**Title**: Assessment of sleep problems and mental health in children identified prenatally with a fragile X premutation based on parental report.

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**Introduction**: Individuals with a fragile X premutation (PM) are at an increased risk for a variety of physical and mental health conditions with psychiatric disorders among the most common of these problems in adults. In addition, individuals with a PM often experience significant sleep disturbances. Sleep problems in children in the general population have been shown to adversely affect development, cognition, behavior, and mood. Additionally, families of children with neurodevelopmental disorders and sleep problems frequently report sleep disturbances themselves. The information on sleep disturbances in children with a fragile X PM is limited. This study aims to explore the extent of sleep problems in an unbiased study cohort of children with a PM *vs.* children with no PM (NC), including the relationship between sleep problems and mental health conditions.

**Method**: This longitudinal study includes 62 children with a PM [35 males, 27 females] and 66 NC [35 males, 31 females] who were prenatally diagnosed or their siblings. The Child Behavior Checklist (CBCL) was completed by parents when the child was 3 to 7 years old (Time 1) and 8 to 13 years old (Time 2) to assess sleep difficulties and identify possible associations between sleep and mental health problems. A sleep score was assigned to children for both Time 1 and Time 2 based on parent rated sleep items found in the CBCL. If any sleep item was rated a 2, (very true or often true), or if any three sleep items were rated a 1 (somewhat or sometimes true), the child was given a sleep score of 2. If the parent rated one or two sleep items a 1, the child was given a sleep score of 1. If the parent rated all sleep items a 0 (not true), the child was given a sleep score of 0. The total scores for the syndrome scales in the CBCL: Depressive Problems, Anxiety Problems, and attention deficit hyperactivity disorder (ADHD), were used to assess the child’s mental health at Times 1 and 2. Effects on the siblings of probands with sleep problems was also evaluated.

**Results**: PM females were 2.75 times more likely to have parent-reported sleep problems compared to NC females, but no difference was seen in the males. Using a mixed-effects model to account for repeated measures at Time 1 and Time 2 in all children in the study sample, sleep problems significantly predicted depression (*p*<.0001), anxiety (*p*<.0001), and ADHD (*p*<.0001). When we looked at individual groups separately (PM females only, NC females only, PM males only, and NC males only) the results were similar to those of the group as a whole except for PM males and ADHD. Using linear regression analysis, the presence of sleep problems at Time 1 was significantly associated with the presence of depression (b=1.06, *p*=5.34e-10), anxiety (b=1.04, *p*=2.38e-8) and ADHD (b=0.61, *p*=.03) at Time 1 for all children. Again, when looking at individual groups separately, these results were similar to the group as a whole except there was not a significant association for ADHD with any individual group. However, when we looked at changes in mental health outcomes across time, a significant association was only seen in PM females for sleep at Time 1 and change in depression at Time 2 (b= -1.57, *p=*.036). Individual sleep items from Time 1 were also found to be associated with depression, anxiety, and ADHD at Time 1. ANCOVA in all children in the study sample revealed sleep problems in siblings is significantly associated with sleep problems in probands (*p*=2.5e-05).

**Discussion:** Our results demonstrate a significant association between sleep problems and depression, anxiety, and ADHD across all children in the study. Notably, PM females were more likely to experience sleep problems compared to NC females and a significant association with a change in depression was exclusively seen for PM females at Time 2. Furthermore, individual sleep items were found to be differentially associated with specific mental health concerns. Additionally, siblings of probands with sleep problems experience elevated rates of sleep problems themselves, highlighting the cascading effect of sleep problems within families. The data suggest a simultaneous occurrence of sleep problems and mental health issues among children at Time 1, making it challenging to definitively establish a causal relationship between the two without data from younger children.

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