes in circadian rhythms with substantially increased risk for development of mental health disorders. Evidence with regard to the associations between disturbed sleep and brain structure in this period could be very informative for understanding long-term health trajectories. Thus, we could expect that certain observed changes may be due to developmental changes respective to life stages, such as pruning in adolescent and age-related atrophy in elderly, and therefore be different from adolescence and adulthood.

The current scoping review is aimed to help establish the knowledge base necessary for conducting further investigations into the associations between sleep and brain structure in children and adults. Considering that different mechanisms may be involved in the alteration of brain structures in different stages of life we felt it important to asses studies assessing every aspect of the human lifespan. We prioritized studies focused on primary sleep disorders, sleep disturbances and brain structure, without limitations on age or stage of life. We aimed to identify the most prominent past research findings and relevant knowledge gaps.

2.2 Methods (SR)

Overview

This review was developed based on the JBI guidelines on knowledge synthesis in scoping reviews[64]. We utilized the framework developed by Arksey and O'Malley[65] with five main scoping review steps: (1) Identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting the results.

We provide further detail for each of the steps in the context of the current scoping review below.

(1) Identifying the research question

We identified three following research questions as the main focus for the review:

1) What is the current knowledge regarding associations between sleep disorders, sleep deprivation, or other sleep disturbances and brain structure across the lifespan?

2) What are the methods applied in the published research studies investigating brain structure changes in sleep disturbances in humans and how consistently are they used?

3) What are the current knowledge gaps with regard to associations between sleep disturbances & brain structure?

(2) Identifying relevant studies

Inclusion Criteria Overview

To summarize, we focused the current scoping review on the studies of primary sleep disorders, sleep deprivation or other sleep disturbances in human participants, where structural brain imaging methods (specifically, structural MRI) were used. We specified our criteria following the *population, concept and context* framework tool[66]. We present further details below.

Participant Criteria

We applied the following criteria for study participants:

1) Studies with human participants of all ages were eligible for inclusion. This was because we aimed to assess associations between sleep disturbance and brain structure across the lifespan.

2) Studies that assessed clinical sleep disorders or problems such as REM behavior disorder or insomnia were included, as these disorders are typically related to frequent sleep issues and can have a variety of causes. Studies investigating sleep apnea and narcolepsy were not included because these disorders have their own unique pathophysiology[67,68] – which differs from other forms of normative sleep disruption such as insomnia.

3) Studies where participants had sleep disturbances comorbid to other conditions such as Alzheimer's disease, Parkinson's disease or depression were not included. This was because such conditions have their own effects on brain structure, and we were primarily interested in associations specific to primary sleep problems in the absence of significant comorbid disorders.

Apart from the above criteria, no further limitations were placed on study participants.

Concept

Due to the focus of the current review on human participants, we were mainly interested in studies using structural brain imaging (primarily, structural MRI). Studies of all designs that reported on sleep disorders or sleep disturbance and any aspects of brain structure were eligible for inclusion, and any grey or white matter regional measures were of interest. Subsequently, we opted to include studies which used T1 or T2 structural brain imaging or diffusion weighted imaging (DWI) and did not include studies focused only on brain function (e.g., those using MR spectroscopy, functional MRI, positron emission tomography and single-photon emission computed tomography).

Context

We did not have any restrictions of the study context except for the fact that only research literature published in English was considered.

Search Strategy

A three-step search strategy was implemented. First, an initial limited search was performed to identify most relevant keywords. The search was then further expanded by using the discovered keywords. Finally, reference lists of the studies which passed the title / abstract screening from the expanded search were examined for additional relevant studies. Databases were reviewed using the PRESS checklist[69].

The following keywords were used in the literature search: *((sleep[Title]) AND (brain[Title])) AND ((brain volume[Title/Abstract]) OR (brain structure[Title/Abstract]) OR imaging).* The search was conducted on the following databases: PubMed, PsycInfo, Embase and Scopus. The final search was carried out on the 19/11/2021.

(3) Study selection

The search results were imported into Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) and the platform was used as the main tool to conduct the review. NH screened titles and abstracts of all articles based on the defined inclusion criteria. Both NH and AS then independently reviewed abstracts and (when necessary) full texts of articles included at the title / abstract screening stage and additionally marked studies outside the scope of the review for exclusion. All inclusion / exclusion conflicts between the two reviewers were discussed and agreements were reached on each article. NH then screened all included records at full text level. The scoping review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for

Scoping Reviews guidelines PRISM-ScR[70] and in accordance with Joanna Briggs Institute *Guidance for conducting systematic scoping reviews*[64].

(4) Data charting

We extracted multiple information from the included studies, the knowledge we aimed to extract was the overall population and sample size in the studies and their main measurements of both brain structure (i.e., what type of neuroimaging study it was) and further what measurement was used to capture sleep, quality, quantity, disorders, or disturbance. Further we extracted all discussion and conclusion from studies to identify their results, which we aimed to condense and synthesize into the results of this study. The extracted data was gathered in order to answer the research questions: to assess the associations between sleep and brain structure and further to identify gaps with regards to the methodology used in the charted data.

(5) Collating, summarizing, and reporting the results

We mainly aimed to qualitatively summarize the findings relevant to our three research questions in a descriptive manner. More specifically, we aimed to identify 1) what are the structural brain measures most frequently reported on in the charted studies, 2) what are the key reported changes in brain structure associated with sleep disturbance, and 3) what are the knowledge gaps that need to be addressed in the future to better understand the links between disturbed sleep and brain structure. In addition to the descriptive summaries, we aimed to present the data charting results in tabular format to aid in data mapping. Consistent with the JBI guidelines for scoping reviews, we did not conduct a more formal or detailed quantitative analysis based on analytical themes.

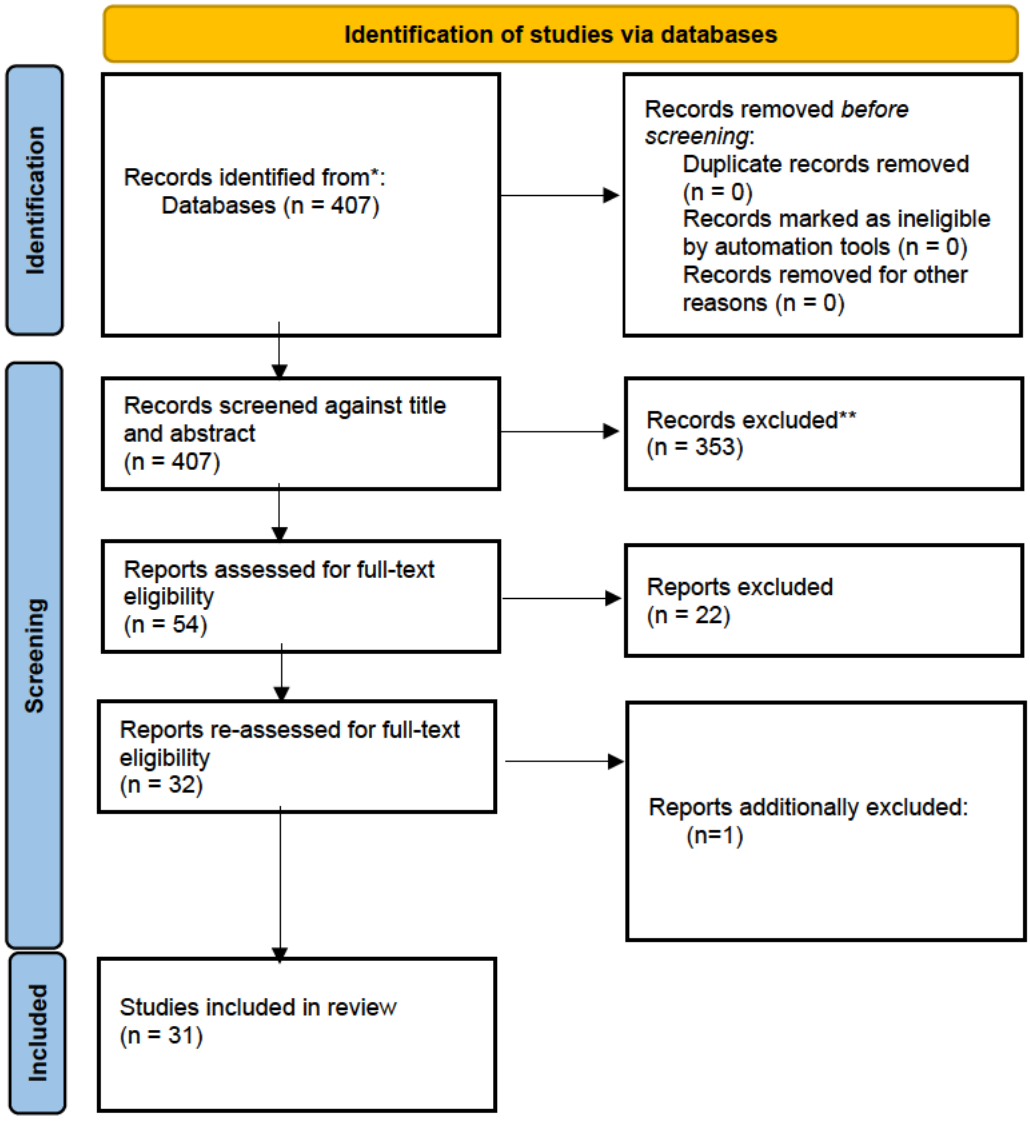
2.3 Results (SR)

Literature search

The literature search revealed 407 results. Of these, 353 were excluded during title and abstract screening as they didn't fulfill the inclusion criteria, leaving 54 studies. Additional 22 were excluded during full text review, due to either wrong study populations or study settings, leaving a final sample of 32. Of these, 8 had study designs or experimental measures (e.g., types of brain scan) beyond the review scope, another 7 studies had out-of-scope outcomes, and another 7 studies had out-of-scope patient populations (e.g. participants with sleep apnea). One final publication was excluded because

it was an editorial piece (after examining the reference list). The final sample of studies included in the scoping review consisted of 31 publications. An overview of study selection and inclusion can be seen in SR Figure 1 below.

SR Figure 1 – PRISMA diagram for literature search and inclusion



Overview of included studies

The vast majority of included studies (77%) investigated changes in grey matter with T1-weighted imaging. White matter integrity was assessed with diffusion tensor imaging (DTI) in 16% of the studies (5 of 31), while one study utilized a FLAIR scan.

Population

Sample sizes ranged from 8 participants (Plante et al., 2014) up to 11,067 (Cheng et al., 2014)[32,33]. In total, 16 of the 31 studies had samples with less than 100 participants, 6 studies had samples of 100 - 500 participants, and finally 4 studies had more than 1000 participants. With regard to age ranges, 14 studies investigated adults (>18 years), 7 had a focus on adolescents, and the remaining 10 studies had a mix of adolescent and adult participants. Youngest participants (2 months - 7 years) were studied in Kocevska et al. (2017)[71], while oldest participants (52 – 87 years) were investigated in Amorim et al. (2018)[72]. The selected studies thus broadly covered the entire lifespan.

A variety of different sleep measurements were used, most frequently it was the Pittsburgh Sleep Quality Index (PSQI) that was utilized. The PSQI is a self-reported questionnaire with 19 items. In the included studies 8 utilized the PSQI as an exposure measure such as the study by Branger et al, 2016.[73] Other studies relayed on polysomnography which is state of the art in sleep surveillance, this was the case for the studies by Dai et al, 2018 and Baril et al, 2021.[74,75] Polysomnography is often expensive and has its own challenges, thus researchers sometime refer to the use of actigraphy data in studies as this is more easily available. This was also the case for the included studies by Lauriola et al, 2017, Teicher et al, 2017, Amorim et al, 2018 and Jalbrzikowski et al, 2021, all utilizing actigraphy data for the measurement of sleep duration and quality.[72,76-78] To also assess individuals with disruption to REM sleep, studies that investigated individuals with idiopathic Rem Behavioral Disorder (iRBD) were included of these there was 5 studies in total, with a total sample size combined of 84 cases and 85 controls. One of the 5 studies, the study by Heller et al, 2017 was a systematic review.[79]

Finally it should be noted that multiple studies focused on age related effects and therefore primarily had a focus on older populations (50 years and above) and samples such as for example the studies by Amorim et al that sought to investigate a normal aging cohort.[80] The same can be said for the study by Liu that investigated the age related atrophy effect upon sleep.[81]

Brain scan types in sleep studies

Most of the included studies (24 of 31) analyzed T1 scan-derived measures, such as grey matter concentrations, cortical region thicknesses and volumes, and subcortical volumes. In contrast, only 5 studies collected DWI scans to assess changes in white matter, of which 2 reported on both T1-derived and DTI measures[34,37,38]. Only two studies had brain measures based on T2 or T2* scans[82,83]. A notable exception from the rest of the studies was reported in Zhang et al. (2021), where the authors

combined T1-weighted imaging, T2*-weighted imaging, susceptibility weighted imaging (SWI) and quantitative susceptibility mapping (QSM) to assess changes in brain global and regional iron depositions, as well as subcortical volumes in iRBD patients.[83] To summarize, most surveyed studies of sleep relied on morphometric brain measures derived from T1 scans, with a smaller proportion focused on DTI-measured changes in white matter, and FLAIR scans looking at WM hyperintensity such as Baril et al, 2021.[75]

Sleep duration, disruption and brain structural changes in adults

Overall 6 studies identified grey matter volume (GMV) reductions related to sleep duration and disruption.

Grey matter volumetric reductions was observed in people with iRBD and golf war veterans who struggled with sleep was observed in two studies.[84,85] More specifically one of these studies identified total and regional frontal lobe volume reductions.[84] This was consistent with other studies that found short sleep duration in healthy adults was associated with higher age related brain atrophy.[60] Subsequently, one study found that nocturnal awakenings was associated with grey matter volume reductions in the insular region.[73] These findings were replicated in a group of younger adults aged 23-29 years in another paper, that found that a reduction in cumulative sleep time and a participant rated poorer subjective sleep quality was associated with white matter structural changes,[86] highlighting that hampered sleep is not only associated with changes to grey matter but also white matter.

With regards to white matter microstructural changes, 3 studies assessed adults and WM changes. Looking at young adults, one paper found in a large (1201) sample of young normal adults that mean diffusivity positively correlated with sleep duration across multiple brain areas such as the prefrontal cortex and dopaminergic system indicating microstructural changes. Subsequently the study also found negative correlations between sleep duration and mean diffusivity in the right hippocampus.[87] Poor sleep quality assessed by PSQI and actigraphy was associated with white matter functional connectivity decreases in the right superior temporal pole, left middle temporal and left inferior occipital in a sample of individuals aged 52-87 years old.[72] Similarly studies also reported that sleep deprivation had consequences to brain structure showing the effects of sleep deprivation of 20, 24, 32 and 36 hours of wakefulness and subsequently assessed brain changes

with T1 scans amongst 39 cases and 22 controls.[74] It was also found that sleep deprivation was associated with grey matter volume reductions in thalamus, cerebellum, insula and parietal cortex.[74]

Sleep and brain structure in children and adolescents

A number of the included studies also assessed brain developmental changes and sleep disturbance and disorder in the context of adolescence. One study found that depression, anxiety and impulsivity was negatively correlated with shorter sleep duration showing an existing relation between sleep and psychopathological development in a large longitudinal adolescent cohort.[82] Further longer sleep duration was correlated with higher GMV in the orbitofrontal, prefrontal and temporal cortex, as well as the precuneus and supramarginal gyrus. Short weekday bedtime, and later weekend sleeping hours was also found in the literature to be correlated with reduced frontal, anterior cingulate, and precuneus cortex volumes, for youth.[88] It was also subsequently found that later wake up times on weekends and bedtimes were associated with specific clusters of reduced GMV.[88] Further one paper found associations between global regions with reduced volumes and sleep disturbances.[12] Finally, we also identified lower white matter integrity associated with variability in sleep duration showing that the findings extend to both grey and white matter findings.[89] Thus these findings suggest that multiple of the same observations in adults are also present in adolescents.

REM sleep behavior disorder and brain structure

Of the included studies, six had a specific focus on REM sleep behavior disorder (RBD) and its associations with brain structure. RBD is characterized by heightened arousal during REM sleep which leads to talking, walking, or other more complex behaviors during sleep.[90] The RBD studies identified several associations of the disorder with brain structure including reduction in GMV in the cerebellum and the hippocampus,[85] and increased cortical volumes in the frontal cortex, caudate nucleus and the thalamus.[91] Widespread cortical and subcortical volume reductions were also found in iRBD patients with cognitive impairment.[92] Taken together, these findings indicate that disruption of sleep at the REM stage are associated with wide-ranging alterations in brain structure, with both increases and decreases in grey matter.

2.4 Discussion

In this scoping review we aimed to assess and chart the existing data on associations between sleep issues and brain structural changes. Our literature searches resulted in inclusion of 31 studies focused on assessment of both grey and white matter. In the following parts of the discussion, we aim to address the three main research questions that we posed at the beginning of the review.

1) What is the current knowledge regarding associations between sleep disorders, sleep deprivation, or other sleep disturbances and brain structure across the lifespan?

Studies surveyed as part of the current review indicate multiple changes in brain structure associated with sleep disturbances in children and adolescents,[12,71,78,82,88,89] and normally ageing adults.[74,75,80,81,86,87,93] We briefly discuss the findings related to 1) children and adolescents, and 2) adults, in the two paragraphs below.

Sleep and brain structure in children and adolescents

With regard to the brain regions identified as structurally altered in adolescents with disturbed sleep, many are related to important cognitive functions such as decision making and problem solving. These regions include the prefrontal, frontal, and temporal cortex, as well as the precuneus and supramarginal gyrus. Importantly, decreased thickness in the dorsolateral prefrontal cortex was found to be related to early-life disturbed sleep amongst children as young as 7 years old.[51] These results could indicate that the neural basis for cognitive deficits due to poor sleep may be forming in early adolescence.

Sleep and brain structure in adults

In normal aging adults more diverse patterns of associations seem to emerge, yet the overall amount of evidence charted in this study clearly suggest an association between disturbed sleep and changes to brain structure, similar to that observed in adolescents. In particular, reductions in frontal and temporal lobe volume are present in both adolescents and adults. One example is the study by Kim et al, 2021 who identified changes to midsleep time (a measure based on participants time spent in sleep) was associated with GMV changes, more specifically changes in frontal and temporal regions, thus showing a volumetric reduction. It seems that sleep disturbances and reductions have a

significant impact on the frontal and temporal lobe showing the effect exist across lifespan. Thus, these established association, which could be suspected to occur due to developmental phases, seemingly exist when sleep disturbance and disruption is present across all ages. Therefore it is fair to assume that these GMV reductions are most likely rooted in the underlying sleep pathology and not merely confounding results representative of different phases in life.
Some of the changes observed such as reductions in frontal and temporal lobes, in adults might further mitigate an increased risk throughout life for the early onset of cognitive decline[46] and potentially dementia[46] due to increased and accelerated brain aging, and should therefore be taken seriously.

Findings observed in this review, indicate that sleep is integral to memory and memory consolidation in adults.[94,95] For example some of the included studies showed that a decrease in slow wave sleep was significantly associated with reduced cortical and subcortical volumes, but also higher WM hyperintensities. Since these are reported to increase with chronological age, this may indicate potential associations between sleep and accelerated biological brain ageing.[75] This has further interest, since slow wave sleep is suspected to be the main restorative phase of sleep.[96] Thus, a potential mechanism in these cortical changes could be speculated to be the disruption of glymphatic activity and restoration during slow wave sleep. This could lead to acceleration of brain aging potentially due to decreased glymphatic clearance and increased buildup of toxins affecting neurogenesis and synaptogenesis.

2) What are the methods applied in the published research studies investigating brain structure changes in sleep disturbances in humans and how consistently are they used?

The vast majority of studies surveyed in the current review (77%) investigated brain measures derived from T1 structural scans. These include, for example, regional cortical thickness, surface area, sulcal depth, or overall grey matter volume measures. Such measures are often derived following standardized protocols with openly available toolkits such as FreeSurfer[97] – which provides an advantage for reproducibility. The drawback of such measures is that they can be relatively coarse (i.e. assessing measures of relatively large regions of the brain, depending on the applied brain atlas), and thus effects of sleep on smaller more specific regions can be missed. An alternative technique which can help assess structural changes across the entire brain is voxel-based morphometry

(VBM),[98] however it requires higher statistical power due to higher fidelity (more statistical tests to correct for). Nonetheless, future studies with large sample sizes could employ VBM, as seen in the included study by Remillard-Pelchat et al, 2021,[92] to identify more specific changes in brain grey and white matter related to sleep deficits and disorders.

Substantially fewer of the surveyed studies (16%) investigated measures based on DTI. All five studies were relatively consistent in their methods when investigating white-matter integrity measures and tested for voxel-wise differences in either fractional anisotropy (FA) or mean diffusivity (MD) maps (although Takeuchi et al., 2018 did not skeletonize MD maps in contrast to others). In contrast to measures of white matter integrity, only one study investigated DWI-derived structural connectivity with probabilistic tractography methods, revealing tentative but specific regional connections altered by poor sleep.[72] Probabilistic tractography techniques are generally computationally intensive, which may have limited their application in studies of sleep – this remains an important avenue for future research as computational resources become less expensive. Finally, only few studies of white matter hyperintensities (WMH) were included. WMH are related to dementia and cognitive impairment and Baril et al. (2021) found that less slow-wave sleep is associated with higher WMH volumes[75]; future studies could e.g., check how WMH volumes are related to other aspects of sleep apart from slow-wave or investigate potential causality.

3) What are the current knowledge gaps with regard to associations between sleep disturbances & brain structure?

Causal directionality: One major limitation in the current literature is the fact that causal directionality in brain-sleep associations has not been established. Low quantity and quality of sleep can be reasonably expected to play a major role to changes in brain structure,[72,88] however associations in the other direction have also been found. For example, Liu et al. (2018) found that atrophy in cerebral, hippocampal and thalamic grey matter mediated the effects of age on subjective sleep quality.[81] Directionality in sleep-brain associations is overall challenging to study, especially because there are many socio-economic, physical and mental health-related confounders that can affect sleep. To address these issues, future studies should employ longitudinal designs with long follow-up periods and assess changes in sleep over time while simultaneously controlling for relevant confounding variables that can affect brain structure. Such designs can help establish the causal effects of changes

in sleep on the brain and can help understand how sleep disorders affect brain development in younger individuals, as well as brain ageing later in life. Finally, in adolescents, multiple changes in brain structure were found to be associated with disturbed sleep. One possible cause for these changes might be the alterations in cortical pruning. Cortical pruning is an important phenomenon related to brain maturation, taking place in adolescence. Another possibility might be that disturbed sleep may lead to changes in cortical pruning, which in turn may lead to changes in brain structure. The potential role of cortical pruning in mediating the association between sleep and brain structure in adolescence remains to be investigated in future studies.

Patterns of relationships, sample sizes and replication:

Not all sleep problems or even problems with different sleep stages are the same. The observed relationship in this scoping review illustrates that although multiple associations can be established, they often differ in multitude of ways, by the scale used for measurement. This is shown by different observed directionalities, and different focus on specific sleep stages. Considering that both objective and subjective sleep measures have large differences, inferring results becomes more difficult. Most of the studies if not all managed to use imaging analysis that have been established with rigid protocols and thus enhance replications in terms of the used imaging modality, nonetheless a clear tendency was shown towards T1 scans, meaning that white matter microstructural knowledge is less studied in this field. Further the sample sizes varied a lot but in general studies with more than 1,000 participants were few. The study by Cheng et al 2020, however did utilize the large ABCD cohort of more than 11,000 children.[36]. More studies of this type are needed seeing a lack of large, scaled neuroimaging studies assessing sleep. Replication is clearly hampered by two major issues the lack of large enough studies that allows for repeated adjustments across studies and a lack of more uniform sleep measures. Filling out these gaps by conducting larger studies would benefit the already vast knowledge base existing on sleep disorders. Further doing it in larger samples allows for more statistically sound methods and adjustments of relevant confounders such as mental disorders that can impact sleep disorders significantly. Finally different sleep disorders might have different effects on the brain, therefore increasing sample sizes will allow for further studies to look at more rare sleep disorders and shed light on potential different etiologies and effects.

Strengths and limitations

To our knowledge, our current work is the first scoping review addressing brain structural changes associated with sleep and sleep disturbances. We utilized the structured framework for conducting

scoping reviews by Arksey and O'Malley (2006) and searched multiple databases. The core strength or our review is that we provide novel insights into what structural brain imaging methods have been used to study sleep previously, thus highlighting where there is a need for future changes. This information will help inform future research into the effects of sleep on the brain by highlighting major strengths, knowledges but also gaps of the current literature.

Several limitations of the current review should be mentioned. First, we deliberately limited the scope to only survey studies of brain structure, but not function. Sleep affects the brain in a multitude of ways and is intrinsically linked to brain activity during wakefulness. In that regard, knowledge of how sleep habits, quality, quantity, and disturbances are linked to brain function, in both short term and long term, can be of tremendous value both for public health and for a better understanding of the brain physiology. This remains an important avenue for further research. Second, in line with the recommendations of Arksey and O'Malley (2006) for scoping reviews, we did not perform a quantitative or detailed analysis of the findings in the literature, but rather charted the key findings and research methods. Detailed quantitative surveys of changes in the brain associated with sleep-related factors should be an avenue for further work. Due to our pre-defined scope, we did not consider animal studies. Studies of rodents, for example, can provide substantial insight into the effects of sleep on the brain at the molecular level,[99] which is largely not possible with human brain imaging. Future scoping reviews could focus on sleep in rodents, which will complement the findings described here.

A further limitation of the current survey is that we did not review studies which considered the role of mental health disorders. Moreover, sleep disorders often co-occur with other psychopathologies in adolescence, and the distinct and cumulative effects of different disorder-related factors on brain development is yet to be fully examined. Another limitation in the existing literature is the wide variety of sleep assessment tools used. Some studies used subjective sleep measures such as the PSQI questionnaire and sleep diaries, others assessed clinician-confirmed sleep disorders (e.g., RBD), and others applied more objective measures of sleep such as those based on actigraphy and polysomnography. All these tools arguably capture different aspects of sleep and sleep disruption, which in turn have different associations with brain structure. Future research should more specifically delineate the different and common aspects of sleep captured by the instruments and describe the brain structure associations characteristic for the different aspects of sleep.

2.5 Conclusion (SR)

In this scoping review we identified that most human brain imaging studies of sleep or sleep disruption applied T1-weighted imaging and performed grey matter or subcortical structure morphometry. We identified that disturbed sleep is related to reductions in volume in an array of brain areas, including prefrontal, frontal and temporal areas and the precuneus and supramarginal gyrus, across lifespan in both adults and adolescents. Further to that, another group of studies applied DTI and found that disruptions in sleep are associated with decreases in white matter integrity in several brain regions. A clear gap in the literature identified in the current review is the lack of knowledge regarding the causal effects of sleep disruption on brain structure and vice versa, and a lack of studies addressing white mater microstructural changes – this will hopefully be addressed in the future longitudinal studies using larger samples. Overall, sleep is very important for brain health and is closely associated with structure of multiple brain regions.

3. Aim and hypothesis

This project aims to address gaps in previous research by assessing associations between sleep, suicidality and brain structure in a large adolescent cohort. Considering how sleep disorders have been found to be a strong predictor of both suicidal ideation but also behaviors, the study question and aim of this study was to investigate whether early adolescents with sleep disorders show signs of altered brain structure and subsequently experience more suicidal ideation and behavior than those without any reported sleep disturbances. Further it was to assess if these suicidal outcomes had associations to brain structural changes. Given that it remains to be discovered in full what the likely underlying biological mechanisms involved between sleep and suicidality are, the aim was to (I) test relationships between sleep and suicidal ideation in a large youth cohort, and (II) Determine relationship between sleep and brain structure, and between (III) Suicidal thoughts and behaviors (STB) and brain structure.

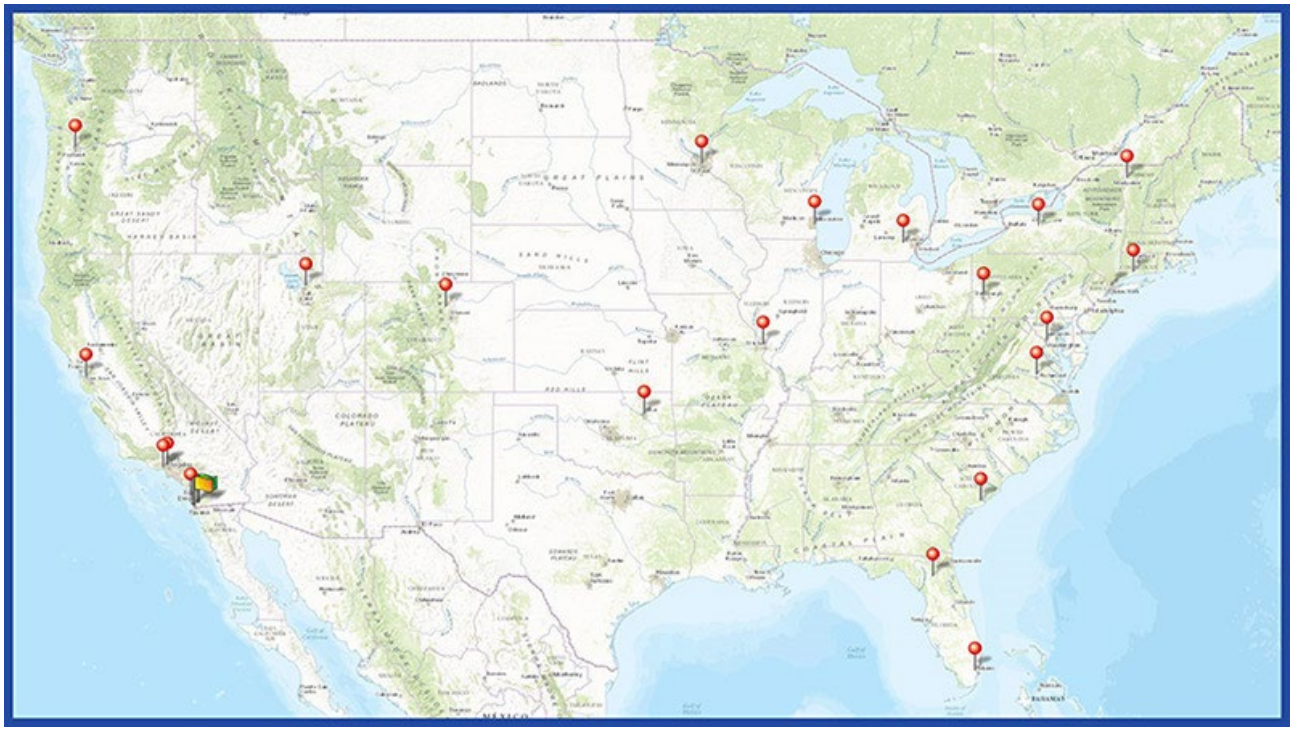
Addressing gaps identified:
Causality: We would like to have addressed directionality between brain structure, sleep disorders and Suicidal thoughts and behaviors (STB), using advanced mediation techniques maximizing the temporal elements of the data, but at the time of the study there were not sufficient longitudinal data to do this in the ABCD study (only baseline year 1 and 2 follow up). Therefore, we opted to examine associations from baseline (exposure) to 2-year follow-up (outcome), to maximize the available data, but stayed clear of formal mediation models or growth curve modelling due to the lack of sufficient follow-up data. These analyses do however examine longitudinal outcomes when examining baseline sleep disorders and STB in relation to 2 year follow up brain structure. Thus, this study addresses some of the major gaps highlighted in the scoping review:
Firstly, by utilizing a large robust sample size with more than 11,000 participants and secondly, by including DTI scans to further assess changes to white matter microstructure changes. Thirdly by using a uniform and often tested measure of sleep disorders in children and by also addressing subscale disorders and overall total score of sleep disorders.

4. Design and methods

4.1 Data source – Adolescent Brain and Cognitive Development Study (ABCD)

Participants included in the current study were from the Adolescent Brain and Cognitive Development Study (ABCD). The ABCD study began in the USA and is a comprehensive and large-scale attempt to capture changes observed during adolescent development. It was initially established to investigate development of substance abuse in early adolescence but has since extended its scope. The ABCD study is a multisite, national representative major study measuring children from the age of 9-10 years through pubertal development over a 10-year period of life. The project started gathering data in 2018 and has continued to the current date. In total 11,886 children and their parents were included at baseline and subsequently followed over the 22 different study sites.[100,101]

Figure 1 - Study sites of the ABCD study:



Biennial assessment has been carried out, measuring mental health measures through various tools such as the Child Behavioral Checklist, neurocognition, family and cultural information, and environmental variables.[101] Substance use, genetic, and other biomarkers are also tracked, as is structural and functional brain development.[102,103] The data source therefore offers unique insights into brain development and allows for measurement of key variables related to mental health. Further, it presents a data source wherein the cohort has approximated the general US population on key sociodemographic variables such as race, sex, ethnicity and income and education.[104] In the current project we focus on sleep, suicide/self harm and mood outcomes as well as brain imaging data, for this reason the description of the variables below focusses on these aspects.

Data collection:

Data was obtained and accessed through the NIMH NDA that facilitates the ABCD data storage after approval was given. Permission was given under the DAR-Number: 10607 (Renewal of 6997)

to the external organization ID:2312301 with the federal wide assurance number: FWA00018101 as The University of Edinburgh.

Follow up lab-interviews of the majority of measures included was conducted every year.[105] As shown in figure 2 at least every year. Brain imaging measures was acquired every two years. We utilized baseline, one year and two years follow up lab interview measures in the Child Behavioral Checklist (CBCL) and Sleep Disturbance Scale for Children (SDSC), and imaging measures at 2 years follow up. Additional details of covariates and timepoints of selection are described below. All these variables were derived from Data release 4.0. Participants not responding or missing data in in all questionnaires were tracked or recorded down as NA. The total usage of data from their respective timepoints can be seen in the following table:

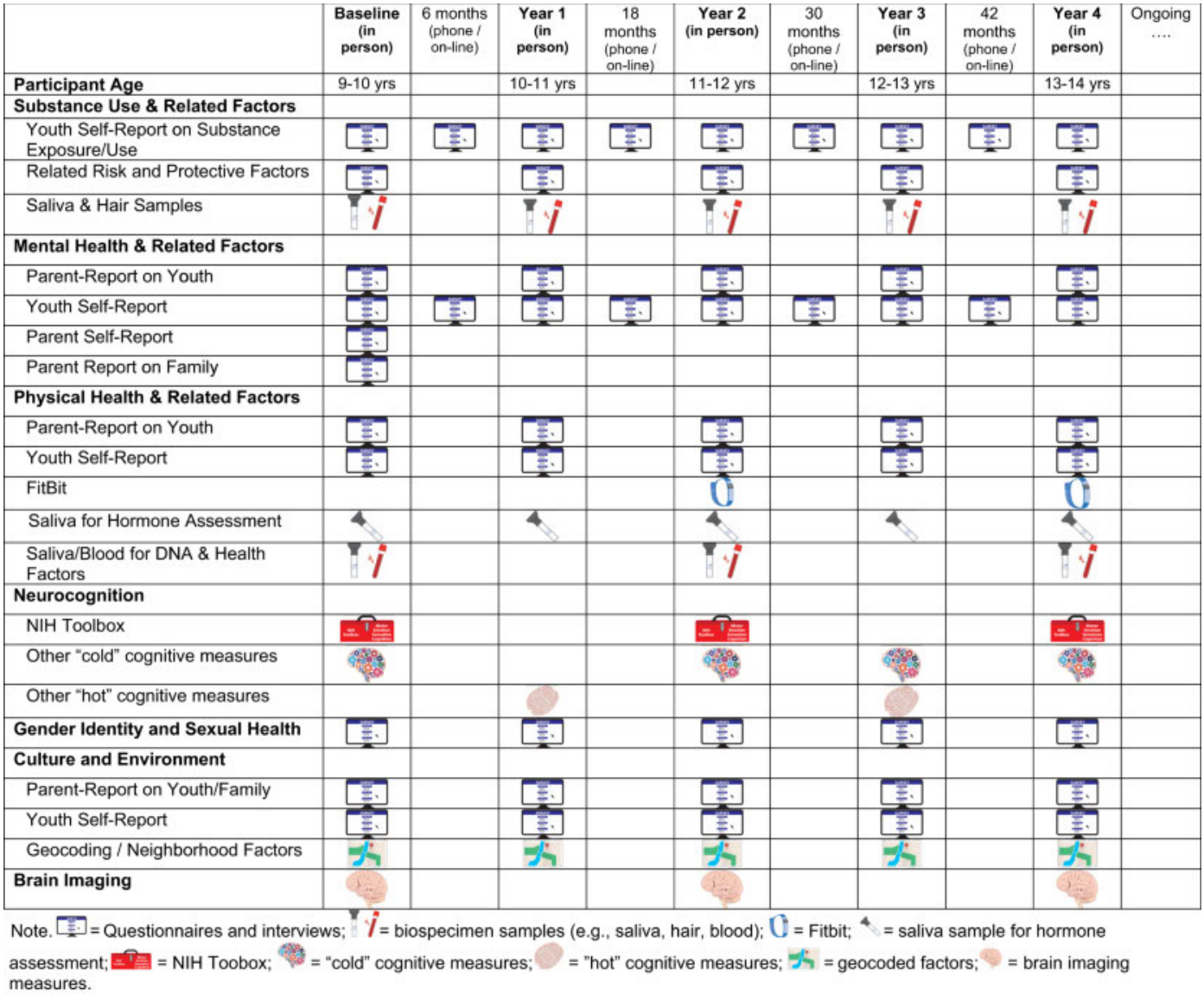
Table 1 – timepoints for all measures and models used.

Measures	Baseline	1 year follow up	2 year follow up
Sleep Disturbance Scale for Children (SDSC)	X	X	X
Suicidal ideation (SI) and suicide attempt/self harm (SH) Child Behavioral Checklist (CBCL)	X	X	X
Imaging Data (T1 and DTI)			X

Models:	
Model 1a	SDSC (baseline)~SI/SH (2 year follow up
Model 1b	residual (SDSC)~SI/SH (2 year follow up)
Model 2	SDSC (baseline)~Imaging (2 year follow up)
Model 3	SI/SH (baseline)~Imaging (2 year follow up)

All data follow up time points can be seen in the following Figure from Karcher et al.[105]

Figure 2 – Follow up time points from Karcher et al.[105].



Note. = Questionnaires and interviews; = biospecimen samples (e.g., saliva, hair, blood); = Fitbit; = saliva sample for hormone assessment; = NIH Toobox; = "cold" cognitive measures; = "hot" cognitive measures; = geocoded factors; = brain imaging measures.

4.2 Exposure – Sleep disturbance in the ABCD study, Sleep Disturbance Scale for Children.

Sleep as the main exposure variable was assessed via the parent reported Sleep Disturbance Scale for Children (SDSC) questionnaire [106]. The SDSC is a 27-item inventory 5 point Likert type scale with six different domains.[106] It is used to derive measures of overall sleep disturbance (the Total Sleep Disorder score, TSD) as well as 6 specific sleep disorders (see table below). The SDSC questionnaire was completed each year at the in-person interview (baseline, year 1 follow up, year 2 follow up). The TSD measure was used as a binary variable (with a cut off score ≥ 39[106]) for descriptive statistics, but as a continuous variable in Linear Mixed Effect Models analyses described below. Further information on the scoring and construction of all the disorders can be found in the original paper by Bruni et al.[106]

Table 2 Sleep disorder abbreviation and full title:

Abbreviation	Full title
TSD	Total Sleep Disorder
DIMS	Disorder of Initiating and Maintaining Sleep
DOES	Disorder Of Excessive Somnolence
SWTD	Sleep Wake Transitions Disorder
DA	Disorder of Arousal/nightmare
SBD	Sleep Breathing Disorder
SHY	Sleep HYperhidrosis

The TSD and the 6 sleep disorders were all utilized as exposure outcomes in separate but linked analyses. Baseline measure of SDSC was utilized as primary predictor variable in imaging and

suicide models, while 1 and 2 years follow up scores were utilized for the construction of residual scores, used to examine changes in sleep across assessments.

4.3 Exposure – Imaging derived brain measures

Imaging data was obtained and processed by the ABCD team. The study utilized 3 Tesla Siemens Prisma, General Electric or Phillips MR scanners for data acquisition. The study team implemented a standard protocol for scanning to avoid across site heterogeneity.[103] T1-weighted image had been produced with gradient echo scans using a 1x1x1 mm3 resolution, to obtain cortical and subcortical structural measures. Diffusion data was obtained by high resolution diffusion imaging in order to obtain microstructural changes in white matter tracts. Quality control was conducted according to recommend quality control offered by the ABCD study in the release notes of data release 4.0. Participants were given simulation and motion compliance training before initiating the scan itself to further avoid in-scanner errors as well as real time motion detection and correction in structural scans using the ABCD DAIC software.[103] All scan types, have previously been found to have an across site completion rate of almost 90%.[103]

In the latest data release the ABCD team created a data frame named *abcd_imgincl01* this has inclusion flags identifying whether or not a participant meets the requirement for QC. This feature existed for all relevant imaging modalities utilized in this study. In this study all individuals that met the recommended inclusion criteria for the T1 scans and the DTI scans were included for analysis. Measures of T1 and DTI scans from the ABCD cohort was obtained in a hierarchical order from global measures to regions measures as tabular data that had been preprocessed and postprocessed by the ABCD team. We assessed global cortical and subcortical metrics, followed by individual regions. We also assessed global FA and MD measures followed by individual tract measures of FA and MD. FA and MD were derived individually for global and tract measures by the ABCD team using "standard linear estimation with log transformed diffusion weighted signals".[102] We added an additional variable to account for frame displacement in DTI scans (ie DTI mean motion) given the vulnerability for movement in DTI scans.[107] For the cortical measures, all four different modalities were selected: Sulcal depth, surface area, cortical thickness, and cortical volume. We utilized the Desikan-Kiliany atlas and thus used the parcellation of first global whole brain measures and 34 bilateral cortical structures and a further 16 bilateral subcortical structures.

For bilateral measures, a mean value was created across hemisphere. This was to reduce the number of multiple corrections required, given we did not have specific hypotheses about laterality effects. The white matter measures utilized were fractional anisotropy (FA) and mean diffusivity (MD), these measures are used to observe changes to microstructural white matter integrity. For the white matter analysis, the atlas 'AtlasTrack' was utilized, consisting of 14 bilateral and 3 unilateral tracts, from which FA and MD values for each tract and global measures, were derived separately. FA and MD models for global and regional measures will further be run separately to avoid multicollinearity.

Thus, all Imaging Data has been controlled and checked and assessed for standard imaging errors and motion disturbance, in advance of analysis. Participants who didn't meet the ABCD imaging inclusion criteria were excluded from imaging analysis.

Figure 3 – ABCD Neuroimaging Protocol

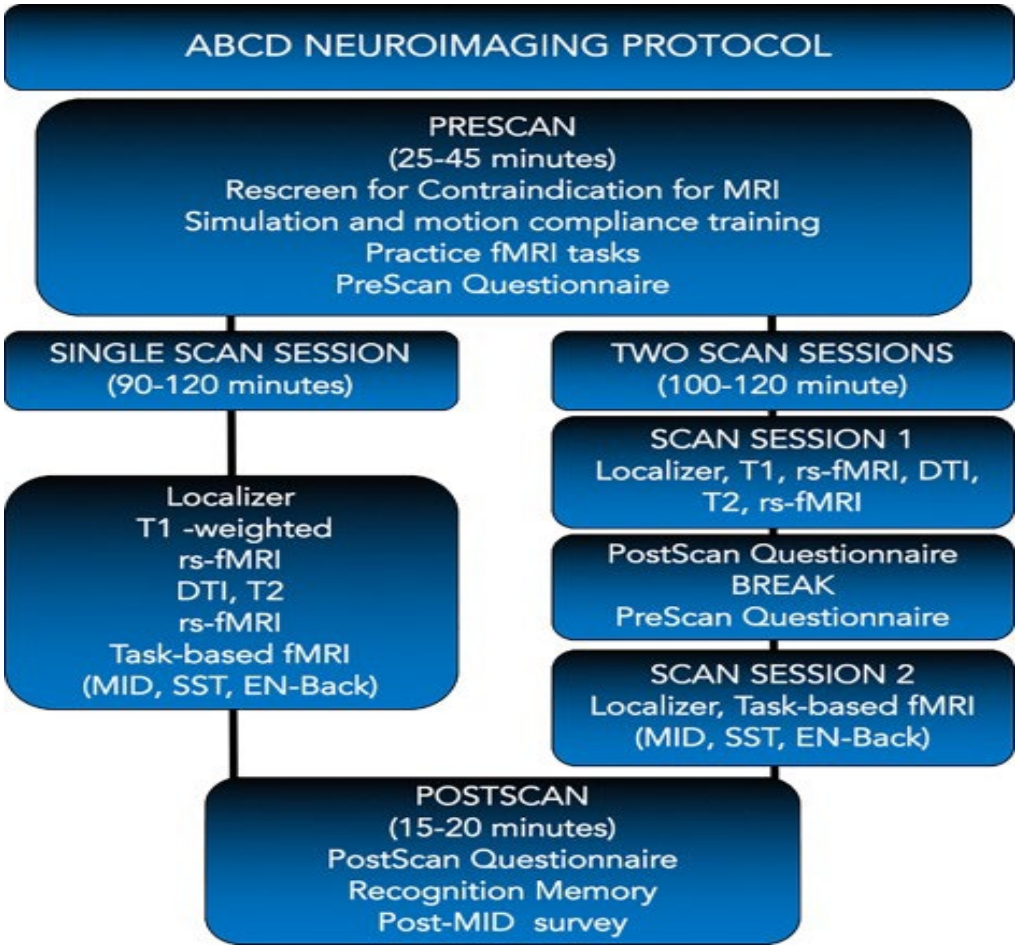


Table 3 Overview of the assessed cortical, subcortical and white matter tract regions:

Cortical Regions	Cortical Regions	Cortical Regions
Banks Of Superior Temporal Sulcus	Pars Orbitalis	Superior Temporal Lobe
Caudal Anterior Cingulate Cortex	Pars Triangularis	Supramarginal
Caudal Middle Frontal Lobe	Pericalcarine	Frontal Pole
Cuneus	Postcentral Gyrus	Temporal Pole
Entorhinal	Posterior Cingulate Cortex	Transversetemporal
Fusiform	Precentral Gyrus	Insula
Inferior Parietal Lobe	Precuneus	Lingual Lobe
Inferior Temporal Lobe	Rostral Anterior Cingulate Cortex	Medial Orbito-Frontal Lobe
Isthmus Cingulate Cortex	Rostral Middle Frontal Lobe	Middle Temporal Lobe
Lateral Occipital Lobe	Superior Frontal Lobe	Parahippocampus
Lateral Orbito-Frontal Lobe	Superior Parietal Lobe	Paracentral Gyrus
		Pars Opercularis

Subcortical regions	White matter tract	White matter tract
Caudate	fornix	forceps major
Putamen	Fornix excluding fimbria	forceps minor
Amygdala	cingulate cingulum	corpus callosum
Thalamus proper	parahippocampal cingulum	superior longitudinal fasciculus
Pallidum	corticospinal tract (pyramidal tract)	temporal superior longitudinal fasciculus
Accumbens area	anterior thalamic radiations	parietal superior longitudinal fasciculus
Hippocampus	uncinate	superior corticostriate
Ventral diencephalon	inferior longitudinal fasciculus	frontal superior corticostriate
Subcortical grey volume	inferior frontal occipital fasciculus	parietal superior corticostriate
	inferior frontal to superior frontal cortical tract	striatal inferior frontal cortex tract

4.4 Outcome measure - suicidality

The primary outcome was suicidal ideation (SI) and/or the measure of suicidal behaviors: self-harm/suicide attempt (SH). These two outcomes are different as ideation is a measure of thoughts and potential intent, and self-harm/attempt is an actual measure of action taken towards either deliberately hurting or ending one's life. These measures were obtained through the Child Behavioral Checklist used in the ABCD data and was measured at each in-person interview (baseline, year 1 follow up and year 2 follow up). The Child Behavior Checklist is a 113 item frequently used interview instrument, used to assess children's behaviors and is completed by both

teachers, parents and self.[108] It has previously been utilized in other studies to measure suicidality.[109] Participants and caregivers were asked questions relating to different aspects of behavior and emotions within the previous 6 months. In this study we utilized questions that were all parent reported and used for measuring suicidality in the ABCD cohort. The question referring to suicidal ideation was:" Talks about killing self: 0 = Not ; 1 = Somewhat/Sometimes True; 2 = Very True/Often True/ " and the question referring to actual self-harm and suicide attempt was: " Deliberately harms self or attempts suicide: 0 = Not True; 1 = Somewhat/Sometimes; 2 = Very True/Often True". For simplicity we wanted to unify these measures into a binary variable considering the rarity of suicidal behaviors and actions in such a young population and therefore the variable of Suicidal Ideation was converted into a binary outcome of either:
(I) "Talks about killing self: 0= Not True; 1=True"
and Self-harm and Suicide Attempt was recoded likewise as:
(II) "Deliberately harms self or attempts suicide: 0 = Not True; 1 =True".
No measure on death by suicide was available.

4.5 Additional Measures

Additional covariates were included to adjust for potential confounding effects that might be present amongst adolescents. As fixed effects, age and sex was used to account for potential age and sex related differences that might exist. We opted to use age seeing how sleep patterns change rapidly in young age from year to year. Sex as a covariate was included because sleep disorders and suicide attempts are known to vary greatly with respect to sex. we further also used the measure of sex to conduct stratified sex analysis. The sex variable only accounted for biological sex at birth and thus, gender identity was not accounted for. Body mass index (BMI) was utilized as a covariate to assess the impact weight has on sleep disorders in particular sleep breathing related disorders.

We further wanted to assess the impact of mood and used Depressed thoughts and anxiety measure as a covariate; these were derived from the corresponding syndrome score in the CBCL of anxiety/depression. This was included in linear mixed effect models as fixed effects. This was done because the relationship between sleep and STB could be impacted by mood severity. Although there are arguments for including such important relationships in analysis, we took the conservative approach to control for mood to parse out relationships that were more closely linked to sleep. We

added in this covariate to make sure mood severity didn't confound our analyses. The impact and role of mood will be described further in the discussion.

Participant ID, Family ID, Scanner ID and Site ID were included as random effects. These were utilized to account for the subjects themselves their families and site or scanner. Family ID, Scanner ID and Site ID were included as random effects.
Subject ID was used to account for each participants unique ID and presence in the study and the changes within each participant, given the longitudinal/temporal nature of the data. Further site was used as a random effect to account for the different geographical settings each interview modality was given in, and for imaging analysis scanner id was utilized as a random effect. This was to account for the variance explained by each scanner utilized for each participant. Finally, family ID was used to account for each participants family and the associated effects of living within each family. This was to account for the different variance between and within families. We opted to use this measure to explain family variance instead of adding on multiple covariates of for example parent education and parent income to avoid overfitting our models.

4.6 Statistical analysis:

Analysis was construed into three different main analysis modes:
Firstly, Linear mixed effect models (LME) were used to assess the relationship between sleep disorders and suicidal outcomes. This type of statistical modelling has previously been used and is recommend for use in the ABCD study.[110] A fully adjusted model was used with the following set of covariates:

sleep disorder ~ Suicidal measure +sex+age+bmi+anx/dep+(1|subject)+(1|site)+(1|family).

Suicidal measures were captured at baseline as was all added covariates. The outcome of sleep disorder was captured at 2 year follow up.

The beta effects derived were utilized to further derive Odds ratio with 95% CI of suicidality in those with sleep disorders. Results were considered significant at pFDR>0.05. Nominal p values p<0.01 are also noted for completeness.

In order to assess potential changes in sleep disorders over the study, rather than a single cross sectional measure at baseline, we opted to derive one total residual change scores for sleep disorders

over the 2 years follow up period. We did this by regressing the scores of sleep disorders at baseline onto the scores of sleep disorders at year 1 (reg-score-1) and year 2 (reg-score-2), and subsequently regress the two scores of year 1 upon year 2 (reg-score-2 ~ reg-score-1) to derive a final residual changes score (reg-score-final) that accounts for changes in sleep over the entire 2 year period. These residual scores were then used as predictor variables in LMEs assessing association between suicidal outcomes and residual changes to sleep disturbance. The residuals were tested for association with suicidal outcomes at year 2 in the following model type:

residual change score sleep disorder ~ Suicidal measure

+sex+age+bmi+anx/dep+(1|subject)+(1|site)+(1|family).

Suicidal measures were captured at baseline as was all added covariates. The outcome of residual sleep disorder was captured as a residual measure covering the whole follow up period.

Secondly, Linear mixed effect models were applied to assess the relationship between sleep disorders or suicidal measures and brain structural changes including cortical, subcortical and white matter changes.

In the LME models the association between sleep disorders and altered brain structure was analyzed as:

sleep disorders ~ brain structure/ROI +sex+age+bmi+anx/dep + (1|subject) +(1|scanner ID) +(1|family).

Sleep disorders were captured at baseline as was all added covariates. The outcome of brain structure changes were captured at 2 year follow up.

Here we implemented subject, family and scanner ID as a random effect. This model was run for all cortical and subcortical (thickness, surface area, volume and sulcul depth) and white matter (fractional anisotropy and mean diffusivity) measures, both global and regional. In all DTI white matter analysis, we further added a covariate of mean DTI scan motion to account for motion during DTI scans, this was treated as a within-participant fixed effect for each participant. For all analyses results were considered significant a pFDR<0.05. For completeness we also note nominal significance at 0,01.

We further wanted to test suicidality at baseline and its effects on brain development. Therefore we changed suicidal measures from outcome to predictor variables and created models similar to those conducted for sleep disorders and brain changes:

suicidal measure ~ brain structure/ROI +sex+age+bmi+anx/dep + (1|subject)+(1|scanner ID)+(

1|family).

Suicidal measure were captured at baseline as was all added covariates. The outcome of brain structure changes were captured at 2 year follow up.

The complete overview of the utilized models can be seen here:

Table 4 – All utilized models, with respective timepoints.

Models:	
Model 1a	SDSC(baseline)~SI/SH(2 year follow up
Model 1b	residual(SDSC)~SI/SH(2 year follow up)
Model 2	SDSC(baseline)~Imaging(2 year follow up)
Model 3	SI/SH(baseline)~Imaging(2 year follow up)

5. Results

5.1 Characteristics of sleep disturbance in early adolescents.

The overall sample of children with sleep disorder and suicidal outcome data was 11,869 at baseline. At 1 year follow up and 2 year follow up, this was reduced to 11,206 and 10,356, respectively. Thus 1513 (12%) participants were not recorded at 2 year follow up for either sleep disorders or suicidal outcomes. At baseline 3,171 (26.6%) children met the clinical cutoff score (scale used≥39) for sleep disorders, while at year 1 and year 2 follow up, 3,012 (26.8%) and 2645 (25.4%) children met the cutoff score for a sleep disorder, respectively. The proportion of sleep disordered children stayed consistent over the 2 years of observation. It should be noted that reaching a score at 39 or higher in the SDSC may be the result of multiple low scores in a lot of different disorders, resolving in a higher cumulative score. Thus, it does not necessary reflect that a child has one unique sleep disorder, rather it might be affected by a variety of sleep related challenges.

Children who met the total sleep disorder cut off score (≥39) had a higher mean score on the CBCL Anxiety Depression syndrome scale at baseline (mean=4.4, SD=3.8, Pnom<0.001), 1 year follow up (mean=4.4, SD=3.9, Pnom<0.001) and at 2 year follow up (mean=4.0, SD=3.8, Pnom<0.001) versus the control population scores at baseline (mean=1.8, SD=2.4, Pnom<0.001), 1 year follow up (mean=1.9, SD=2.4, Pnom<0.001) and at 2 year follow up (mean=1.7, SD=2.3, Pnom<0.001). Regarding ethnicity differences, close to 25% of all individuals in each race met or exceeded the cut off score (Pnom <0.001 at baseline, 1 and 2 year follow up). A significantly higher mean value of BMI was also observed in those with sleep disorders compared to those without sleep disorders (mean=19.1, SD=4.2, Pnom<0.001) as can be seen in Table 1. Finally, no significant sex difference was observed with regards to the mean scores of sleep disorders at any of the timepoints. For the

most part mean scores and distribution of cases on ethnicity, Depression/anxiety and sex (albeit non-significant) was stable and constant over time.

Table 5 - Characteristics of covariates and sleep disturbance.

Baseline		**No sleep disorder**	**Sleep disorder**	**p**
Race	White	5614 (74.6)	1909 (25.4)	<0.001
	Black	1332 (71.3)	537 (28.7)	
	Asian	214 (77.5)	62 (22.5)	
	AIAN/NHPI	57 (73.1)	21 (26.9)	
	Other	395 (75.2)	130 (24.8)	
	Mixed	961 (67.0)	473 (33.0)	
Sex	F	4220 (74.3)	1460 (25.7)	0.020
	M	4485 (72.4)	1711 (27.6)	
Anxiety and depression	Mean (SD)	1.8 (2.4)	4.4 (3.8)	<0.001
BMI	Mean (SD)	18.6 (3.9)	19.1 (4.2)	<0.001
Age	Mean (SD)	9.9 (0.6)	9.9 (0.6)	0.418
1-year follow-up				
Race	White	5357 (74.1)	1874 (25.9)	<0.001
	Black	1237 (74.4)	426 (25.6)	
	Asian	195 (74.4)	67 (25.6)	
	AIAN/NHPI	52 (72.2)	20 (27.8)	
	Other	347 (73.1)	128 (26.9)	
	Mixed	885 (65.9)	458 (34.1)	
Sex	F	3918 (73.2)	1435 (26.8)	0.970
	M	4295 (73.1)	1577 (26.9)	
Anxiety and depression	Mean (SD)	1.9 (2.4)	4.4 (3.9)	<0.001
BMI	Mean (SD)	19.5 (4.2)	19.9 (4.4)	<0.001
Age	Mean (SD)	10.9 (0.6)	10.9 (0.7)	0.944
2-year follow-up				
Race	White	3328 (74.4)	1146 (25.6)	0.001
	Black	607 (75.6)	196 (24.4)	
	Asian	121 (78.6)	33 (21.4)	
	AIAN/NHPI	31 (70.5)	13 (29.5)	
	Other	199 (77.4)	58 (22.6)	

	Mixed	500 (67.4)	242 (32.6)	
Sex	F	3702 (74.6)	1260 (25.4)	1.000
	M	4067 (74.6)	1385 (25.4)	
Anxiety and depression	Mean (SD)	1.7 (2.3)	4.0 (3.8)	<0.001
BMI	Mean (SD)	20.2 (4.3)	20.7 (4.6)	<0.001
Age	Mean (SD)	12.0 (0.7)	12.0 (0.7)	0.481

Distribution of sleep disorders at baseline.

Mean scores for each of the specific sleep disorders can be seen in Table 2. The mean score for TSD (Total Sleep Disturbance) was close to the clinical cutoff at 39 points for both males and females. Further, mean scores between females and males were in some cases not significantly different and overall, the mean scores for all the different sleep disorders were similar across sexes, thus not suggesting that any sleep disorder was more prevalent amongst one sex. The highest score for any of the specific sleep disorders was for DIMS, this is also expected as DIMS was the item comprised of most questions therefore leaving baseline scoring in this domain higher. TSD, SWTD and SHY had significantly higher scores for males than females at baseline. At 1 year follow up only mean scores of SHY remained significantly higher for males. At 2 year follow up there is a significant higher mean score in SWTD, SBD, SHY and DA for males compared to females. Although it should be noted that these differences in mean scores are low.

Table 6 – Mean scores of sleep disorders divided by sex.

	Females mean score (SD)	Males mean score (SD)	Pnom
Baseline			
TSD	36.2 (7.9)	36.8 (8.5)	<0.001
DIMS	11.7 (3.6)	11.8 (3.8)	0.299
SWTD	8.1 (2.5)	8.3 (2.7)	<0.001
SBD	3.7 (1.2)	3.8 (1.3)	0.022
SHY	2.3 (1.0)	2.6 (1.3)	<0.001
DA	3.4 (0.9)	3.5 (1.0)	0.014
DOES	7.0 (2.4)	6.9 (2.4)	0.148
1-year follow-up			
TSD	36.5 (7.9)	36.8 (8.3)	0.095
DIMS	12.0 (3.8)	11.9 (3.8)	0.090
SWTD	8.0 (2.4)	8.1 (2.6)	0.001
SBD	3.7 (1.2)	3.7 (1.2)	0.242
SHY	2.3 (0.9)	2.5 (1.2)	<0.001
DA	3.3 (0.7)	3.4 (0.8)	0.003
DOES	7.2 (2.6)	7.2 (2.6)	0.228
2-year follow-up			
TSD	36.2 (7.8)	36.5 (8.3)	0.080
DIMS	12.1 (3.8)	12.0 (3.7)	0.016
SWTD	7.7 (2.3)	7.9 (2.5)	<0.001
SBD	3.6 (1.1)	3.7 (1.2)	<0.001
SHY	2.2 (0.8)	2.4 (1.1)	<0.001
DA	3.3 (0.7)	3.3 (0.8)	<0.001
DOES	7.2 (2.6)	7.1 (2.6)	0.156

Abbreviations: TSD: Total Sleep Disturbance, DIMS: Disorder of initiating and maintaining sleep, SWTD: Sleep-wake transition disorder, SBD: Sleep breathing disorder, SHY: Sleep Hyperhydrosis, DA: Disorder of nightmare/arousal, DOES: Disorder of excessive somnolence.

5.2 Characteristics of suicidality in early adolescents

Suicidal ideation

In the complete sample, scores on the measure of suicidal ideation were low, and scores on the measure of suicide attempts/self-harm were even lower. However, 260 (2.2%), 275(2.4%) and 217(2.1%) children had suicidal ideation at baseline, 1-year follow-up and 2-year follow-up, respectively (Table 3). Males accounted for more than half of suicidal ideation cases at baseline with 168 (64%) out of 260 cases (P<0.001). This pattern was also observed at 1-year follow-up with 68% of the cases being males (P<0.001). However, at 2-year follow-up the amount of SI cases attributed to males had dropped to 53%, although sex differences at 2-year follow up was not significantly different. Finally, mean scores of anxieties and depression syndromes were significantly higher in children with suicidal ideation present, across all timepoints. Here and throughout, the characteristic tables will contain data on samples captured at baseline, 1 year follow up and 2 year follow up, respectively.

Table 7 - Characteristics of covariates and suicidal ideation.

Baseline		**No Suicidal Ideation**	**Suicidal Ideation**	**P**
Race	White	7355 (97.8)	163 (2.2)	0.004
	Black	1838 (98.3)	29 (1.6)	
	Asian	270 (97.8)	6 (2.2)	
	AIAN/NHPI	77 (98.7)	1 (1.3)	
	Other	517 (98.5)	8 (1.5)	
	Mixed	1383 (96.4)	51 (3.6)	
Sex	F	5584 (98.3)	92 (1.6)	<0.001
	M	6025 (97.2)	168 (2.7)	
Sleep disturbance	Not True	8605 (98.9)	93 (1.1)	<0.001
	True	3004 (94.7)	167 (5.3)	
Anxiety and depression	Mean (SD)	2.4 (2.8)	8.9 (5.1)	<0.001
BMI	Mean (SD)	18.7 (4.0)	19.1 (3.7)	0.142
Age	Mean (SD)	9.9 (0.6)	9.9 (0.6)	0.614
1-year follow-up		**No Suicidal Ideation**	**Suicidal Ideation**	**P**
Race	White	7039 (97.3)	179 (2.5)	0.036

	Black	1631 (98.1)	29 (1.7)	
	Asian	258 (98.5)	4 (1.5)	
	AIAN/NHPI	72 (100.0)	0 (0.0)	
	Other	465 (97.9)	10 (2.1)	
	Mixed	1296 (96.5)	46 (3.4)	
Sex	F	5258 (98.2)	87 (1.6)	<0.001
	M	5673 (96.6)	188 (3.2)	
Sleep disturbance	Not True	8078 (98.4)	116 (1.4)	<0.001
	True	2853 (94.7)	159 (5.3)	
Anxiety and depression	Mean (SD)	2.4 (2.9)	8.1 (4.6)	<0.001
BMI	Mean (SD)	19.6 (4.3)	19.9 (4.4)	0.356
Age	Mean (SD)	10.9 (0.6)	10.9 (0.7)	0.714
2-year follow-up		**No Suicidal Ideation**	**Suicidal Ideation**	**P**
Race	White	4364 (97.5)	107 (2.4)	0.261
	Black	793 (98.8)	10 (1.2)	
	Asian	152 (98.7)	2 (1.3)	
	AIAN/NHPI	43 (97.7)	1 (2.3)	
	Other	250 (97.3)	7 (2.7)	
	Mixed	720 (97.0)	22 (3.0)	
Sex	F	4831 (97.4)	101 (2.0)	0.800
	M	5308 (97.4)	116 (2.1)	
Sleep disturbance	Not True	7620 (98.1)	96 (1.2)	<0.001
	True	2519 (95.2)	121 (4.6)	
Anxiety and depression	Mean (SD)	2.2 (2.8)	7.9 (4.6)	<0.001
BMI	Mean (SD)	20.4 (4.4)	20.7 (4.4)	0.335
Age	Mean (SD)	12.0 (0.7)	12.0 (0.7)	0.574

All numbers are frequencies and total sums, except for Anxiety Depression, BMI and Age, these were all mean scores.

Suicide attempt and self-harm

With regards to suicide attempt and self-harm we observed 89, 112 and 133 cases of suicide attempt/self-harm at baseline, 1-year follow-up and 2-year follow-up, respectively. At baseline and 1-year follow-up males account for more cases than females, with 61 (68%) and 70 (62%) of cases at these respective timepoints, although it was non-significant. This pattern changed to a significant difference ($P<0.001$) at 2-year follow-up were females have the highest fraction of suicide attempt / self-harm, with 83 (62%) of cases attributed to them. Similarly, we observed a significantly higher mean score of the anxiety and depression syndrome in those children who had a suicide attempt or self-harm, across all follow-up times.

Table 8 Characteristics of covariates and suicide attempt and self-harm (SA/SH).

Baseline		**No SA/SH**	**SA/SH**	**p**
Race	White	7461 (99.2)	57 (0.8)	0.457
	Black	1853 (99.1)	14 (0.7)	
	Asian	275 (99.6)	1 (0.4)	
	AIAN/NHPI	77 (98.7)	1 (1.3)	
	Other	524 (99.8)	1 (0.2)	
	Mixed	1419 (99.0)	15 (1.0)	
Sex	F	5648 (99.4)	28 (0.5)	0.003
	M	6132 (99.0)	61 (1.0)	
Sleep disturbance	Not True	8664 (99.5)	34 (0.4)	<0.001
	True	3116 (98.3)	55 (1.7)	
Anxiety and depression	Mean (SD)	2.5 (3.0)	9.3 (5.7)	<0.001
BMI	Mean (SD)	18.7 (4.0)	19.2 (3.5)	0.256
Age	Mean (SD)	9.9 (0.6)	9.9 (0.6)	0.598
1-year follow-up		**No SA/SH**	**SA/SH**	**p**
Race	White	7146 (98.8)	72 (1.0)	0.759
	Black	1647 (99.0)	13 (0.8)	
	Asian	260 (99.2)	2 (0.8)	
	AIAN/NHPI	71 (98.6)	1 (1.4)	
	Other	470 (98.9)	5 (1.1)	
	Mixed	1324 (98.6)	18 (1.3)	
Sex	F	5303 (99.1)	42 (0.8)	0.038
	M	5791 (98.6)	70 (1.2)	
Sleep disturbance	Not True	8151 (99.2)	43 (0.5)	<0.001
	True	2943 (97.7)	69 (2.3)	
Anxiety and depression	Mean (SD)	2.5 (3.0)	8.0 (4.6)	<0.001
BMI	Mean (SD)	19.6 (4.3)	20.0 (4.7)	0.322
Age	Mean (SD)	10.9 (0.6)	10.9 (0.6)	0.687
2-year follow-up		**No SA/SH**	**SA/SH**	**p**
Race	White	4408 (98.5)	63 (1.4)	0.592
	Black	795 (99.0)	8 (1.0)	
	Asian	154 (100.0)	0 (0.0)	
	AIAN/NHPI	43 (97.7)	1 (2.3)	
	Other	253 (98.4)	4 (1.6)	
	Mixed	730 (98.4)	12 (1.6)	
Sex	F	4850 (97.7)	83 (1.7)	0.001
	M	5374 (98.6)	50 (0.9)	
Sleep disturbance	Not True	7669 (98.7)	48 (0.6)	<0.001
	True	2555 (96.6)	85 (3.2)	
Anxiety and depression	Mean (SD)	2.2 (2.9)	7.7 (5.2)	<0.001

BMI	Mean (SD)	20.3 (4.4)	22.0 (4.5)	0.001
Age	Mean (SD)	12.0 (0.7)	12.2 (0.7)	0.006

All numbers are frequencies and total sums, except for Anxiety Depression, BMI and Age, these were all mean scores.

5.3 Sleep disturbance and its association with suicidality

Over the 2-year study period more than half of the children struggling with suicidal outcomes (i.e., ideation or behavior i.e. attempt / harm) also had sleep disorders (i.e., met the clinical cut off score, or higher on the SDSC). As can be seen from Table 9, the complete cases for the Linear Mixed Effect Models showed that most of the children suffering from suicidal ideation also suffered from sleep disorders.

Table 9 – Complete cases of children with suicidality and sleep disorders

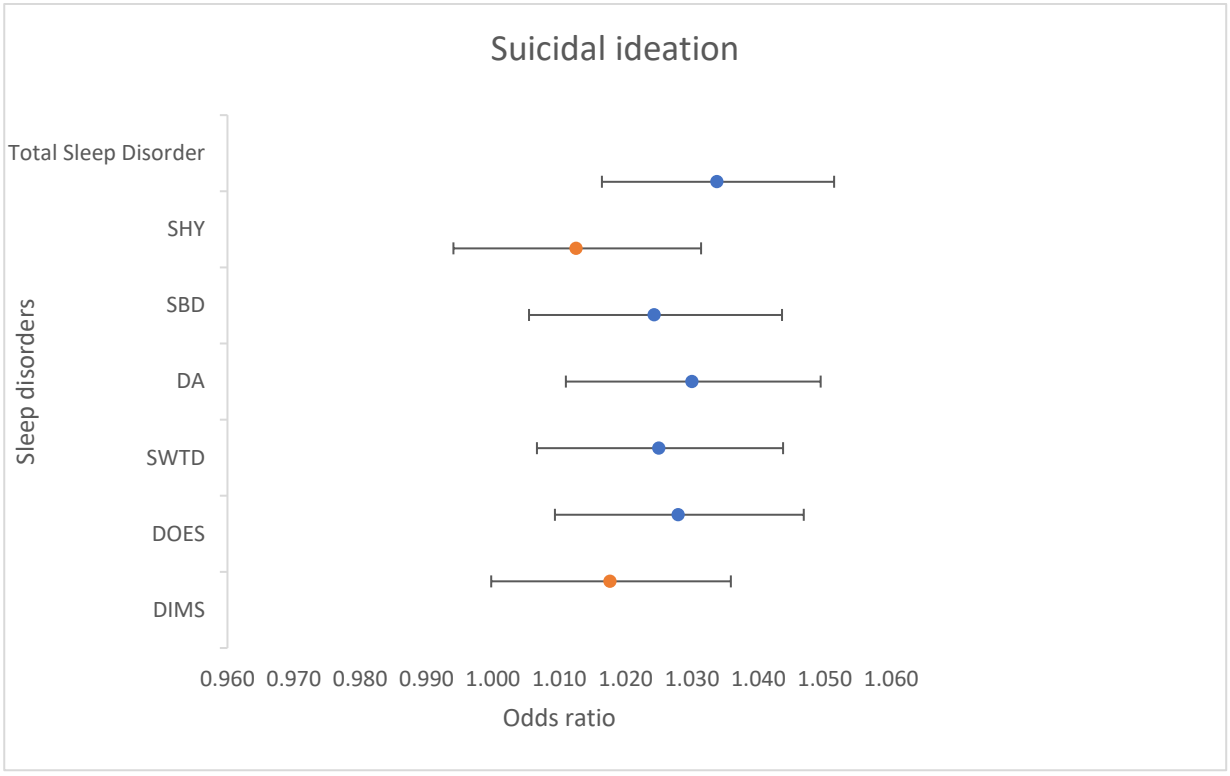
Suicidal Ideation	**No Sleep disorder**	**Sleep disorder**	**Total**
Baseline			
No Suicidal Ideation	8,605 (74.1%)	3,004 (25.9%)	11,609
Suicidal Ideation	93 (35.7%)	167 (64.3)	260
1 year follow up			
No Suicidal Ideation	8,078 (74.0%)	2,853 (26.0%)	10,931
Suicidal Ideation	116 (42.1%)	159 (57.9%)	275
2 year follow up			
No Suicidal Ideation	7,620 (75.1%)	2,519 (24.9%)	10,139
Suicidal Ideation	96 (44.2%)	121 (55.8%)	217
Suicide attempt	**No Sleep disorder**	**Sleep disorder**	**Total**
Baseline			
No Suicide Attempt	8,664 (73.5%)	3,116 (26.5%)	11,780
Suicide Attempt	34 (38.2%)	55 (61.8%)	89
1 year follow up			
No Suicide Attempt	8,151 (73.4%)	2,943 (26.6%)	11,094
Suicide Attempt	43 (38.4%)	69 (61.6%)	112
2 year follow up			
No Suicide Attempt	7,669 (75.0%)	2,555 (25.0%)	10,224
Suicide Attempt	48 (36.0%)	85 (64:0%)	133

Suicidal ideation, Suicide attempt/self-harm and sleep disorders were all captured together at Baseline, 1 year follow up and 2 year follow up respectively.

Associations between sleep disorders and suicidality

In LMEs utilizing the total sample (N=11,869) assessing total sleep disorder score and all the 6 sleep disorders, we observed significant FDR corrected estimates of associations between baseline sleep problems and increases in suicidal ideation at 2-year follow-up, albeit with small effect sizes and OR (Table 6: TSD (OR:1.03, 95% CI, 1.02-1.05), SBD (OR:1.02, 95% CI, 1.01-1.04), DA (OR:1.03, 95% CI, 1.01-1.05), SWTD (OR: 1.02, 95% CI, 1.01-1.04) and DOES (OR: 1.03, 95% CI, 1.01-1.05). Models were all adjusted for Sex, Age, BMI, Race, Anxiety/Depression, Family, Subject ID, and Site.

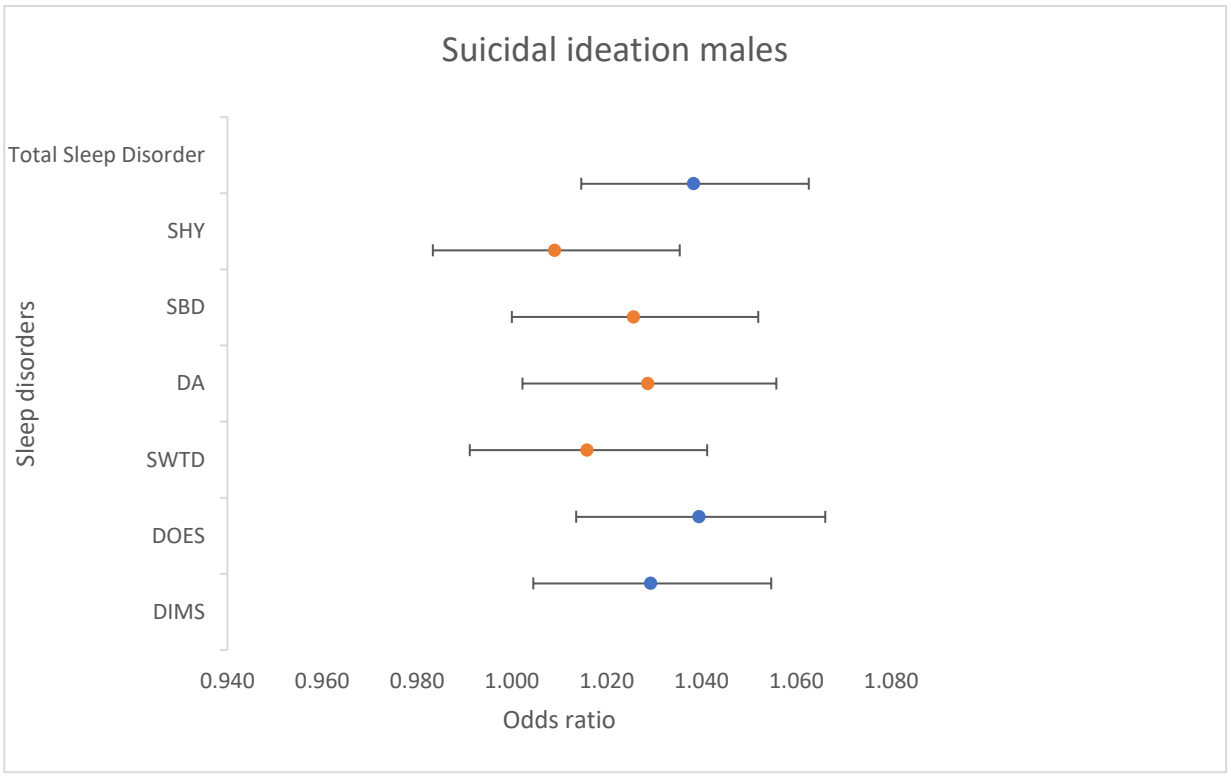
Figure 4 – Odds ratio of the association between baseline sleep disorders and suicidal ideation at 2 year follow up, in the whole sample.

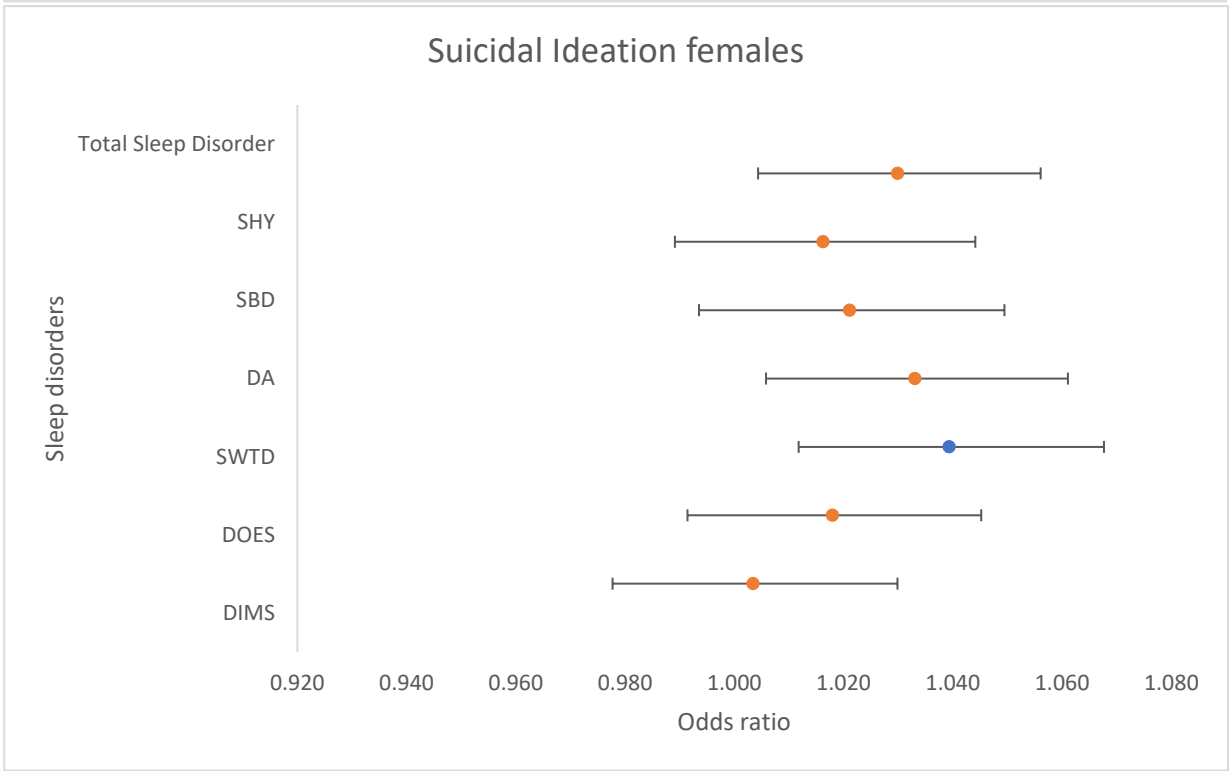


Y axis represents each individual sleep disorder, X axis represents Odds ratio for each sleep disorder. Blue color indicates FDR corrected significant results. Orange color indicates non-significant FDR corrected results.

Considering the previous mentioned sex difference, we opted to also stratify by sex. Here we saw diverging results. For males only baseline total sleep disorder (OR: 1.04, 95% CI, 1.01-1.06), DIMS (OR: 1.03, 95% CI, 1.00-1.05) and DOES (OR: 1.04, 95% CI, 1.01-1.07) were significantly (pFDR ≤0.05) associated with increase in suicidal ideation at year 2, when adjusting for Age, BMI, Race, Anxiety/Depression, Family, Subject ID, and Site. In females, however only SWTD (OR: 1.04, 95% CI, 1.01-1.07) was significantly associated with an increase in suicidal ideation (pFDR ≤0.05).

Figure 5a and 5b Odds ratio of suicidal ideation in males and females, respectively.





Y axis represents each individual sleep disorder, X axis represents Odds ratio for each sleep disorder. Blue color indicates FDR corrected significant results. Orange color indicates non-significant FDR corrected results.

Table 10 – Associations between sleep disorders at baseline and suicidality 2 years later[1]

	Odds Ratio (95%CI)	Std error	T value	P value	pFDR
Suicidal ideation (whole sample)					
DIMS	1.02 (1.00-1.04)	0.009	1.930	0.053	0.062
DOES	1.03 (1.01-1.05)	0.009	2.958	0.003	**0.007**
SWTD	1.02 (1.01-1.04)	0.009	2.675	0.007	**0.013**
DA	1.03 (1.01-1.05)	0.009	3.108	0.001	**0.006**
SBD	1.02 (1.01-1.04)	0.009	2.530	0.011	**0.015**
SHY	1.01 (0.99-1.03)	0.009	1.324	0.185	0.185
Total Sleep Disorder	1.03 (1.02-1.05)	0.008	3.845	<0.001	**<0.001**
Suicidal ideation Males					
DIMS	1.03 (1.00-1.05)	0.012	2.321	0.020	**0.047**
DOES	1.04 (1.01-1.07)	0.012	3.003	0.002	**0.009**
SWTD	1.02 (0.99-1.04)	0.012	1.249	0.211	0.246
DA	1.03 (1.00-1.06)	0.013	2.126	0.033	0.058
SBD	1.03 (1.00-1.05)	0.012	1.958	0.050	0.070
SHY	1.01 (0.98-1.04)	0.013	0.682	0.495	0.495
Total Sleep Disorder	1.04 (1.01-1.06)	0.011	3.190	0.001	**0.009**
Suicidal ideation Females					
DIMS	1.00 (0.98-1.03)	0.013	0.259	0.795	0.795
DOES	1.02 (0.99-1.05)	0.013	1.320	0.186	0.261
SWTD	1.04 (1.01-1.07)	0.013	2.812	0.004	**0.034**
DA	1.03 (1.01-1.06)	0.013	2.383	0.017	0.050
SBD	1.02 (0.99-1.05)	0.013	1.494	0.135	0.236
SHY	1.02 (0.99-1.04)	0.013	1.167	0.243	0.283
Total Sleep Disorder	1.03 (1.00-1.06)	0.012	2.298	0.021	0.050
Suicide attempt and self harm (whole sample)					
DIMS	1.03 (1.01-1.05)	0.008	3.047	0.002	**0.008**
DOES	1.03 (1.01-1.05)	0.009	2.820	0.004	**0.011**
SWTD	1.01 (0.99-1.03)	0.009	1.170	0.241	0.241
DA	1.02 (1.01-1.04)	0.009	2.605	0.009	**0.016**
SBD	1.02 (1.00-1.04)	0.009	2.304	0.021	**0.029**
SHY	1.01 (1.00-1.03)	0.009	1.436	0.150	0.176
Total Sleep Disorder	1.03 (1.01-1.05)	0.008	3.602	0.000	**0.002**
Suicide attempt and self harm Males					
DIMS	0.98 (0.96-1.01)	0.012	-1.407	0.159	0.278

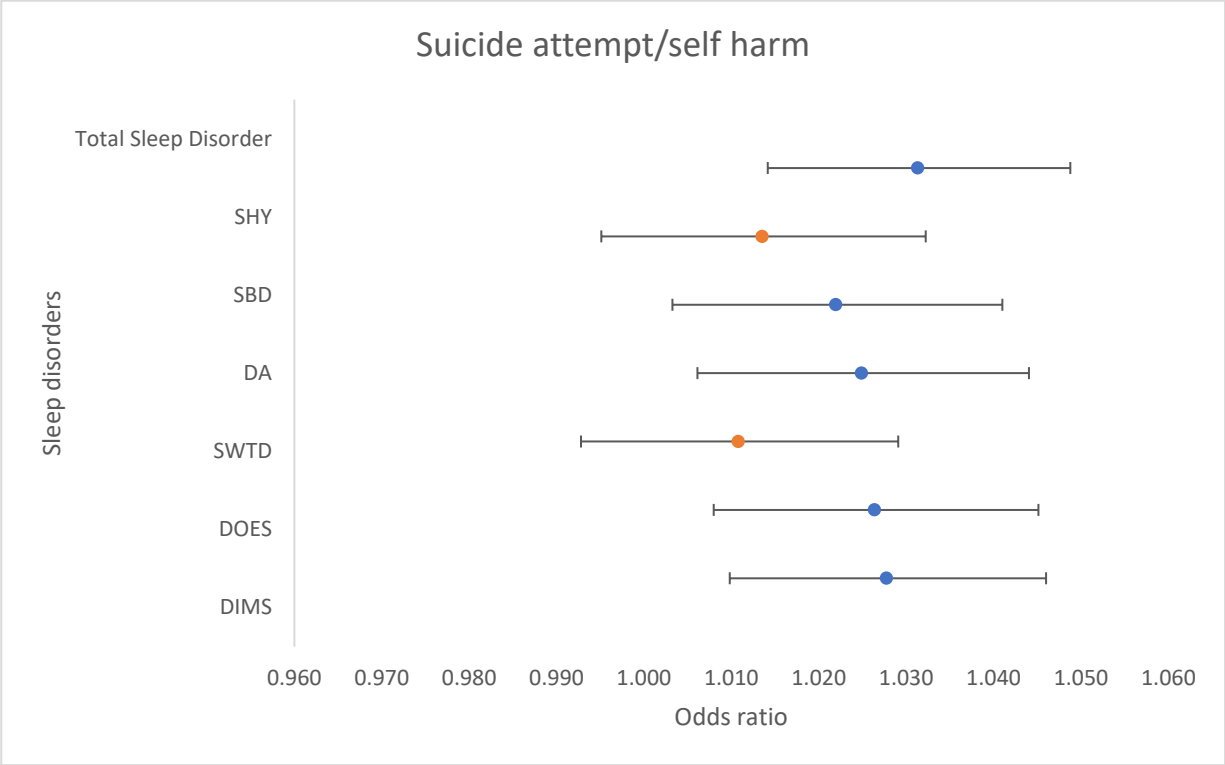
DOES	1.00 (0.98-1.03)	0.012	0.364	0.715	0.758
SWTD	0.98 (0.96-1.01)	0.012	-1.452	0.146	0.278
DA	1.00 (0.97-1.02)	0.013	-0.370	0.710	0.758
SBD	1.00 (0.98-1.03)	0.012	0.307	0.758	0.758
SHY	0.97 (0.95-1.00)	0.013	-2.250	0.024	0.171
Total Sleep Disorder	0.98 (0.96-1.01)	0.011	-1.470	0.141	0.278
Suicide attempt and self harm Females					
DIMS	1.07 (1.04-1.10)	0.013	5.221	<0.001	**<0.001**
DOES	1.05 (1.02-1.07)	0.013	3.402	<0.001	**<0.001**
SWTD	1.03 (1.01-1.06)	0.013	2.519	0.011	**0.011**
DA	1.05 (1.03-1.08)	0.013	3.890	<0.001	**<0.001**
SBD	1.04 (1.01-1.07)	0.013	2.635	0.008	**0.009**
SHY	1.06 (1.03-1.09)	0.013	4.423	<0.001	**<0.001**
Total Sleep Disorder	1.08 (1.05-1.11)	0.012	5.971	<0.001	**<0.001**

[1]**All models were adjusted for sex, race, age, anxiety and depression, family, site, BMI and subject id.**

In models with the outcome as suicide attempt/self-harm we found significant associations (pFDR ≤0.05) in the combined total sample, between TSD and SA/SH (OR: 1.03, 95% CI, 1.01-1.05), DA and SA/SH (OR: 1.02, 95% CI, 1.01-1.04), SBD and SA/SH (OR:1.02, 95% CI, 1.00-1.04) DOES and SA/SH (OR: 1.03, 95% CI, 1.01-1.05) and DIMS and SA/SH (OR: 1.03, 95% CI, 1.01-1.05). In sex stratified analysis we found no significant associations between sleep disorders and suicide attempt / self-harm in males. On the other hand, all sleep disorders (TSD, DIMS, DOES, SWTD, DA, SBD, SHY) were significantly associated with an increase in suicide attempt / self-harm at 2-year follow-up for females, when adjusting for Age, BMI, Race, Anxiety/Depression, Family, Subject ID, and Site, including after FDR correction. TSD Revealed the highest OR in females, with an OR of 1.08 (95% CI, 1.05-1.11), while DIMS had the second highest; OR: 1.07(95% CI, 1.04-1.10). DOES revealed an OR for suicide attempt in females of 1.05(95% CI, 1.02-1.07) while SWTD showed OR of 1.03(95% CI, 1.01-1.06). DA, SBD and SHY in females all revealed OR of 1.05(95% CI, 1.03-1.08),
1.04(95% CI, 1.01-1.07) and 1.06(95% CI, 1.03-1.09), respectively.

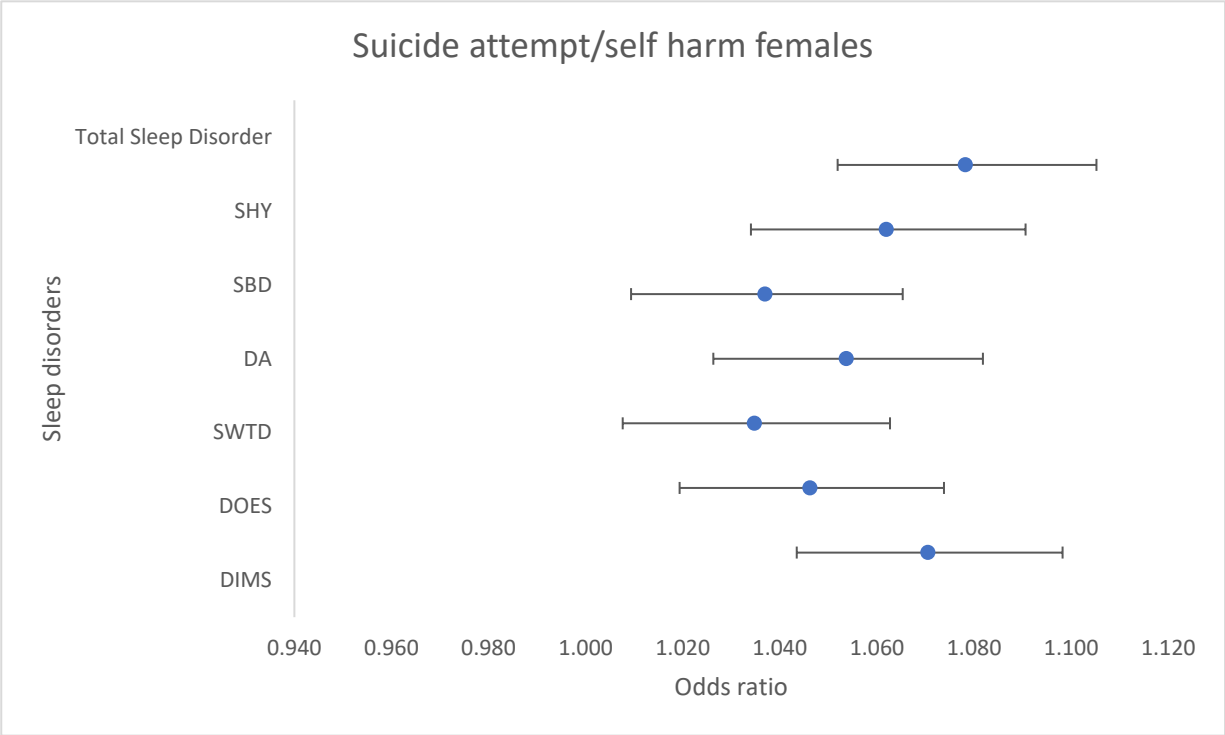
In sum – greatest ORs seen for suicide attempt and self-harm in association with baseline sleep disorders was observed in females.

Figure 6a – Odds ratio of suicide attempt/ self-harm in the whole sample. (Blue color indicates significant)



Y axis represents each individual sleep disorder, X axis represents Odds ratio for each sleep disorder. Blue color indicates FDR corrected significant results. Orange color indicates non-significant FDR corrected results.

Figure 6b – Odds ratio of suicide attempt/ self-harm in females. (Blue color indicates significant)



Y axis represents each individual sleep disorder, X axis represents Odds ratio for each sleep disorder. Blue color indicates FDR corrected significant results. Orange color indicates non-significant FDR corrected results.

Residual change scores for sleep disorders and suicidality

In models utilizing residual change scores for sleep disorders between baseline and the follow up period, the residual scores for all sleep disorders except SWTD and DA, were significantly (pFDR ≤0.05) associated with an increased risk for suicidal ideation at year 2. An increase in the score for total sleep disorder was associated with an OR of 1.05(95% CI, 1.04-1.06) for suicidal ideation in the full sample (Table 4). Further an increase in scores for DIMS and DOES revealed significant increases in suicidal ideation with odds ratios of; 1.05(95% CI, 1.04-1.07) and 1.03(95% CI, 1.02-1.04), respectively. Increases in the residual scores for SBD and SHY were also significantly associated with an increase of suicidal ideation with an odds ratio of 1.01(95% CI, 1.00-1.02) and 1.05(95% CI, 1.04-1.06), for the two disorders, respectively.

We also assessed residual change scores for sleep disorders with suicide attempt/ self-harm. In these models we found significantly (pFDR ≤0.05) elevated odds ratios for the residual change score of Total Sleep Disturbance (OR: 1.03, 95% CI, 1.02-1.04), DIMS (OR: 1.04, 95% CI, 1.02-1.05), SWTD (OR: 1.01, 95% CI, 1.00-1.02), DA (OR: 1.03, 95% CI, 1.02-1.04) and SHY (OR:1.05, 95%

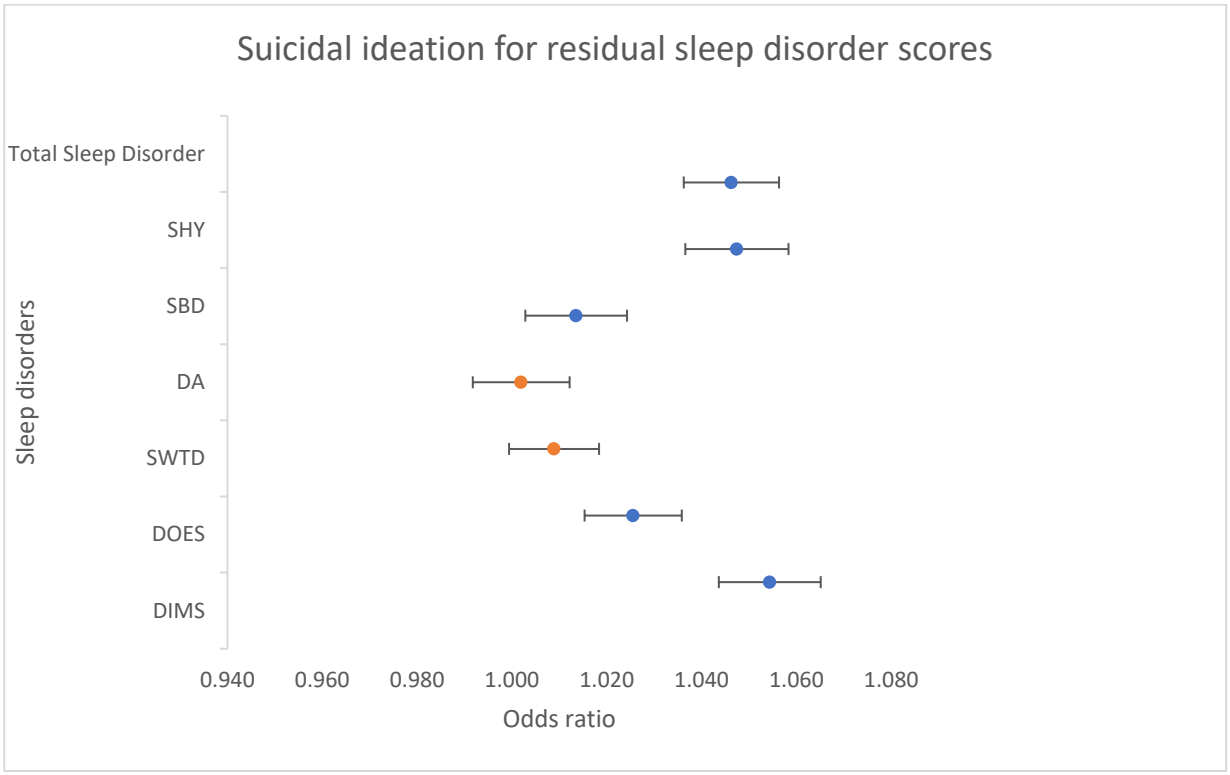
CI, 1.04-1.06). Thus, we observed increases in the risk of suicidal outcomes at year 2 follow up, across the overall change in sleep disorders.

Table 11 - Associations between residual change scores of sleep disorders and suicidality at 2-year follow-up[1]

	Odds Ratio	beta	std	t.value	p.value	p.corrected
Suicidal Ideation						
DIMS	1.05 (1.04-1.07)	0.052	0.005	10.105	<0.001	**<0.001**
DOES	1.03 (1.02-1.04)	0.025	0.005	4.902	<0.001	**<0.001**
SWTD	1.01 (1.00-1.02)	0.008	0.004	1.811	0.070	0.081
DA	1.00 (0.99-1.01)	0.001	0.005	0.356	0.721	0.721
SBD	1.01 (1.00-1.02)	0.013	0.005	2.486	0.012	**0.018**
SHY	1.05 (1.04-1.06)	0.046	0.005	8.802	<0.001	**<0.001**
TSD	1.05 (1.04-1.06)	0.045	0.004	9.268	<0.001	**<0.001**
Suicide Attempt/ Self-harm						
DIMS	1.04 (1.02-1.05)	0.034	0.005	6.531	<0.001	**<0.001**
DOES	1.01 (1.00-1.02)	0.005	0.005	1.119	0.263	0.263
SWTD	1.01 (1.00-1.02)	0.014	0.004	2.916	0.003	**0.004**
DA	1.03 (1.02-1.04)	0.030	0.005	5.732	<0.001	**<0.001**
SBD	1.01 (1.00-1.02)	0.008	0.005	1.544	0.122	0.142
SHY	1.05 (1.04-1.06)	0.051	0.005	9.615	<0.001	**<0.001**
TSD	1.03 (1.02-1.04)	0.031	0.004	6.347	<0.001	**<0.001**

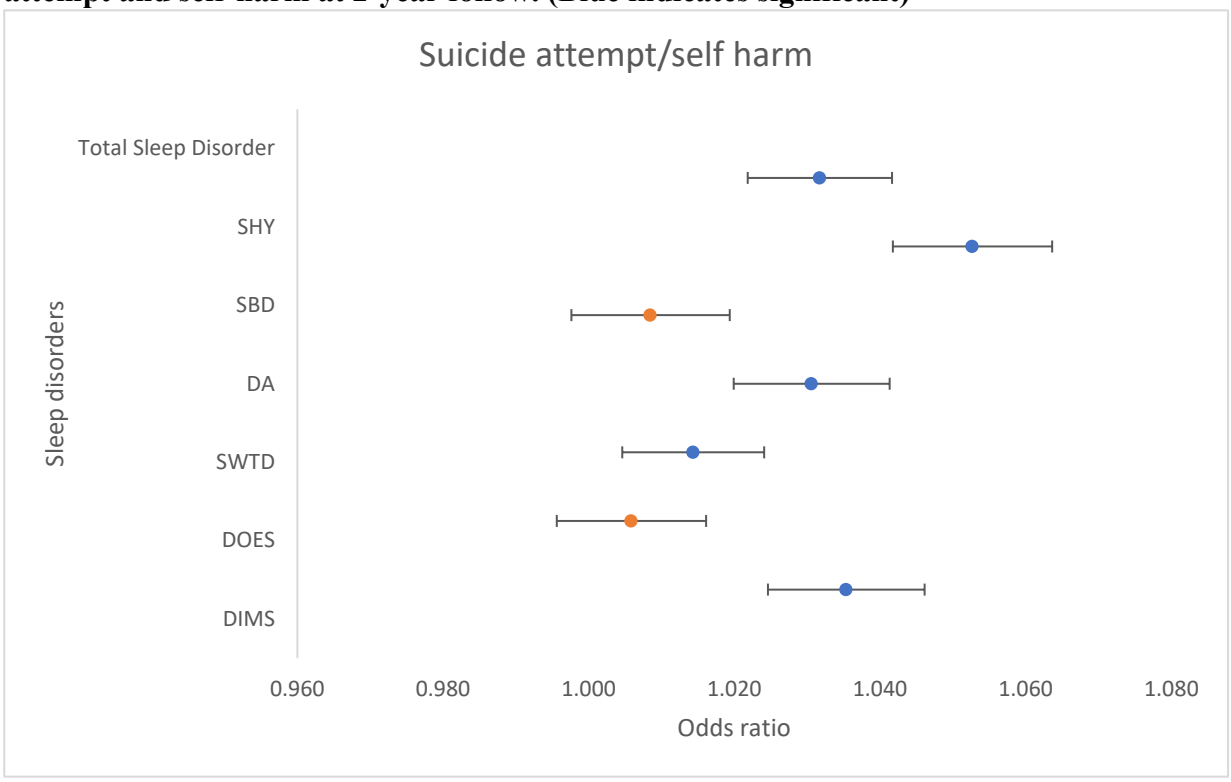
[1]All models were adjusted for sex, race, age, anxiety and depression, family, site, BMI and subject id.

Figure 7a – Associations between residual change scores of sleep disorders and suicidal ideation at 2-year follow. (Blue indicates significant)



Y axis represents each individual sleep disorder, X axis represents Odds ratio for each sleep disorders residual score. Blue color indicates FDR corrected significant results. Orange color indicates non-significant FDR corrected results.

Figure 7b – Associations between residual change scores of sleep disorders and suicide attempt and self-harm at 2-year follow. (Blue indicates significant)



Y axis represents each individual sleep disorder, X axis represents Odds ratio for each sleep disorder residual score. Blue color indicates FDR corrected significant results. Orange color indicates non-significant FDR corrected results.

6.0 Brain structural changes and sleep disorders

In linear mixed effect models, associating all cortical, subcortical regions and white matter tracts with sleep disorders we found multiple regions that had nominally significant associations with multiple sleep disorders. We will describe them in the following way, looking first at global, and then regional differences. Due to few NAs with regards to QC, the overall sample size was reduced to 11,876 after QC, this sample was used for all imaging analyses – across modalities.

6.1 Global structural changes and sleep disorders

We assessed overall global changes that might be associated with sleep disorders. The results of this analysis can be seen in Table 9. In the following, results at pFDR are described, followed by results at Pnom≤0.01. We found that baseline DIMS was significantly associated with a reduction in overall surface area (β=-0.03, STD=0.01, pFDR≤0.05) and overall cortical volume (β=-0.03, STD=0.01, pFDR≤0.05) at 2 year follow up, after correcting for multiple comparisons. Further results at the nominal level were also found, see Table 12, such as an association between an overall MD reduction across all fibers (β=-0.02, STD=0.01, Pnom≤0.01). SHY was associated with an overall increase in overall surface area (β=0.02, STD=0.01, Pnom≤0.01). SBD was associated with reductions in Total cortical volume (β=-0.02, STD=0.01, Pnom≤0.01).

Table 12 - Association between sleep disorders at baseline and global brain changes at year 2.

	beta	std	t.value	p.value	p. FDR corrected
DIMS					
Total Surface Area	-0.033	0.012	-2.726	0.006	**0.019**
Total cortical volume	-0.036	0.012	-3.010	0.002	**0.015**
DA					
MD all fibers	-0.028	0.012	-2.341	0.019	0.115
SHY					
Total Surace area	0.029	0.011	2.587	0.009	0.058
SBD					
Total cortical volume	-0.026	0.011	-2.347	0.018	0.113

Abbreviations: MD: Mean Diffusivity, FDR: False Discovery Rate.

[1]All models were adjusted for sex, race, age, anxiety and depression, family, scanner, BMI and subject id, whole brain volume. and DTI mean motion for all white matter analysis.

6.2 Regional structural changes and sleep disorders

In the analysis assessing associations between specific sleep disorders and cortical, subcortical and white matter microstructural changes, multiple sleep disorders and regions showed significant associations. The results that remained significant after FDR correction are described below, with the nominally significant findings detailed in Table 13. All analyses were adjusted for sex, race, age, anxiety and depression, family, scanner, BMI and subject id, whole brain volume and DTI mean motion for all white matter analysis.

We identified No FDR significant relationships with Total Sleep Disorder. For individual sleep disorders however, DIMS had multiple FDR corrected significant associations with volumetric reductions of the lateral orbito-frontal lobe (β=-0.02, STD=0.009, pFDR$\leq$0.05) and the medial orbito-frontal lobe (β=-0.03, STD=0.009, pFDR$\leq$0.05). DA showed significant associations with a reduced MD in Uncinate fasciculus (β=-0.03, STD=0.01, pFDR$\leq$0.05). SWTD was significantly associated with an increase in subcortical volume of the ventral diencephalon (β=-0.02, STD=0.008, pFDR$\leq$0.05), Table 13.

Table 13 - Association between sleep disorders at baseline and regional brain changes at year 2.[1]

	beta	Std error	T value	P value	pFDR
Total Sleep Disturbance					
Volume Entorhinal	-0.037	0.014	-2.697	0.007	0.238
Volume Ventral Diencephalon	-0.022	0.009	-2.433	0.015	0.120
FA Anterior Thalamic Radiations	-0.037	0.014	-2.636	0.008	0.167
DIMS					
Surface Area Lateral Orbito-Frontal Lobe	-0.027	0.009	-2.919	0.003	0.065
Surface Area Medial Orbito-Frontal Lobe	-0.025	0.008	-2.889	0.003	0.065
Volume Entorhinal	-0.031	0.013	-2.337	0.019	0.220
Volume Lateral Orbito-Frontal Lobe	-0.029	0.009	-3.207	0.001	**0.022**
Volume Medial Orbito-Frontal Lobe	-0.031	0.009	-3.221	0.001	**0.022**
FA frontal superior corticostriate	-0.033	0.013	-2.396	0.016	0.195
FA Fornix excluding fimbria	-0.031	0.013	-2.336	0.019	0.195
DA					
Surface area Frontal Pole	-0.027	0.010	-2.610	0.009	0.308
MD uncinate	-0.037	0.012	-3.055	0.002	**0.045**
DOES					
Cortical Thickness Lateral Orbito-Frontal Lobe	-0.042	0.013	-3.012	0.002	0.088
Cortical Thickness Pericalcarine	-0.034	0.013	-2.583	0.009	0.166
Cortical Thickness Rostral Middle Frontal Lobe	-0.032	0.013	-2.347	0.018	0.214
Surface Area Transverse Temporal	0.029	0.011	2.513	0.012	0.407
FA Fornix	-0.028	0.012	-2.338	0.019	0.193
FA Fornix excluding fimbria	-0.033	0.012	-2.563	0.010	0.193
SWTD					
Cortical Thickness supramarginal	0.031	0.013	2.337	0.019	0.331
Volume Ventral Diencephalon	-0.024	0.008	-2.871	0.004	**0.032**
SHY					
Cortical Thickness Entorhinal	-0.033	0.014	-2.350	0.018	0.186
Cortical Thickness Lingual Lobe	-0.032	0.012	-2.588	0.009	0.164
Cortical Thickness Parahippocampus	-0.038	0.013	-2.776	0.005	0.164
SBD					

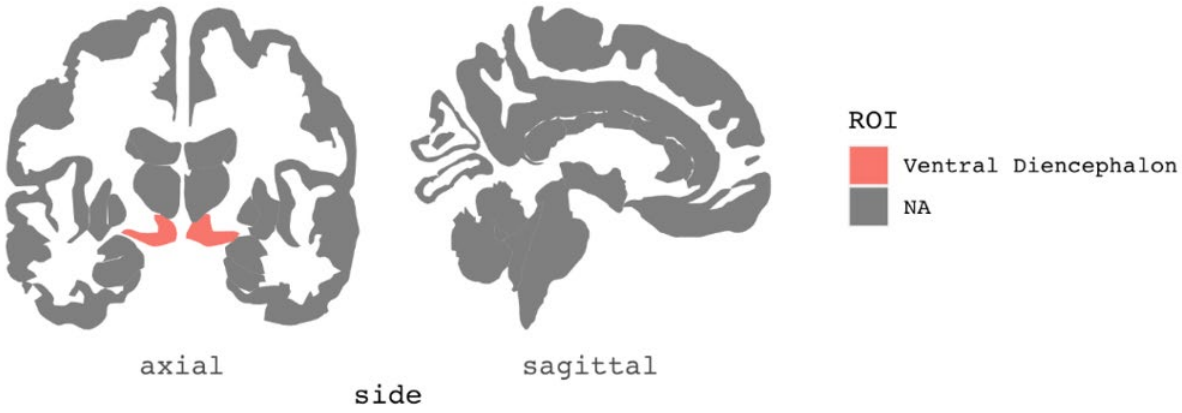
Cortical Thickness Lateral Occipital Lobe	-0.028	0.011	-2.428	0.015	0.268
Surface Area Fusiform	0.022	0.008	2.625	0.008	0.147
Surface Area Parahippocampus	0.029	0.011	2.634	0.008	0.147
FA anterior thalamic radiations	-0.030	0.012	-2.354	0.018	0.249

Abbreviations: FA: Fractional Anisotropy, MD: Mean Diffusivity, FDR: False Discovery Rate.

[1]All models were adjusted for sex, race, age, anxiety and depression, family, scanner, BMI and subject id, whole brain volume and DTI mean motion for all white matter analysis.

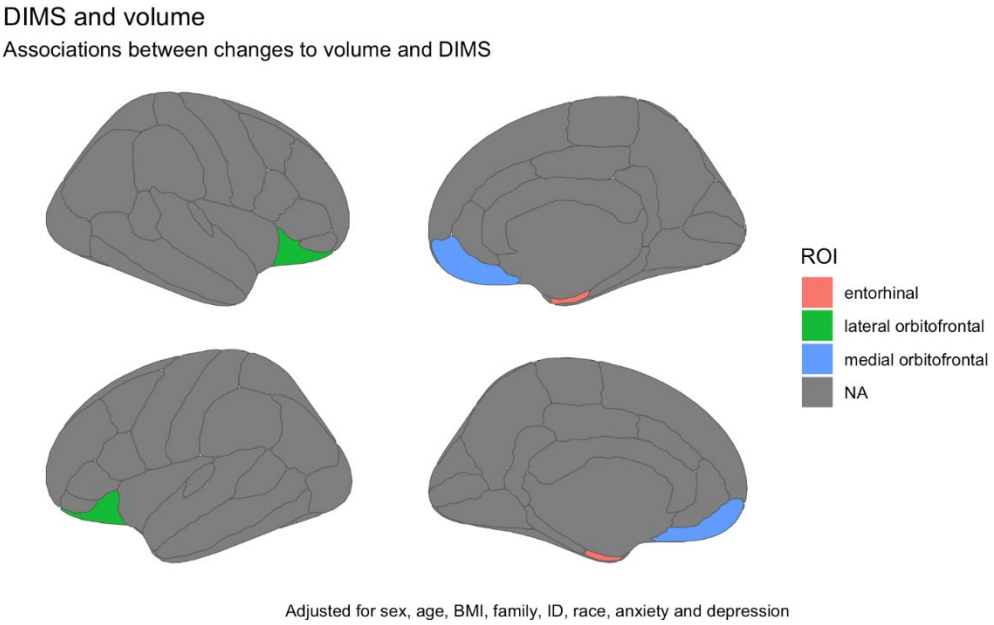
A graphical representation of the above-mentioned associated areas can be seen in the following figures, to highlight main pattern of findings.

Figure 8 – Subcortical areas associated with Total sleep disorder



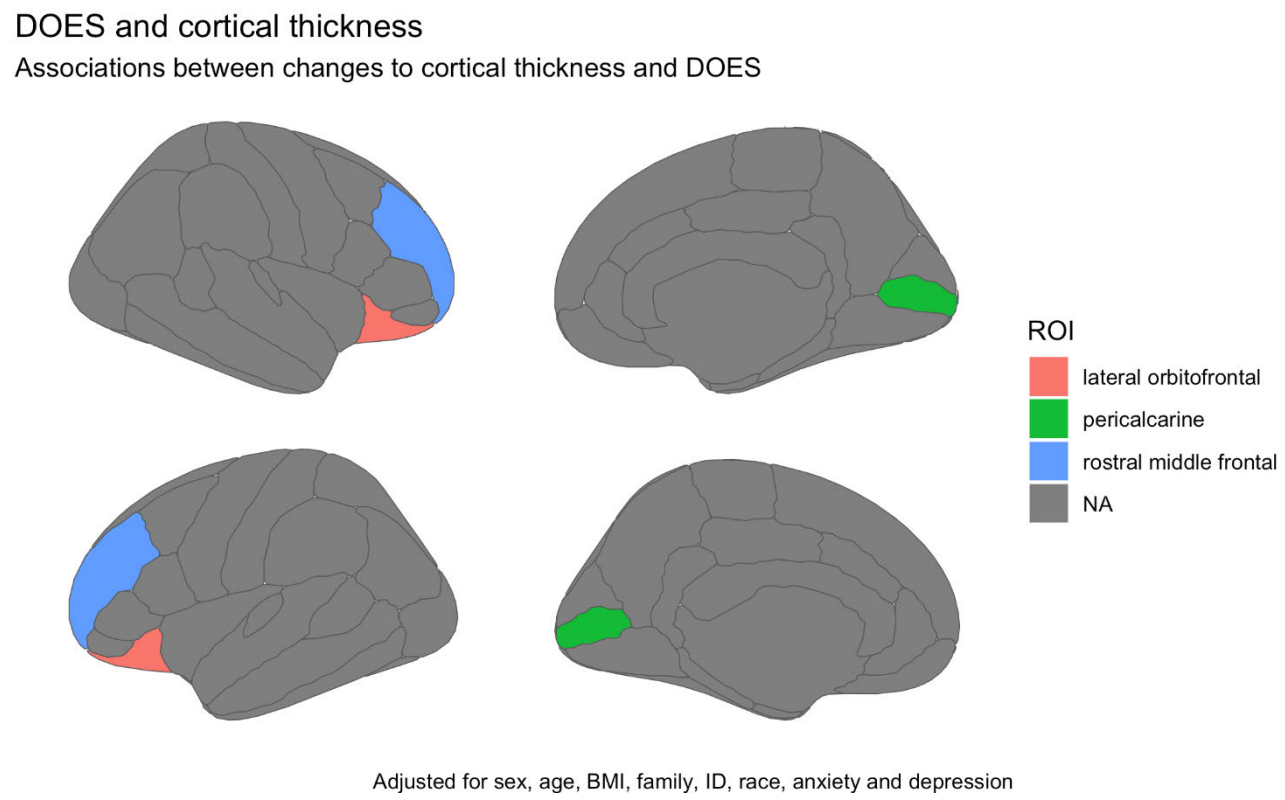
Associations were nominal significant.

Figure 9 – Cortical volume changes associated with DIMS



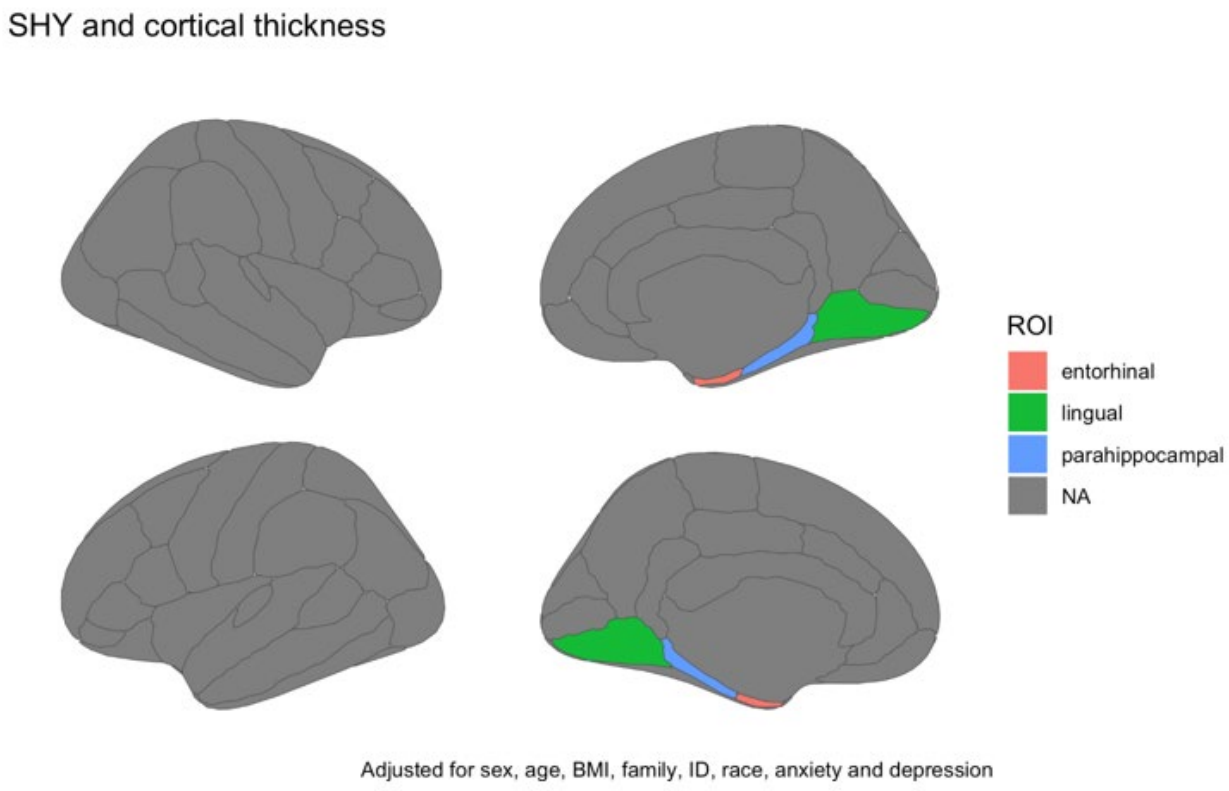
Associations between entorhinal and DIMS was nominal significant, however orbitofrontal volume changes and DIMS was significantly associated even after FDR correction.

Figure 10 – Cortical thickness changes associated with DOES



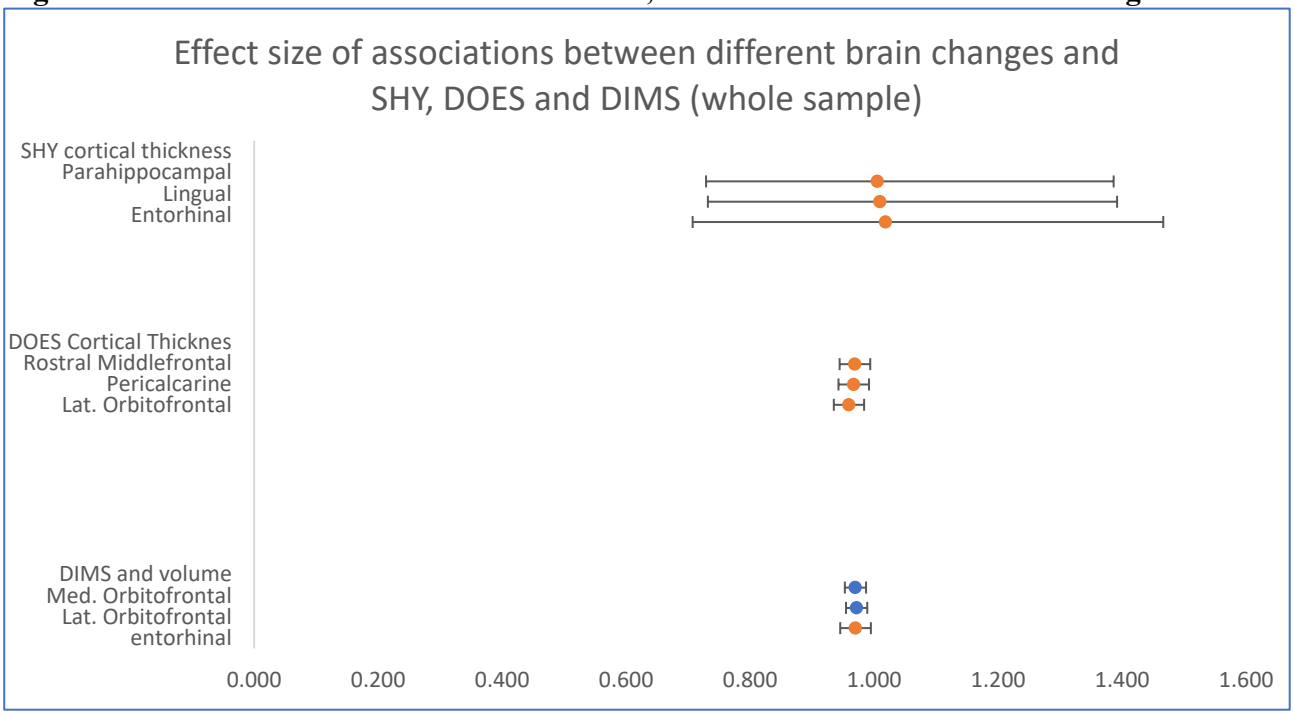
Associations were nominal significant.

Figure 11 – Cortical thickness changes associated with SHY



Associations were nominal significant.

Figure 12 – Effect sizes for associations of SHY, DOES and DIMS with brain changes.



Y axis represents the specific sleep-brain associated change. X axis represents effect sizes for these associations. Blue color indicates FDR corrected significant results. Orange color indicates non-significant FDR corrected results.

6.3 Regional and global structural changes and sleep disorders in males and females, respectively.

Males:

In order to assess potential differences with respect to gender in the sample we split the sample into males (N=6,196) and females (N=5,680) and ran the same models for the sex separated groups.
In males Global bulk analysis revealed FDR corrected significant association between DA and an overall decrease in MD across all fibers (β=-0.05, STD=0.01, pFDR≤0.05). SHY was associated with increases in total surface area (β=0.05, STD=0.01, pFDR≤0.05), and total cortical volume (β=0.04, STD=0.01, pFDR≤0.01). Only one FDR corrected significant result was found in all the regional analysis. SBD showed FDR corrected significant (pFDR≤0.05) associations to an increase in surface area in the Inferior Parietal Lobe in males (β=0.04, STD=0.01, pFDR≤0.05).

Table 10a - Association between sleep disorders at baseline and regional and global brain changes at year 2 in males.

	beta	Std error	T value	P value	pFDR
Global results					
DA					
MD All Fibers	-0.050	0.017	-2.831	0.004	**0.027**
SHY					
Total Surface Area	0.052	0.017	2.964	0.003	**0.018**
Total Volume	0.043	0.017	2.513	0.012	**0.036**
Regional results					
Total sleep disturbance					
Volume Entorhinal	-0.055	0.020	-2.691	0.007	0.242
DIMS					
Volume Entorhinal	-0.046	0.019	-2.392	0.016	0.295
Volume Frontal Pole	0.042	0.017	2.380	0.017	0.295
DA					
Cortical Thickness Transverse Temporal	0.052	0.020	2.606	0.009	0.312
Sulcul Depth Supramarginal	-0.061	0.020	-3.081	0.002	0.070
MD Forceps Major	-0.045	0.017	-2.529	0.011	0.054
MD Forceps Minor	-0.042	0.018	-2.341	0.019	0.054
MD Corpus Callosum	-0.044	0.018	-2.358	0.018	0.054
MD parahippocampal cingulum	-0.040	0.017	-2.380	0.017	0.054
MD uncinate	-0.052	0.017	-2.938	0.003	0.054
MD inferior frontal occipital fasciculus	-0.048	0.018	-2.581	0.009	0.054
MD striatal inferior frontal cortex tract	-0.043	0.017	-2.414	0.015	0.054
DOES					
Cortical Thickness frontal pole	-0.049	0.019	-2.497	0.012	0.230
Cortical Thickness Rostral Middle Frontal Lobe	-0.045	0.019	-2.366	0.018	0.230
Sulcul Depth Frontal Pole	0.043	0.018	2.354	0.018	0.316
Sulcul Depth Pars Opercularis	-0.050	0.019	-2.549	0.010	0.316
Surface Area Fusiform	0.032	0.013	2.362	0.018	0.247
Surface Area Transverse Temporal	0.044	0.016	2.611	0.009	0.247
Volume Fusiform	0.033	0.014	2.412	0.015	0.180
Volume Pars Opercularis	0.041	0.016	2.426	0.015	0.180
Volume Transverse Temporal	0.042	0.016	2.528	0.011	0.180

SWTD					
Cortical Thickness Middle Temporal Lobe	0.047	0.019	2.452	0.014	0.161
Cortical Thickness Precuneus	0.051	0.019	2.637	0.008	0.161
Cortical Thickness Supramarginal	0.046	0.018	2.470	0.013	0.161
Volume Precuneus	0.033	0.013	2.393	0.016	0.569
FA Fornix	0.043	0.017	2.491	0.012	0.222
SHY					
Cortical Thickness Entorhinal	-0.051	0.018	-2.699	0.006	0.118
Cortical Thickness Lingual	-0.046	0.017	-2.699	0.006	0.118
Cortical Thickness Superior Frontal Lobe	-0.044	0.018	-2.378	0.017	0.197
SBD					
Sulcul Depth Frontal Pole	0.046	0.017	2.603	0.009	0.315
Surface Area Fusiform	0.039	0.013	2.959	0.003	0.052
Surface Area Inferior Parietal Lobe	0.047	0.014	3.280	0.001	**0.035**
Volume Inferior Parietal Lobe	0.037	0.014	2.600	0.009	0.317

Females:

In females the only significant global results observed were the association between DIMS and a global decrease in whole brain surface area (β=-0.05, STD=0.02, pFDR≤0.05) and cortical volume (β=-0.06, STD=0.01, pFDR≤0.05).

In females regional associations between brain structure and sleep disorders was also established. TSD in females was associated with an increase in sulcal depth in the supramarginal gyrus (β=0.05, STD=0.02, Pnom≤0.01), while also associated with an FDR corrected significant decrease in FA in the anterior thalamic radiations (β=-0.06, STD=0.01, pFDR≤0.05). DIMS in females was associated with multiple altered brain structures such as surface area in the lateral and medial orbito-frontal lobe (β=-0.03, STD=0.01, Pnom≤0.01) and (β=-0.04, STD=0.01, Pnom≤0.01), respectively. Cortical volume in both the lateral (β=-0.05, STD=0.01, pFDR≤0.05), and medial (β=-0.06, STD=0.01, pFDR≤0.05), orbito-frontal lobe was also negatively associated with DIMS even after FDR correction, as well as the cortical volume in the pars orbitalis (β=-0.04, STD=0.01, Pnom≤0.01). Further DIMS in females also showed negative associations with FA in multiple tracts such as The anterior thalamic radiations (β=-0.05, STD=0.01, Pnom≤0.01), frontal superior corticostriate tract (β=-0.05, STD=0.02, Pnom≤0.01) and the fornix (excluding the fimbira) (β=-0.05, STD=0.01, Pnom≤0.01). DOES showed significant associations with cortical thickness in the

pericalcarine cortex (β=-0.04, STD=0.01, Pnom≤0.01) and cortical volume in the precuneus. SWTD in females was associated with altered sulcul depth in the pars triangularis (β=-0.05, STD=0.02, Pnom≤0.01), surface area in the caudal anterior cingulate cortex (β=-0.04, STD=0.01, Pnom≤0.01). SWTD was also associated with changes to cortical volume in the pericalcarine (β=-0.04, STD=0.01, Pnom≤0.01). Subcortical changes in the ventral diencephalon (β=-0.03, STD=0.01, Pnom≤0.01) and the caudate (β=0.03, STD=0.01, Pnom≤0.01) was also associated with SWTD. Finally, FA changes in the anterior thalamic radiations (β=-0.05, STD=0.01, Pnom≤0.01) were also associated with SWTD. SHY in females had FDR corrected significant associations with sulcal depth changes in the fusiform gyrus (β=-0.07, STD=0.02, pFDR≤0.05) while white matter changes with regards to FA in the cingulate cingulum (β=-0.05, STD=0.01, Pnom≤0.01) and MD changes in the uncinate (β=0.04, STD=0.01, Pnom≤0.01), were noted.

Table 10b - Association between sleep disorders at baseline and regional and global brain changes at year 2 in females.

	beta	Std error	T value	P value	pFDR
Total Sleep disturbance					
Sulcul Depth Supramarginal	0.055	0.022	2.495	0.012	0.429
FA Anterior Thalamic Radiations	-0.064	0.019	-3.307	<0.001	**0.019**
DIMS					
Surface Area Lateral Orbito-Frontal Lobe	-0.038	0.015	-2.584	0.009	0.166
Surface Area Medial Orbito-Frontal Lobe	-0.045	0.014	-3.162	0.001	0.053
Volume Lateral Orbito-Frontal Lobe	-0.054	0.014	-3.787	<0.001	**0.002**
Volume Medial Orbito-Frontal Lobe	-0.061	0.015	-3.896	<0.001	**0.002**
Volumes Pars Orbitalis	-0.042	0.017	-2.363	0.018	0.206
FA Anterior Thalamic Radiations	-0.050	0.019	-2.581	0.009	0.065
FA Frontal Superior Corticostriate	-0.058	0.020	-2.875	0.004	0.065
FA Fornix without excluding fimbria	-0.052	0.019	-2.652	0.008	0.065
DOES					
Cortical Thickness Pericalcarine	-0.044	0.019	-2.346	0.019	0.411
Volume Precuneus	-0.038	0.013	-2.763	0.005	0.195
SWTD					
Sulcul Depth Pars Triangularis	-0.054	0.020	-2.674	0.007	0.256
Surface Area Caudal Anterior Cingulate Cortex	-0.041	0.016	-2.499	0.012	0.425
Volume Pericalcarine	-0.044	0.018	-2.452	0.014	0.484

Volume Caudate	0.038	0.016	2.340	0.019	0.077
Volume Ventral Diencephalon	-0.033	0.013	-2.479	0.013	0.077
FA Anterior Thalamic Radiations	-0.051	0.018	-2.848	0.004	0.088
SHY					
Sulcul Depth Fusiform	-0.077	0.021	-3.564	0.000	**0.012**
FA cingulate cingulum	-0.050	0.019	-2.576	0.010	0.200
MD Uncinate	0.045	0.018	2.527	0.011	0.230
Global results					
DIMS					
Total Surface Area	-0.057	0.020	-2.863	0.004	**0.012**
Total Cortical Volume	-0.060	0.019	-3.111	0.001	**0.011**

7. Brain structural changes and suicidality

7.0 Regional and global brain structural change and suicidal ideation, suicide attempt and self-harm

We conducted analyses looking at baseline suicidality and its association with cortical, subcortical and white matter changes at year 2. This was to assess the potential underlying interplay between suicidality and brain structure that might occur in suicidal individuals, an whether or not the same areas affected by sleep disorders were present in those with STB. While none of these models survived FDR correction, the nominally significant results are described below.

In combined sex analysis we found that suicidal ideation at baseline was nominally ($P_{nom} \leq 0.01$) associated with reductions in overall global cortical thickness at year 2 (β=-0.03, STD=0.01, $P_{nom} \leq 0.01$). Further, cortical thickness across the fusiform gyrus (β=-0.03, STD=0.01, $P_{nom} \leq 0.01$), inferior parietal lobe(β=-0.03, STD=0.01, $P_{nom} \leq 0.01$), pars orbitalis(β=-0.03, STD=0.01, $P_{nom} \leq 0.01$), pars triangularis(β=-0.03, STD=0.01, $P_{nom} \leq 0.01$), supramarginal gyrus(β=-0.03, STD=0.01, $P_{nom} \leq 0.01$), and superior frontal lobe(β=-0.03, STD=0.01, $P_{nom} \leq 0.01$), was associated with baseline suicidal ideation (Table 11). Suicidal ideation at baseline was also nominally associated with increases to surface area across multiple areas: paracentral gyrus(β=0.02, STD=0.01, $P_{nom} \leq 0.01$), pars triangularis(β=0.03, STD=0.01, $P_{nom} \leq 0.01$), precuneus (β=0.02, STD=0.008, $P_{nom} \leq 0.01$), rostral middle frontal lobe(β=0.02, STD=0.009, $P_{nom} \leq 0.01$) and the frontal lobe (β=0.02, STD=0.008, $P_{nom} \leq 0.01$), as can be seen in figure 2. Suicide attempt/self-harm only showed nominal associations with increased sulcul depth in the caudal middle frontal lobe (β=0.03, STD=0.01, $P_{nom} \leq 0.01$). These findings are interesting in light of previous findings from Vidal-Ribas et al, 2021[111], who found that caregiver reported suicidal ideation was only significantly associated with thinner left bank of the superior temporal sulcus, albeit while using 90% confidence intervals. Thus, our current finding highlights multiple nominally significant (not FDR significant) regions associated with brain changes, different from previous studies.

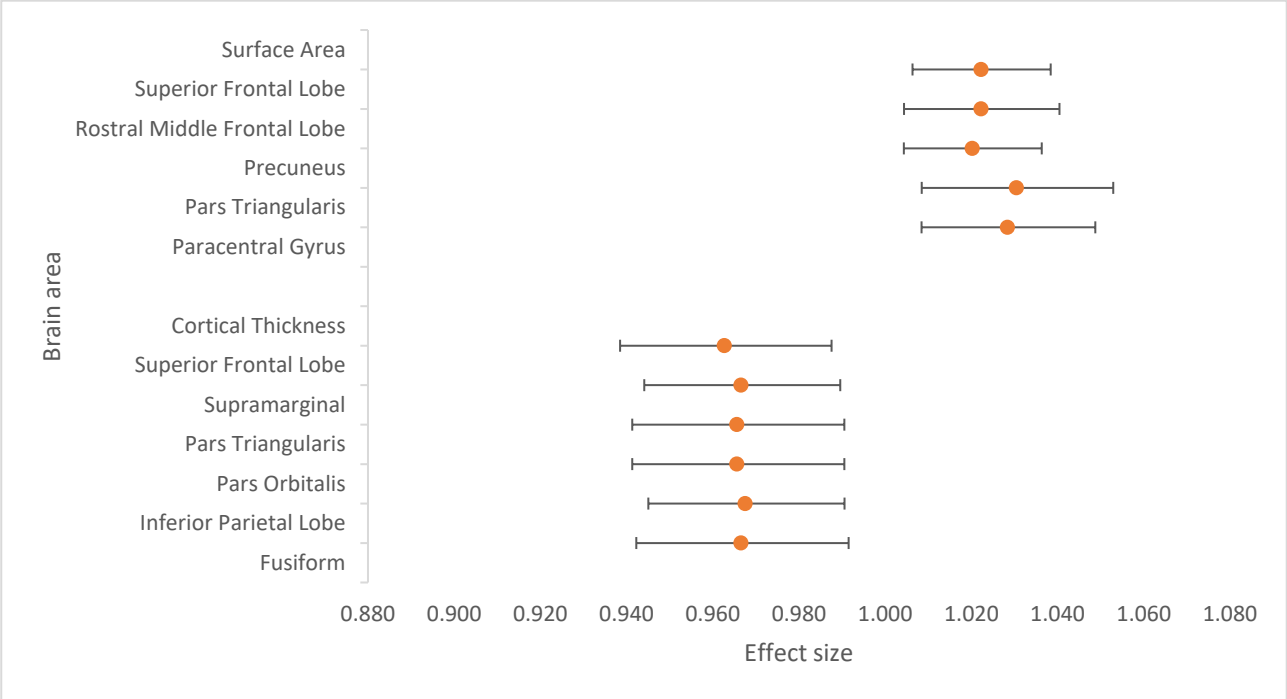
Table 11 – Regional and Global associations between and suicidality at baseline and brain structural changes at year 2[1]

Regional measures	beta	Std error	T value	P value	pFDR
Suicidal Ideation					
Cortical Thickness Fusiform	-0.034	0.013	-2.617	0.008	0.051
Cortical Thickness Inferior Parietal Lobe	-0.033	0.012	-2.618	0.008	0.051
Cortical Thickness Pars Orbitalis	-0.035	0.013	-2.636	0.008	0.051
Cortical Thickness Pars Triangularis	-0.035	0.013	-2.611	0.009	0.051
Cortical Thickness Supramarginal	-0.034	0.012	-2.731	0.006	0.051
Cortical Thickness Superior Frontal Lobe	-0.038	0.013	-2.943	0.003	0.051
Surface Area Paracentral Gyrus	0.028	0.010	2.764	0.005	0.069
Surface Area Pars Triangularis	0.030	0.011	2.743	0.006	0.069
Surface Area Precuneus	0.020	0.008	2.349	0.018	0.127
Surface Area Rostral Middle Frontal Lobe	0.022	0.009	2.512	0.012	0.102
Surface Area Superior Frontal Lobe	0.022	0.008	2.802	0.005	0.069
Suicide Attempt and Self-harm					
Sulcul Depth Caudal Middle Frontal Lobe	0.035	0.014	2.395	0.016	0.496
Global measures					
Suicidal ideation:					
Global Cortical Thickness	-0.032	0.012	-2.549	0.010	0.064

Abbreviations: FA: Fractional Anisotropy, MD: Mean Diffusivity, FDR: False Discovery Rate.

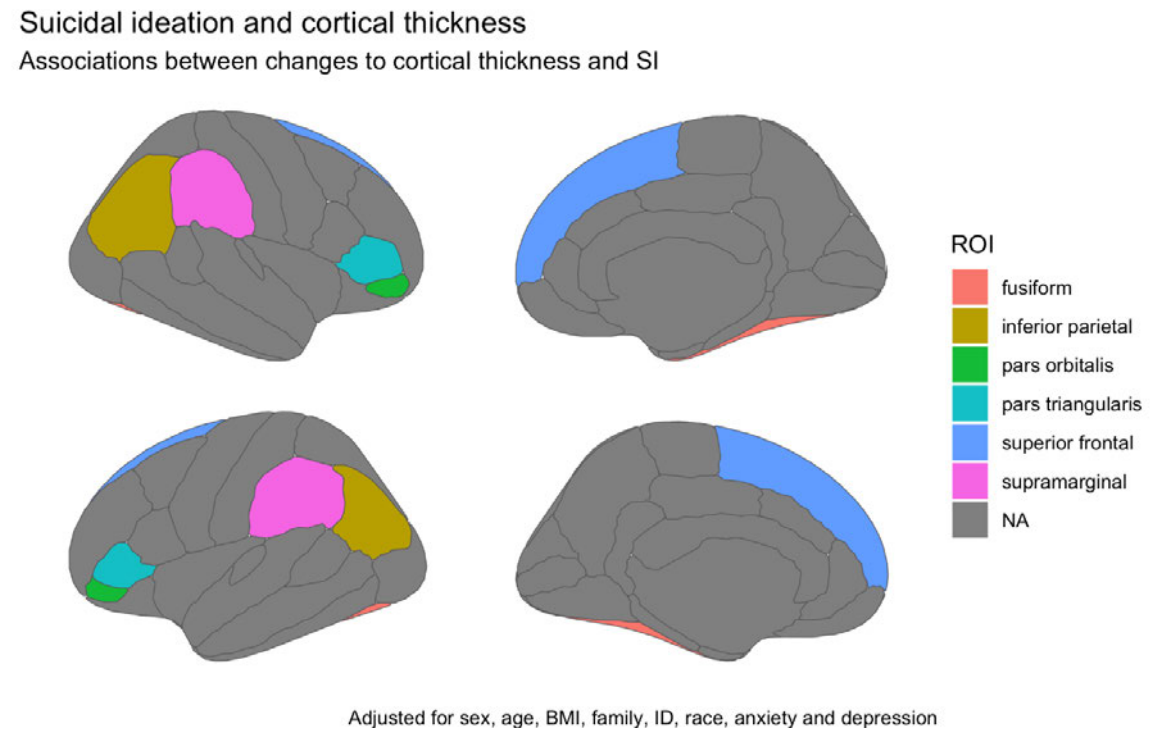
[1]All models were adjusted for sex, race, age, anxiety and depression, family, scanner, BMI and subject id, whole brain volume and DTI mean motion for all white matter analysis.

Figure 13 – Effect Sizes for associations between brain structural changes and suicidal ideation (in whole sample)



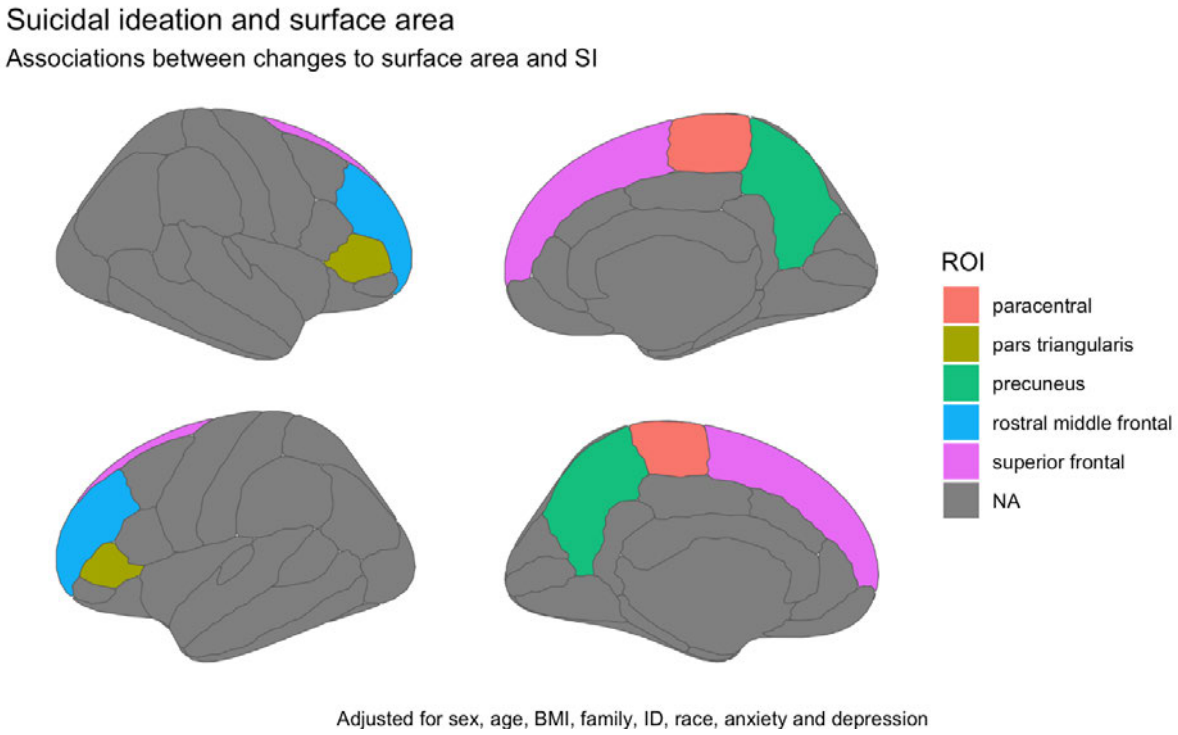
Y axis represents the specific suicide-brain associated change. X axis represents effect sizes for these associations. Blue color indicates FDR corrected significant results. Orange color indicates non-significant FDR corrected results.

Figure 14 – Changes to cortical thickness associated with Suicidal Ideation.



Associations were nominal significant.

Figure 15 – Changes to surface area associated with Suicidal ideation



Associations were nominal significant.

7.1 Brain structural change and suicidal ideation, suicide attempt and self-harm in males and females, respectively.

Males:

In models assessing the associations between suicidal ideation, suicide attempt/self-harm at baseline with brain structural changes at year 2 follow up in males, no results remained significant after FDR correction. Suicidal ideation was associated with reduction in cortical thickness in a variety of brain regions including: Banks of superior temporal sulcus(β=-0.04, STD=0.01, Pnom≤0.01), fusiform gyrus(β=-0.04, STD=0.01, Pnom≤0.01), inferior parietal lobe(β=-0.04, STD=0.01, Pnom≤0.01), pars orbitalis(β=-0.04, STD=0.01, Pnom≤0.01), pars triangularis(β=-0.04, STD=0.01, Pnom≤0.01), supramarginal gyrus(β=-0.04, STD=0.01, Pnom≤0.01) and superior frontal lobe(β=-0.04, STD=0.01, Pnom≤0.01), (Table 12a). Sulcul depth reduction was also associated with suicidal ideation in the pars opercularis (β=-0.04, STD=0.01, Pnom≤0.01). Sulcul depth increases was associated with precuneus (β=0.04, STD=0.01, Pnom≤0.01), and temporal pole (β=0.04, STD=0.01, Pnom≤0.01). Finally suicidal ideation at baseline in males was also associated with increases in surface area in the entorhinal cortex (β=0.04, STD=0.01, Pnom≤0.01), paracentral gyrus (β=0.03, STD=0.01, Pnom≤0.01), pars triangularis (β=0.03, STD=0.01, Pnom≤0.01), and superior frontal lobe (β=0.02, STD=0.01, Pnom≤0.01). Overall males showed significant associations between suicidal ideation at baseline and overall global cortical thickness reductions (β=-0.04, STD=0.01, Pnom≤0.01). No significant (Pnom≤0.01) results were found for suicide attempt/self-harm and brain regions in males.

Table 12a – Regional and Global associations between and suicidality at baseline and brain structural changes at year 2, in males[1]

	beta	Std error	T value	P value	pFDR
Suicidal Ideation					
Cortical Thickness Banks Of Superior Temporal Sulcus	-0.047	0.018	-2.621	0.008	0.081
Cortical Thickness Fusiform	-0.042	0.017	-2.396	0.016	0.081
Cortical Thickness Inferior Parietal Lobe	-0.043	0.017	-2.507	0.012	0.081
Cortical Thickness Pars Orbitalis	-0.043	0.018	-2.374	0.017	0.081
Cortical Thickness Pars Triangularis	-0.046	0.018	-2.554	0.010	0.081
Cortical Thickness Supramarginal	-0.044	0.016	-2.612	0.009	0.081
Cortical Thickness Superior Frontal Lobe	-0.041	0.017	-2.334	0.019	0.081
Sulcul Depth Pars Opercularis	-0.046	0.018	-2.520	0.011	0.223

Sulcul Depth Precuneus	0.040	0.017	2.348	0.018	0.223
Sulcul Depth Temporal Pole	0.040	0.017	2.333	0.019	0.223
Surface Area Entorhinal	0.046	0.017	2.631	0.008	0.143
Surface Area Paracentral Gyrus	0.038	0.014	2.593	0.009	0.143
Surface Area Pars Triangularis	0.038	0.015	2.452	0.014	0.143
Surface Area Superior Frontal Lobe	0.028	0.012	2.366	0.018	0.143
Global results					
Suicidal ideation					
Total Cortical Thickness	-0.043	0.017	-2.505	0.012	0.073

[1]All models were adjusted for sex, race, age, anxiety and depression, family, scanner, BMI and subject id, whole brain volume and DTI mean motion for all white matter analysis.

Females

In models assessing suicidality at baseline in females and its association with brain regions 2 years later, we found significant regional associations between reduction in the sulcul depth of the insula (β=-0.04, std=0.02, Pnom≤0.01) with suicidal ideation (Table 12b). Suicidal ideation and increase of the surface area of the Isthmus Cingulate Cortex (β=0.04, std=0.01, Pnom≤0.01) was also observed. Cortical volume of the parahippocampus (β=-0.05, std=0.01, Pnom≤0.01) was also significantly associated with suicidal ideation at baseline in females.

Suicide attempt/self-harm was associated with changes to cortical volume and subcortical volume in the rostral middle Frontal lobe (β=0.04, std=0.01, Pnom≤0.01) and for the hippocampus (β=0.04, std=0.01, pFDR≤0.01), respectively, the latter being significant after FDR correction.
Sulcul depth in both the caudal middle frontal lobe(β=0.06, std=0.02, Pnom≤0.01) and the medial orbito-frontal lobe(β=-0.04, std=0.01, Pnom≤0.01) was also found to be associated with suicide attempt / self-harm. Finally, females also showed significant associations between baseline suicide attempt/self-harm and reductions to FA in the inferior frontal occipital fasciculus (β=-0.04, std=0.01, Pnom≤0.01).

Table 12b – Regional and Global associations between and suicidality at baseline and brain structural changes at year 2, in males[1]

Suicidal ideation	beta	Std error	T value	P value	pFDR
Sulcul Depth Insula	-0.047	0.020	-2.372	0.017	0.603
Surface Area Isthmus Cingulate Cortex	0.041	0.016	2.472	0.013	0.459
Volume Parahippocampus	-0.051	0.019	-2.671	0.007	0.258
Suicide attempt					
Sulcul Depth Caudal Middle Frontal Lobe	0.060	0.020	2.933	0.003	0.112
Sulcul Depth Medial Orbito-Frontal Lobe	-0.048	0.017	-2.718	0.006	0.112
Volume Rostral Middle Frontal Lobe	0.040	0.014	2.819	0.004	0.164
Volume Hippocampus	0.043	0.014	3.002	0.002	**0.021**
FA inferior frontal occipital fasciculus	-0.045	0.017	-2.559	0.010	0.211

[1]All models were adjusted for sex, race, age, anxiety and depression, family, scanner, BMI and subject id, whole brain volume and DTI mean motion for all white matter analysis.

8. Discussion

8.1 Summary

In this thesis we observe multiple associations in children aged 9-10 years showing how brain structural changes are associated with both suicidal ideation and sleep disorders. We further also identify that certain sleep disorders in this young cohort are significantly associated with suicidality at 2 years follow up, thus fulfilling the main aim of this study, to identify if sleep disorders had associations with suicidality in early adolescents. Despite low effect sizes these findings remained significant after FDR corrections. These small effects sizes should be seen in the light of an early age cohort and an overall low prevalence, considering the rare outcomes studied. We further identified different changes to brain regions that are associated with the presence of sleep disorders, highlighting the study goal of identifying the neurodevelopmental changes that might be observed in sleep disordered children. One of the key findings was the differences in patterns in these relationships between males and females. The following discussion first focusses on findings within the sample as a whole, then integrates the differences seen between the sexes

8.2 Sleep and suicidal ideation

The results in this study highlight that sleep disorders are associated with later measures (2 years) of suicidality, albeit with small effect sizes. The findings indicate that the total sleep disorder measure was associated with increased ideation and behaviours of suicidality. This is highly consistent with previous studies that have identified sleep disorders in both adults[41] and adolescents[112,113] as a risk factor for suicidal ideation, behaviours and death. The current work is consistent with this literature and extends it by assessing such a young cohort, and with multiple adjustments of important sleep related confounders. The exact disorders that we observe that are significant after FDR correction, highlight new important findings. Disorder of arousal/nightmare (DA) is a disorder that is comprised of sleep talking, sleep walking and nightmares. Not only was it associated in the whole sample with suicidal ideation, - in females, DA showed the largest OR for attempt/self-harm. Nightmares have previously been found to exist as a strong predictor of suicide[26] and we here replicate this, but in a larger and younger sample. However, in a more recent prospective cohort study with a cohort of 40,902 adults (18-94 years old) showed that nightmare wasn't associated

with rates of suicide.[114] Indicating that nightmares might not be highly influential after all, at least in adults, which makes an inconsistent picture. This could be due to methodological differences and cohort differences such as adult populations vs adolescent population. Nonetheless, the image presented here is that nightmares and other parasomnias could play a role in the development of suicidality in early adolescence.

Sleep-wake transition disorder was also associated with increased suicidality. This sleep disorder covers issues with timing, regarding waking up and falling asleep. It is known that the circadian rhythm tends to undergo massive changes in the adolescent developmental phase[9,115,116], thus it is important to consider how these changes if unmet and not respected might potentially lead to development of mental health issues that could develop into suicidal distress. This highlights how sleep disorders are important targets for intervention when it comes to improving mental health in youth, especially considering optimizing school days to better suit the chronobiological needs of early adolescents. Sleep breathing disorder (snoring and apnea symptoms) was also associated with increased risk of suicidal ideation; this is interesting considering how sleep apnea recently has been demonstrated to be associated with suicide death in adults in large registry studies from Denmark.[25,41] To our knowledge this is the first study of such a young cohort that demonstrates early onsets of sleep breathing disorders are associated with suicidal ideation, even when controlling for other lifestyle factors such as BMI. Finally, the disorder of excessive somnolence was also associated with increased suicidal ideation, this replicates previous results showing that hypersomnia or increased sleep pressure are associated with suicidal outcomes, potentially because they are proxies or markers of underlying mood disorders. This pattern still existed after controlling for mood using the CBCL syndrome of depression/anxiety. When stratifying analysis by sex, suicidal ideation was only significantly predicted in males with DOES and TSD.

8.3 Sleep and suicide attempt/self-harm

In the whole sample, suicide attempt/self-harm (SA/SH) was predicted by multiple sleep disorders. Disorder of initiating and maintaining sleep was associated with SA/SH, which replicates previous findings that symptoms of insomnia have associations with SA/SH and in some studies even death.[7,117,118] DOES was associated with increases in SA/SH, this might again be related to an underlying association between hypersomnia and mental health disorders which has been shown

previously.[27] As with suicidal ideation, DA also showed significant association with SA/SH. DA is interesting given that very little is known regarding the role of parasomnias in terms of mental health. Dreams themselves have been speculated to have different roles in terms of their effect on mental health. The sleep stage known as REM sleep in which dreams often take place is known to be of significant importance to emotional regulation.[119,120] Parasomnias might be reflective of altered REM sleep and potential deficits in emotional regulation[119] such as a decrease in inhibitory control, leading to impulsivity which is known to play a role in suicidal behaviors.[121] Sleep hyperhidrosis, a condition in which the child sweats excessively during sleeping or waking[122], was also significantly associated with SA/SH. Hyperhidrosis has previously been shown to be associated with depression, stress and sleep disorders of other kinds[123] and might be reflective of dysfunctions in the Hypothalamus pituitary adrenal axis. These findings might highlight the very worst-case scenarios of hormonal changes in children undergoing puberty. This is a potential area for further neurobiological studies which attempt to further understand what takes place in children undergoing rapid and early pubertal changes.

Overall though we observe small effect sizes, they are however comparable to effect sizes previously observed in large scale epidemiological studies.[104] We also identify multiple different sleep disorders in this study that are associated with increases in both ideation and behaviours of suicidality. Different neurobiological and psychological mechanisms will potentially play a key role in explaining how each sleep disorder impacts suicidality. Most likely, across disorders, the impact on emotional regulation due to reduced REM sleep and the decrease in cognitive abilities due to a lack of sleep quality and quantity, as well the overall feeling of hopelessness in these children, must be seen as the main explaining factors for any increase in suicidality. All in all, we would also expect that a large part of the increased suicidality can be attributed to underlying mood disorders seeing how the mean score of anxiety and depression syndrome is significantly higher in children with sleep disorders across baseline and follow up years. Further, the symptoms of mood disorders are deeply intertwined with sleep disorders, and vice versa, even though we control for mood we cannot exclude that what we are observing is prodromal sleep disturbances emerging before a depression. Finally, the fact that all investigated sleep disorders were significantly (pFDR) associated with suicide attempts and self-harm in females highlights young girls' struggles in early age with self-harm and suicidality. Especially when considering that trouble sleeping, such as

insomnia often occur more frequently in women and the knowledge that young females have a higher risk of self-harm and suicide attempt than males of the same age.[11]

8.4 Sleep and brain changes

In this study we observed multiple changes to brain structure at year 2 associated with sleep disorders present at baseline. This illustrates the importance and role of sleep in the developing adolescent brain.[9,124] Firstly, we observe that overall total sleep disorder is associated with volumetric reductions in the entorhinal and the ventral diencephalon, a finding that we also observe for some of the specific sleep disorders such as DIMS and SWTD. The entorhinal cortex has been found to have reduced cortical thickness in individuals with low subjective sleep quality,[125] making this finding interesting. Further it has been speculated that the entorhinal plays a key role in memory consolidation during sleep and awake states in conjunction with other regions.[126] The Ventral diencephalon on the other hand is important for sleep regulation in particular due to the fact that it contains the hypothalamus. The hypothalamus plays a key role in waking and sleep due to the placement of the supra and preoptic nucleis which works as pacemakers for circadian rhythm. Changes to these structures could potentially be an expression of changes to circadian stability, this might explain why we observe this change in those with sleep wake transition disorders and disorders of initiating sleep.

Further, important changes were observed in FA reductions for the anterior thalamic radiations associated with both SBD and TSD. Reductions of FA in the fornix was associated with DIMS and DOES. This is indicative of microstructural changes to white matter in these tracts, which could represent underlying biological changes such as altered axon density.[127] This is interesting given that the anterior thalamic radiations connect the thalamus with the frontal lobe and are speculated to play a role in cortical arousal and consciousness.[128] One could speculate that the tiredness observed in sleep deprived individuals might be occurring via microstructural changes to anterior thalamic radiations which could alter levels of arousal. The fornix on the other hand is extremely important for memory[129] and these changes observed in association with certain sleep disorders might be illustrative of the impact a lack of sleep has on memory in adolescents. Further the negative associations between sleep disorders and the fornix are important given that early adolescents might be more vulnerable to memory issues as they could lead to social consequences in classroom settings and learning settings.

8.5 Suicidality and brain changes

Multiple brain areas were negatively associated at 2 years follow up with baseline presence of STB, although none of these survived FDR correction. Overall negative associations between suicidal ideation and cortical thickness were observed on the whole brain measure with a global reduction in thickness, in both temporal-parietal areas (the Supramarginal Gyrus, fusiform gyrus, inf. Parietal lobe) and frontal areas (Pars Orbitalis, Pars Triangularis Sup. Front. Lobe.) suggesting the implication of language associated areas and higher cognitive functioning areas. These associations are interesting in light of the functions of the regions; The fusiform is important for recognition of, for example, faces, bodies, and words – it has previously been shown that suicidal individuals often are more likely to interpret stimuli such as faces or words in a negative manner.[130] Thus, these changes are potentially reflective of how suicidal thoughts are affecting a region of the brain critical to interpretation of the outside world. In similar fashion and perhaps more importantly the inferior parietal lobe is important in the understanding of emotional body language, again something that can be highly affected and altered in suicidal individuals.[131] The pars orbitalis, pars triangularis and supramarginal gyrus are primarily involved in language understanding and processing, thus these areas are language related and important areas that are involved in the production of speech and the interpretation of language and speech[132-134]. Changes here may reflect the altered affective state suicidal individuals are in, given that they can react more negatively or differently towards otherwise normal language and auditory stimuli. Thus, this might be a key component of suicidal distress in early adolescents – changes to language interpretation.

Reductions in cortical thickness in the superior frontal lobe, an area associated with higher cognitive functioning like planning, emotion regulation and self-control were shown.[135] Yet, this might be reflective of alterations in brain maturation, seeing how cortical thickness is observed decreasing in normal developing adolescents.[15,136] Nonetheless changes in the frontal lobe have previously been found in suicidal individuals, in particular in the prefrontal cortex.[137] Numerous arguments as to how suicidality impacts the frontal lobe can be made. The main hypothesis is that impaired inhibitory control (i.e. increased impulsivity) is normally tightly regulated through frontal lobe activity, thus the increased impulsivity often observed in suicidal individuals and the decreased emotional regulation may be expressive of disturbed neurobiological activity.[138] This might be a

reason for the finding that cortical thickness is reduced in suicidal individuals.

Besides reduction in cortical thickness, we also observed increases in surface area in the following areas: Paracentral lobule, Pars Triangularis, Precuneus, Rostral Middle Frontal Lobe, and Superior Frontal lobe. These findings show that changes to frontal lobe structure, which is a common neuroradiological finding in individuals with STB are present but also changes to more diffuse areas such as the Pars Triangularis, involved in language. Interestingly the precuneus is important for mental imagery of the self[139], and self-awareness[140], these are all critical processes when an individual is in distress, the increased precuneus surface area may indicate and overly active self-awareness bound by negative self-understanding.

Finally, we also found that self-harm and suicide attempt were associated with increases in the sulcul depth of the caudal middle frontal lobe, this might be indicative of changes to working memory as prefrontal changes to sulcul depth have previously been associated with changes to verbal working memory.[141] Thus illustrating some of the previous mentioned effects of suicidality upon brain areas involved in language.
Through this study we managed to address some of the previous identified gaps identified through the scoping review. We manged to use a uniform and frequent utilized sleep measure to assess sleep disorders in a large cohort to establish associations between sleep disorders and brain changes. Further we also utilised the vast data source to establish associations between sleep disorders and future suicidality, while controlling for many of the potential confounders impacting the study of sleep disorders.

8.6 Strengths and limitations

The major strength of this study is the use of the largest neuroimaging cohort of early adolescents to date, allowing for multiple adjustments of important factors. With more than 11,000 participants the data is based on multiple participants and allows for the study of statistically rare events in youth such as suicide attempts. The ABCD study is continuously updated, with updated releases[101], leaving a data source of high quality. At the same time the entire study sample is geographically diverse as well as demographically diverse with respect to the US population, increasing the representability of the findings.[100] Further the neuroimaging variables used have been validated and

pre and post processed by the ABCD team, and around 90% of all participants completed their scans leaving a high sample size for these analyses.[103] Furthermore the possibility to control for a large variety of important confounders strengthens the results and the interpretation of them, given that important covariates such as a participant's family and potential anxiety/depression has been accounted for in the analyzed models. Finally, the CBCL and The SDSC have previously been found to be of strong validity and reliability for testing of psychometric and sleep related problems in children.[106,108]

This study also contains multiple limitations that should be noted. Although formal growth curve modelling would have been optimal, these models need more than 2 timepoints of imaging[142], this wasn't feasible with current data available and therefore proper longitudinal modelling hasn't been conducted, nor did this allow for any proper mediation to be conducted. The covariates were all based on their values at baseline, thus they were not time varying, this again hinders proper impact of the covariates upon the analysis (although we would expect most of the covariates to remain fairly fixed and appropriate to use considering the adjustment of subject ID). The measures used to cover sleep disorders and suicidality were all parent-reported, therefore the potential for parent/caregiver bias can't be ignored. We would however expect this bias to be less severe than the potential recall bias in children within this young age group. Considering how rare suicidal thoughts and behaviors are in children this young, the interpretation of this study should also be taken with extra caution. Subgroup analysis and mediation analysis although important, remain improper when dealing with exposure groups with so few exposed participants, thus hindering how much we can interpret from this research. Further, we have no way of validating the severity of thoughts and self-harm cases given that we decided to compile the variable into a binary measure to increase statistical power. This further makes it hard to conduct subgroup analyses, even when considering the large overall sample size of the study. We also had no way of tracking if participants with STB actually died by suicide within the study period.

The measure for total sleep disorder is a composite score that can be comprised of a child scoring medium scores in multiple different domains and thus reaching the clinical threshold. Therefore, it does not necessarily indicate any one specific sleep disorder, rather a composite of multiple issues in multiple sleep domains. This makes any proper interpretation of this predictor variable more complicated. Both the SDSC and CBCL are questionnaires delivered with retrospective questions. Thus, "yes" answers by parents and hereby scores of either sleep issues or suicidality are not

necessarily representative of present issues, rather recent struggles. Finally other potential confounders that we haven't controlled for such as family income, education and geographical location such as urbanicity could also have downstream effects and these were not added into our models.

8.7 Clinical implications

Sleep disorders have previously been shown to have an impact on mental health, in this study we identify that they do associate with early adolescents' later risk of suicidal ideation, but also behaviors, and with brain structure. The fact that sleep disorders, which might otherwise be ignored by caregivers, increase suicide risk, should be taken seriously in the context of the current crisis regarding increased suicidality in youth. Furthermore it is important to recognize that sleep disorders increase risk for both ideation and behaviors, which is important considering that not all who may have suicidal ideation attempt suicide, thus sleep disorders serve as a universal predictor for increased suicidal outcomes in early adolescence. Clinicians and caregivers should be attentive to sleep issues early on as they serve as potential downstream interventions, not only for suicidality, but overall psychopathological development in early adolescence. Seeing how cognitive behavioral therapy for insomnia has previously been shown to help in children with insomnia and depression, and online applications exist, this treatment should be further used and expanded upon.[49,143] Even more so when sleep interventions aimed to reduce suicidality exist and have showed promising results.[28,29] It should also be tested further what other important confounders/covariates play a role in inducing potential sleep problems in adolescent, in order to understand downstream sleep disorder prevention. Further, society should carefully consider how environmental and societal norms and rules may impact the health of early adolescents undergoing development. This is reflected in the ongoing debate around start time and length of school days, and the debate regarding day light savings time. Handling sleep disorders early is nonetheless key to avoiding the onset of comorbid psychiatric disorders created by the emergence of sleep disorders in early adolescence. Treating these issues can potentially offer a protection for vulnerable children undergoing development and in the long run potentially shelter them from suicidal distress.

8.8 Conclusions

In this cohort study with more than 11,000 early adolescent children we find that sleep disorders are associated with increased risk for suicidal outcomes, such as ideation, self-harm and suicide attempt. Albeit with small risk increases, in both male and females, in particular females irrespective of the type of sleep disorder all had higher risks of attempting suicide or self-harming. Further we identify multiple changes to brain areas associated with sleep and suicidality during the ongoing neurodevelopment in early adolescents. This highlights the power of suicidal distress and sleep disorders on the developing brain. This further illustrates the need to care for sleep quality and treat sleep disorders in children and adolescents as these sleep disorders might increase the risk of adolescent psychopathological development, such as suicidal distress. Finally, even though small in absolute numbers we do observe that amongst a cohort of more than 11,000 diverse and demographically representative 9 to 10 year old's that approximately 2% of children suffered from suicidal ideation as reported by caregivers. In such a young age group this is extremely concerning, and such early emergence of suicidality in children warrants further action taken to alleviate early adolescents in distress. This study underscores the fact that sleep is extremely important in adolescence, being one third of a human life. For individuals in high distress sleep is the only biological phenomenon that offers the alleviation and peace so desperately needed to combat the struggles and pain that may be present, therefore we need to protect sleep in early adolescence.

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