Genetic and Environmental Factors Shape Infant Sleep Patterns: A Study of 18-Month-Old Twins

Sonia Brescianini, Anna Volzone, Corrado Fagnani, Valeria Patriarca, Valentina Grimaldi, Roberta Lanni, Laura Serino, Pierpaolo Mastroiacovo and Maria Antonietta Stazi

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abstract

OBJECTIVE: Between 25% and 30% of children and adolescents experience sleep disorders. These disorders are complex phenotypes that are regulated by many genes, the environment, and gene-environment interactions. The objective of this study was to evaluate the contribution of genetic and environmental factors to sleep behaviors in early childhood and to contribute to the knowledge on appropriate therapeutic approaches, using a twin design.

PATIENTS AND METHODS: Data on sleeping behavior were collected from 314 18-month-old twin pairs (127 monozygotic and 187 dizygotic) using a parent-rated questionnaire. We used structural equation modeling to estimate genetic and environmental variance components for different sleep behaviors (cosleeping, sleep duration, and night awakenings).

RESULTS: Shared environment explained almost all (98.3%) of the total variance in cosleeping. Sleep duration was substantially influenced by shared environmental factors (64.1% nocturnal sleep and 61.2% diurnal sleep), with a moderate contribution of additive genetic effects (30.8% and 36.3% for nocturnal and diurnal sleep, respectively). For nocturnal waking episodes, we found a shared environmental contribution of 63.2% and a heritability estimate of 35.3%.

CONCLUSIONS: Most sleep disturbances during early childhood are explained by common shared environmental factors, and behavioral interventions adopted by parents and focused on modifying sleep behavior could contribute to solving sleep disturbances in this age group. However, the influence of genetic factors should not be underestimated, and research in this area could clarify the physiologic architecture of sleeping and contribute to selecting appropriate personalized therapeutic approaches. Pediatrics 2011;127:e1296–e1302

WHAT'S KNOWN ON THIS SUBJECT: Sleeping behavior is associated with health in general, behavioral disorders, and school performance. To distinguish between the genetic and environmental factors that influence sleeping behavior, twin studies can be of use, although few have been performed.

WHAT THIS STUDY ADDS: We evaluated the contribution of genetic and environmental factors to sleep measures in early childhood using a twin design. We found evidence of strong shared environmental influences, although heritability was not negligible. These results are important for choosing appropriate therapy.
The self-organization of sleep and awakenings in infants represents a significant milestone in early child development and reflects developmental changes in neural activity that occur in different regions of the brain.\textsuperscript{1} Between 25% and 30% of children and adolescents experience sleep disorders, which can range from short-term difficulties in falling asleep and night awakenings to more serious primary sleep disorders, such as obstructive sleep apnea.\textsuperscript{2–7} There is evidence that sleep disorders in infants in most cases persist through early childhood\textsuperscript{6–11} and that they can be linked to future behavioral, emotional, and cognitive disorders.\textsuperscript{12–15}

The most common concerns reported by parents in early childhood are related to going to bed or falling asleep and night awakenings. These sleep behaviors not only involve the infant’s capacity to self-soothe on transitioning to sleep and to maintain it but also place continuous stress on the family. It is also important to consider that sleep problems are often associated with a wide spectrum of chronic medical, neurodevelopmental, cognitive, and psychiatric conditions at various ages, and recent studies have reported an association between short sleep duration and health problems, such as obesity, in pediatric populations.\textsuperscript{7,16–19}

Sleep and sleep disorders are complex phenotypes that are regulated by many genes, gene interactions, the environment, and gene-environment interactions. To understand the aetiology of these phenotypes in terms of the clinical and etiologic definitions. Moreover, it is still not clear which sleep behaviors are more likely to develop into future sleep disorders, and the etiology of many sleep disorders remains unknown. In addition, there exist various therapies for infants and children, including behavioral and cognitive-behavioral interventions, drug therapy, or a combination of these; yet how, which, when, and for how long they have to be used is not always easy to establish. The objective of the present study was to evaluate the contribution of genetic and environmental factors to sleep behaviors in early childhood and ultimately to contribute to the knowledge on appropriate therapeutic approaches. To this end, we studied a cohort of 18-month-old twins.

\textbf{PATIENTS AND METHODS}

The study participants were all included in the Italian Multiple Pregnan\-cies Registry, which was created in 1993 to collect data about twins born in 47 hospitals located throughout Italy and was part of a larger survey, the “Mercurio Project.”\textsuperscript{23} Children were enrolled in the registry at birth. In each hospital participating in the registry, the twins’ parents were informed about the goals of the registry and the evaluations to be performed on the twins. After having obtained the parents’ verbal consent, telephone interviews were conducted when the twins reached 3, 9, and 18 months of age. At 18 months, a shortened version of the parent-rated Zygosity Questionnaire for Young Twins,\textsuperscript{24} which has been shown to have an accuracy of 93.8%,\textsuperscript{25} was applied to assign zygosity. All twins who participated in the 18-month follow-up and with no prenatal or perinatal difficulties, chromosomal anomalies, or specific medical conditions were included in the analysis. Triplets and higher order births were excluded.

At 3 months of age, background information, including the characteristics of the family environment, smoking habits, pregnancy and delivery modality, gestational age at birth, and feeding habits, was obtained. At 9 and 18 months of age, the general health conditions and some developmental aspects were evaluated. At 18 months, sleep habits were assessed using a specifically designed questionnaire, administered during the telephone interview. In particular, the questionnaire is used to investigate the following:

\textbf{Presence or Absence of Cosleeping and Sleep Context}

Specific questions:
- “Does he/she sleep in his/her room?”
- “Does he/she sleep in the parents’ room?”

\textbf{ARTICLES}

PEDIATRICS Volume 127, Number 5, May 2011

Downloaded from www.pediatrics.org by on April 18, 2011
TABLE 1  Twin Characteristics: Means and SDs

<table>
<thead>
<tr>
<th></th>
<th>Monozygotic</th>
<th></th>
<th>Dizygotic SG</th>
<th></th>
<th>Dizygotic OG</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (N = 132)</td>
<td>Female (N = 122)</td>
<td>Male (N = 112)</td>
<td>Female (N = 80)</td>
<td>Male (N = 91)</td>
<td>Female (N = 91)</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>36.2 ± 3.0</td>
<td>36.3 ± 2.5</td>
<td>36.1 ± 2.3</td>
<td>36.5 ± 1.7</td>
<td>36.5 ± 2.4</td>
<td>36.5 ± 2.4</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>2397.7 ± 537.5</td>
<td>2351.5 ± 489.5</td>
<td>2505.5 ± 501.8</td>
<td>2394.4 ± 451.1</td>
<td>2569.1 ± 484.8</td>
<td>2515.3 ± 915.8</td>
</tr>
<tr>
<td>Maternal age, y</td>
<td>29.7 ± 4.4</td>
<td>30.2 ± 5.0</td>
<td>29.5 ± 4.8</td>
<td>30.1 ± 5.0</td>
<td>30.3 ± 4.5</td>
<td>30.3 ± 4.5</td>
</tr>
</tbody>
</table>

SG indicates same-gender; OG, opposite-gender.

TABLE 2  Twin Characteristics: Frequencies and Percentages

<table>
<thead>
<tr>
<th></th>
<th>Monozygotic</th>
<th></th>
<th>Dizygotic SG</th>
<th></th>
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<td>Female (N = 80)</td>
<td>Male (N = 91)</td>
<td>Female (N = 91)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>16 (12.1)</td>
<td>17 (13.9)</td>
<td>9 (8.0)</td>
<td>14 (17.5)</td>
<td>9 (9.9)</td>
<td>5 (5.5)</td>
</tr>
<tr>
<td>North/centre*</td>
<td>64 (48.5)</td>
<td>64 (52.5)</td>
<td>60 (53.6)</td>
<td>44 (55.0)</td>
<td>37 (40.7)</td>
<td>37 (40.7)</td>
</tr>
<tr>
<td>Any other sibling</td>
<td>70 (53.0)</td>
<td>70 (57.4)</td>
<td>40 (35.7)</td>
<td>36 (45.0)</td>
<td>48 (52.7)</td>
<td>43 (47.3)</td>
</tr>
</tbody>
</table>

SG indicates same-gender; OG, opposite-gender.

* Percentage of twins born in a hospital located in northern or central region of Italy as opposed to South of Italy and 2 main islands.

Sleep-wake Organization and Sleep-Related Problems

Specific questions:
- “How many hours does your child spend in nocturnal sleep?”
- “When he/she is in good health, does he/she wake up at night?”
- “Does he/she wake up at night?”
- “How many times during the week?”
- “How many times during the night?”
- “Does your child cry and scream when waking up at night?”
- “How many hours does your child spend in diurnal sleep?”

Statistical Analysis

Comparisons among the twin pairs by zygosity and gender were performed for the descriptive statistics in Tables 1 and 2 using the t test for continuous measures and the \( \chi^2 \) test for frequencies. The analysis of twin correlations included 2 dichotomous variables (ie, the presence of cosleeping and the presence of 7 or more nocturnal waking episodes per week) and 2 continuous variables (ie, time (in hours) spent in nocturnal and diurnal sleep). Tetra-choric twin correlations (for the dichotomous sleep measures) and Pearson twin correlations (for the continuous sleep measures) were estimated in monozygotic and dizygotic twin pairs separately and were interpreted under the assumptions of the classical twin design.26 These correlations provide information on the relative contribution of genetic and environmental factors to interindividual phenotypic differences. A significantly higher correlation in genetically identical monozygotic twins, compared with dizygotic twins who share an average of 50% of their segregating genes, indicates that genetic factors contribute to the variation.

To estimate the heritability of the sleep measures (ie, the proportion of the total phenotypic variance attributable to genetic variance), structural equation twin models were used. These models assume that the total phenotypic variance (V) in a measure can be decomposed as:

\[
V = A + C + E
\]

where A refers to additive genetic variance, C is the contribution of shared environmental influences (ie, environmental influences that are shared by twins reared together and thus a source of within-pair similarity), and E indicates the influence of unique (unshared) environmental factors (ie, environmental factors—including measurement error—that are specific to an individual and that are responsible for phenotypic correlations between monozygotic twins of <1). Assuming that shared environmental factors correlate 100% between both monozygotic twins and dizygotic twins (equal environments assumption27), and that additive genetic influences correlate 100% in monozygotic twins and 50% in dizygotic twins, the expected twin covariances can be expressed as:

\[
cov(MZ) = A + C \\
cov(DZ) = 0.5 * A + C
\]

Variance components were estimated by the maximum-likelihood method using Mx software (Richmond, VA).28 Different models (full ACE and submodels AE, CE, and E) were fitted to the raw data of each sleep measure in monozygotic and dizygotic pairs. The fitting of the submodels was compared with that of the full model by means of
likelihood-ratio χ² tests, and the estimates of genetic and environmental variance components were reported under the most parsimonious solution (best model).

Ethical Aspects

At the time of the study, in Italy, observational studies with no intervention or treatment were not required to go through the ethical approval process. However, informed consent was given verbally by the parents at the time of enrollment and again at the time of telephone follow-up interview, and all the ethical requirements (ie, respect of the dignity of the individuals, right to withdraw, right to access their own data, etc) were fulfilled.

RESULTS

Of the 1076 children enrolled in the registry, 134 were part of triplets or quadruplets and were not included in this study. Of the remaining 471 pairs, 34 were excluded because at least 1 of the 2 children was malformed or experienced pre- or perinatal difficulties. Of the remaining 437 pairs, 314 (127 monzygotic and 187 dizygotic) completed the study.

Approximately 49% of the families in the sample had no children other than the twins; 12.7% of the twins attended day care. For 58% of the families, both parents were regularly employed before the pregnancy with the twins; after the twins’ birth, this percentage decreased to 36%, in most cases because the mother stopped working.

The characteristics of the twins and families, by zygosity and gender are described in Tables 1 and 2. The average gestational age was around 36 weeks, with no significant differences by zygosity or gender, and the average maternal age was ~30 years, again with no significant differences. Birth weight was between 2300 and 2600 g, and between 9.9% and 17.5% of the twins were small for gestational age; no significant differences were found. The percentage of families with children other than the twins ranged from 35.7% to 57.4%, with significant differences (P < .05, using the χ² test). Geographically, the sample was equally distributed.

The sleep behavior of the twins, by gender and zygosity, is shown in Table 3. Female and male twins did not differ for any of the variables, whereas the prevalence of 7 or more waking episodes per week was significantly higher in monzygotic twins (31%) compared with dizygotic twins (19%) (P < .001). The parents reported cosleeping in 53% of monzygotic and dizygotic twins. The mean durations of diurnal and nocturnal sleep did not significantly differ by zygosity.

The estimated twin correlations and genetic and environmental variance components for the various sleep measures are reported in Table 4. The unshared environmental contribution was marginal for all of the sleep measures; this is consistent with a very high correlation observed between monzygotic twins, being the unshared environmental proportion of variance equal to the complement to 1 of monzygotic correlation.26 With respect to cosleeping, we found very high and similar correlations in monzygotic and dizygotic pairs (0.996 vs 0.972, respectively). As a consequence, no genetic effects on this measure emerged, whereas there were strong shared environmental influences (98.3%), with a minor contribution (1.7%) of unshared environmental factors. For sleep duration, we found slightly higher correlations in monzygotic pairs (0.946 nocturnal sleep and 0.977 day sleep), compared with dizygotic pairs (0.808 nocturnal sleep and 0.797 day sleep). Sleep duration was mainly influenced by shared environmental factors (64.1% nocturnal sleep

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Descriptive Statistics for the Sleep Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Measure</td>
<td>All</td>
</tr>
<tr>
<td>Cosleeping, % (W)</td>
<td>53 (335)</td>
</tr>
<tr>
<td>Night, mean (SD)</td>
<td>9.7 (1.2)</td>
</tr>
<tr>
<td>Day, mean (SD)</td>
<td>2.1 (0.8)</td>
</tr>
<tr>
<td>7 or more night awakenings weekly, % (W)</td>
<td>24 (150)</td>
</tr>
</tbody>
</table>

* P < .001.

| TABLE 4 | Estimates of Twin Correlations and Genetic and Environmental Proportions of Variance for the Sleep Measures |
| --- | --- | --- |
| Sleep Measure | Correlations | Additive Genetic Influences | Shared Environmental Influences | Unshared Environmental Influences |
| Monozygotic | Dizygotic | Monozygotic | Dizygotic |
| Cosleeping | 0.996 | 0.972 | — | 0.017 (0.006–0.038) |
| Night, mean (SD) | 9.7 (1.2) | 9.6 (1.2) | 9.8 (1.1) | 9.7 (1.2) | 9.7 (1.3) |
| Day, mean (SD) | 2.1 (0.8) | 2.1 (0.8) | 2.1 (0.8) | 2.1 (0.8) | 2.1 (0.8) |
| 7 or more night awakenings weekly | 0.990 | 0.790 | 0.353 (0.141–0.684) | 0.632 (0.303–0.856) | 0.015 (0.002–0.055) |

* Fixed to 0 in the best model.
DISCUSSION

We attempted to determine the contribution of genetic and environmental factors to sleep behavior in early childhood, considering the major sleep behaviors, reported by parents of 18-month-old twins. Cosleeping was reported for 53% of the twins. The prevalence of cosleeping in the first 4 years of life has been reported to be between 6% and 70%29–32 and to be common among African, American, and Asiatic populations.33,19 This variability in the prevalence of cosleeping could be because of differences in the definitions of “cosleeping” and in study designs. In our study, “cosleeping” was considered as sleeping in the same room as the parents, which did not necessarily mean bed-sharing. Moreover, in many cultures, bed-sharing for long periods is not considered to be indicative of a problem and is thus often not considered in the evaluation of sleep disturbances. Nonetheless, the prevalence of cosleeping in our twin cohort is consistent with that found in Italy’s general population of young children,44 which could indicate that genetic factors do not play a major role for this phenotype at early ages. In fact, our results show that cosleeping is almost exclusively influenced by shared environmental factors, and it could be hypothesized that this measure is mainly influenced by family habits.

In terms of sleep duration, overall, the time spent in nocturnal sleep was lower in our study, compared with that in other studies, with no differences by zygosity. It is known that, between the first and second year of life, the time spent in nocturnal sleep is around 11 hours, whereas the time spent in diurnal sleep is ~2 to 3 hours.35

For nocturnal and diurnal sleep duration and the presence of at least 7 waking episodes per week, we found strong shared environmental influences, although (differently from cosleeping) heritability also seems to play a role. However, it is not possible to determine if the behavior of the 2 twins is truly similar or whether there is simply a tendency to report similar behavior for twins. Although it has been reported that parents tend to underline differences in dizygotic twins and similarities in monozygotic twins,36 we also found high correlations between dizygotic twins.

Although all of the considered sleep characteristics seem to be mainly influenced by environmental factors, the role of heritability should not be underestimated. In addition, we expect that, with time, the shared environmental contribution would decrease and the genetic effect would increase as a result of the accumulation of unshared environmental effects and of increasing gene expression levels with growth. Our heritability estimates reveal that, for sleep duration and night awakening, genetic factors explain approximately one-third of individual differences. This proportion is not negligible and may have important practical implications. For example, this information could help parents and clinicians to recognize that any intervention aimed at modifying sleep behaviors should carefully consider children’s individual sleep needs. It is possible that our estimates of genetic effects were influenced by personality traits, which are known to be moderately heritable, and thus the identification of such traits would be important to implement behavioral interventions for improving sleep quality. Moreover, to define normal sleep patterns, it is necessary to consider neuropsychological and physical development. In fact, the prevalence and the various types of sleep problems that occur in the first years of life must be understood in the context of the achievement of motor and cognitive milestones and normal separation anxiety.7 Determining whether these heritability estimates vary among population subgroups characterized by different exposures (eg, mother’s well-being) would also be useful in identifying risk factors that can modify the genetic predisposition to a given sleep problem. Hiscock and Wake demonstrated that a brief behavioral sleep intervention on the basis of teaching mothers how to implement controlled crying led to a 20% reduction in infants’ sleep problems and a significant decrease in symptoms of maternal depression.37 One of the limitations of our study is that we were not able to describe the history of sleeping behavior because we did not collect data on sleeping before 18 months of age. In addition, we did not investigate all known sleep disturbances; in fact, given that this study was part of a larger research project for evaluating overall health, for the sake of brevity we only considered the main components of sleeping behavior. Moreover, the accuracy and validity of parental reporting is uncertain; however, our interview concerned current (and not past) behavior and thus may not have been greatly influenced by recall bias. Another limitation is related to the limited statistical power of this study. For example, the relatively
small sample size did not allow us to test for gender differences in the genetic and environmental variance components of the various sleep measures, although the estimates (not shown) of twin correlations in the 5 zygo-acity-by-gender groups (monozygotic males, monozygotic females, dizygotic males, dizygotic females, dizygotic opposite gender) indicated that such differences were unlikely. In addition, the relatively small sample size prevented us from reliably investigating the correlational structure of the sleep measures by fitting multivariate models. To this regard, a tentative bivariate analysis of nocturnal and diurnal sleep duration showed that the phenotypic correlation between the 2 measures was modest (0.1), as were the cross-twin/cross-trait correlations in monozygotic and dizygotic pairs (0.1 and 0.07, respectively); this suggests that such an analysis would not have provided any interesting additional information. We also compared the 314 twin pairs to the 123 twin pairs that did not participate, in terms of characteristics recorded at birth and at 3 and 9 months of age. The participants were more likely to live in northern-central Italy, have a higher birth weight and higher maternal age, and they were less likely to be breastfed. Thus we probably selected a healthier sub-sample, which could have created a bias only if the genes that make an individual susceptible to sleeping disorders are the same as those that influence the factors for which the groups differ. The twins who participated in this study are currently being re- contacted to assess, with a prospective design, the association of early sleep patterns with metabolic, cognitive, and psychiatric conditions later in life.

CONCLUSIONS
According to our results, the majority of sleep disturbances during early childhood are explained by common shared environmental factors, and we believe that behavioral interventions adopted by parents and focused on modifying sleep behavior could substantially contribute to solving sleep disturbances in this age group. However, because the influence of genetic factors on the genesis and maintenance of sleep disturbances among young children should not be underestimated, research in this area could clarify the physiologic architecture of sleeping and contribute to the selection of appropriate personalized therapeutic approaches.

ACKNOWLEDGMENT
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REFERENCES


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