Clinically Oriented Subtyping of Chronic Insomnia of Childhood

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Objectives To identify different profiles of pediatric insomnia, based on the most frequent clinical presentations (nocturnal awakenings, difficulty in falling asleep, nocturnal restlessness, early morning awakenings).

Study design A structured parent interview was conducted in 338 children (mean age 21.29 months, SD 10.56) referred by pediatricians because of insomnia resistant to behavioral approaches and common drug treatments. The aim was to assess the characteristics of insomnia in children, together with family sleep-related history. A latent class analysis was run to identify profiles of insomnia. ANOVA and the χ^2 test were used to examine differences between profiles.

Results A 3-class model was built by latent class analysis: 17% (n = 58) of children constituted the first class, characterized by difficulties in falling asleep, with restlessness, nocturnal restlessness, and awakenings during the night; the second class, characterized by early morning awakenings, comprised 21% (n = 71) of children; 62% (n = 209) of children fell within the third class because of their high frequency of nocturnal awakenings and difficulties in falling asleep. The first class reported longer sleep latency and the presence of restless legs syndrome and anemia in the family history; depression and/or mood disorders were more frequent in class 2 and allergies and/or food intolerance were more frequent in class 3.

Conclusions Our study suggests the existence of 3 different phenotypes of insomnia in children, based on clinical, personal, and familial data. The identification of these different phenotypes might help to optimize the assessment and treatment of insomnia in young children. *(J Pediatr 2018;■■:■■-■■).*

Over the past decades, several studies have been carried out to understand the link between sleep problems and child development in different areas. Significant associations have been found between childhood sleep problems and socioemotional disturbances, school difficulties, and physical diseases.[1-6] According to these and other studies, identifying children's sleep problems and their prevalence is important for improved treatment and prevention of negative socioemotional and cognitive outcomes.[7]

Researchers have suggested that the parental perception of an overall sleep problem correlates significantly with nocturnal awakenings and difficulties in falling asleep[8-11] and that the frequency of nighttime awakenings is one of the main factors determining the parent judgment of the quality of child sleep.[12]

The prevalence of pediatric insomnia in children and adolescents has been reported to range from 10% to 50%, with greater percentages in children with neurodevelopmental or psychiatric problems.[7,13-15] Previous studies have reported a prevalence of pediatric insomnia ranging from 25% to 50% in preschoolers,[16] to 37% in children aged 4-10 years,[17] and up to 40% during adolescence.[18] Different definitions and classifications of pediatric insomnia have been used in research or clinical contexts.[19] In the *International Classification of Sleep Disorders, Third Edition* (ICSD-3),[20] pediatric insomnia has been incorporated into a single entity with that of adults, under the term of chronic insomnia disorder.

The ICSD-3 defines chronic insomnia as "a persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment" and reports in the comments that pediatric insomnia may be described considering the following 3 subtypes:

1) *Sleep-Onset Association Type*, which includes children who refuse to sleep because they need a specific object or person to fall asleep or get back to sleep. This subtype of pediatric insomnia is quite common in younger infants and characterized by multiple nocturnal awakenings;
2) *Limit-Setting Type*, which occurs when parents lose control of the child's behavior during bedtime or awakenings from sleep. This subtype of pediatric insomnia is often observed in older infants, who tend to oppose their parents, especially during bedtime; and
3) *Combined Type*, which is characterized by mixed symptoms of the 2 previous subtypes.

ICSD-3	*International Classification of Sleep Disorders, Third Edition*
LCA	Latent class analysis

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The absence of a specific symptom-based classification of insomnia for children may explain the inadequacy of the screening for sleep problems, as well as the underdiagnosis of insomnia in childhood.[11,21]

This conceptual discussion also has been reported in adults. Subtypes of insomnia have been proposed in the major classification systems; however, a seminal study concluded that the reliability and validity of the different nosological entities included was so poor that they did not improve diagnostic accuracy and that alternate diagnostic paradigms for insomnia classification should be considered.[22] As a consequence, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* and the ICSD-3 abandoned further subtyping of chronic insomnia.[20,23] Thus, from a clinical point of view, the ICSD-3 generic classification of insomnia might limit the identification of symptomatic subtypes of pediatric insomnia and does not guide specific treatment for the different manifestations of insomnia.[7]

It is largely accepted that various phenotypes exist, but their specific identification is lacking. Recent studies have emphasized the role of genetic factors in the development of insomnia of childhood: heritability contributed to a large extent to specific symptoms such as nocturnal sleep duration and nighttime awakenings,[24,25] suggesting that a more accurate method of investigating the heritability of insomnia needs to focus on the specific symptoms constituting the disorder separately, rather than relying on an overall "insomnia" construct.[26]

Based on these considerations, in this study, we sought to describe whether specific sleep complaints and clinical features might represent different pathophysiologic subtypes of insomnia. We aimed to identify different profiles of pediatric insomnia based on the sleep problems reported by parents, patient factors, and sleep-related family history.

Methods

Three hundred thirty-eight children (227 boys) aged 6-48 months (mean = 21.29, SD = 10.56) were consecutively recruited during their first medical visit for "insomnia" at the Pediatric Sleep Center of the Sapienza University, Rome, Italy. Children were referred by pediatricians because of their insomnia resistant to common treatments (mainly over-the-counter products) and not responding to behavioral approaches.

All parents reported that they tried to apply the extinction or graduated extinction, based on instructions found in specific books or the Internet, or that they were guided by the pediatricians without success. Most of the parents affirmed that they found extinction sleep interventions too difficult and stressful to implement for several reasons (eg, enduring crying, practical considerations, fear of possible repercussions, incongruence with individual beliefs, different cultural practices).[27]

The following exclusion criteria were used: (1) presence of diagnosed medical problems (ie, recurrent otitis, persistent snoring or sleep apnea noted by parents, intercurrent lung or bowel diseases, etc), malformations, or neurologic/psychiatric disorders; and (2) intercurrent diseases that would require treatment with drugs that affect sleep (eg, steroids, antihistamines). The study was approved by the Ethics Commission of the Department of Developmental and Social Psychology (Sapienza University of Rome), and parental written consent was obtained for all children.

Interview on Pediatric Insomnia

A semistructured interview was conducted by trained physicians to assess the characteristics of the child's insomnia, together with the patient's medical history and family history. The interview contained questions addressing the presence or absence of difficulties in falling asleep, difficulties in falling asleep with restlessness, nocturnal restlessness, multiple night awakenings (≥3), and early morning awakening. We chose these variables based on the most frequently reported sleep complaints according to the literature[28-32] and on the authors' own clinical experience. These attributes were selected for subsequent latent class analysis (LCA). The parental perception of a sleep problem is mediated by 2 main descriptors: awakenings and difficulties falling asleep[9]; however, other common complaints also are related to nocturnal restlessness, sleep onset, and early morning awakenings.

The semistructured interview also included questions regarding child bedtime, wake-time, and sleep latency. Finally, questions on family history for difficulties potentially related to sleep (eg, depression/mood disorders, anemia, restless legs syndrome) and additional child complaints (eg, colic, allergies, gastroesophageal reflux, anemia) were included. These last questions were coded in terms of presence or absence.

Statistical Analyses

Descriptive analyses were run on the overall sample with SPSS for Windows, Version 18.1 (SPSS Inc, Chicago, Illinois). Then, an LCA by using Mplus 5.1 (Los Angeles, California)[33] was conducted to identify different profiles of pediatric insomnia. LCA was run considering the following sleep dichotomous variables: (1) difficulties in falling asleep, (2) difficulties in falling asleep with restlessness, (3) nocturnal restlessness, (4) early morning awakenings, and (5) multiple night awakenings (≥3). All of these variables were coded in terms of presence or absence.

To better identify the best solution of profiles of pediatric insomnia, we ran several models (ranging from 2 to 4 classes). The best model was chosen considering 2 criteria[34,35]: the Akaike information criterion and the Bayesian information criterion. We chose the best solution based on the smallest Akaike information criterion and Bayesian information criterion. We also considered the entropy index with values close to 1, meaning better homogeneity among groups. Finally, the resulting classes were compared with each other, considering both additional child complaints and family history for sleep problems. Specifically, ANOVAs were run considering differences between classes regarding sleep continuous variables (ie, bedtime, wake-time, and sleep latency). The Bonferroni post-hoc analysis was used to test specific differences among classes. The χ^2 test was used to analyze differences between the classes on dichotomous variables related to the child (eg, allergies, gastroesophageal reflux, and anemia) or family (eg, depression/

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mood disorders, headache/migraine, restless legs syndrome) characteristics. The adjusted standardized residuals was examined to understand differences between observed and expected frequencies in each class.

Results

Table I displays the descriptive statistics of the study variables for the overall sample. We found that 43.8% of children had difficulties in falling asleep and 18.3% had also restlessness during the act of falling asleep. Nocturnal restlessness was reported in 29.0% of children, multiple night awakenings (≥3) in 78.7%, and early morning awakenings in 21.3%. The average bedtime was 9:41 p.m., the mean wake-time was 7:11 a.m., and mean sleep latency was 32 minutes.

Regarding the family history, 30.2% of children had family history of insomnia, 8.6% history of parasomnias, 12.4% history of restless legs syndrome, 27.5% history of depression/mood disorders, 30.2% history of headache/migraine, 23.7% history of anemia, and 42.6% history of allergies/food intolerance. In addition, 47.6% of children had colic, 26.3% had gastroesophageal reflux, 12.1% of children had dermatitis, 5.3% had anemia, and 17.2% had allergies/food intolerance.

Table I. Descriptive statistics for the total sample

	Total sample	
Child sleep	**Mean**	**SD**
Bedtime, hour:min	9.41 p.m.	0.53
Wake-time, hour:min	7.11 a.m.	0.58
Sleep latency, min	32.0	23.0
Insomnia characteristics	**No.**	**%**
Difficulties in falling asleep	148	43.8
Difficulties in falling asleep with restlessness	62	18.3
Nocturnal restlessness	98	29.0
Early morning awakenings	72	21.3
Multiple night awakenings (≥3)	266	78.7
Family history	**No.**	**%**
Insomnia	102	30.2
Parasomnias	29	8.6
Headache/migraine	102	30.2
Depression/mood disorders	93	27.5
Anemia	80	23.7
Restless legs syndrome	42	12.4
Allergies/food intolerance	144	42.6
Child medical complaints	**No.**	**%**
Colic	161	47.6
Allergies/food intolerance	58	17.2
Dermatitis	41	12.1
Gastroesophageal reflux	89	26.3
Anemia	18	5.3

Latent Class Analysis

An LCA was run to identify different groups of children based on their insomnia characteristics. We computed various models (ie, 2, 3, and 4 classes; Table II). According to the fit indices and to the principle of parsimony and theoretical interpretation, the best model was found to be the 3-class model.

The Figure displays the characteristics of each class of the best LCA model. The first class (n = 58, 17% of children) comprises children who had difficulties in falling asleep with restlessness, as well as nocturnal restlessness and multiple awakenings. The second class (n = 71, 21%) is composed of children with early morning awakenings. Finally, the third class (n = 209, 62%) is composed of children with a high frequency of awakenings during the night and difficulties in falling asleep without restlessness.

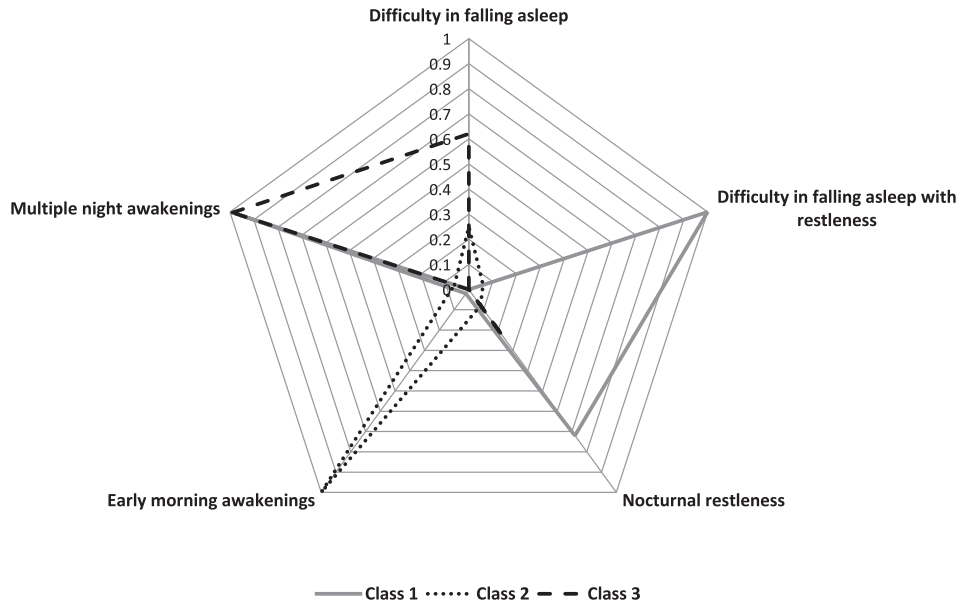

Figure. The 3 classes identified by the best solution of LCA.

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Table II. Fit indices for the different LCAs

Number of latent classes	AIC	BIC	Entropy
2	1604.767	1646.821	0.995
3	1474.132	1539.124	0.969
4	1472.141	1560.071	0.959

AIC, Akaike information criterion; *BIC*, Bayesian information criterion.

Characterization of the Classes Derived by the LCA

To better differentiate the 3 classes, ANOVAs were used to compare bedtime, wake-time, and sleep latency (Table III). Differences between the 3 classes emerged only in sleep latency. The Bonferroni post-hoc analysis revealed that the first class had greater mean sleep latency compared with the second and third classes. No other differences emerged.

We performed a series of χ^2 tests to compare the classes by family history (insomnia, parasomnias, headache/migraine, depression/mood disorders, anemia, restless legs syndrome, allergies and/or food intolerance) and child medical complaints (colic, allergies, food intolerance, dermatitis, gastroesophageal reflux, anemia). As shown in Table III, differences emerged in family history variables with observed frequencies greater than the expected frequencies: anemia and restless legs syndrome were more represented in class 1 (adjusted standardized residuals: 6.2 and 7.4) and less in class 3 (adjusted standardized residuals: –3.3 and –4.8);depression and/or mood disorders were more frequent in class 2 (adjusted standardized residual: 7.6) compared with class 1 and 3 (adjusted standardized residuals: –2.9 and –4.1); allergies and/or food intolerance were more frequent in class 3 compared with class 2 (adjusted standardized residuals: 3.9 vs –3.9).

Regarding the children's medical complaints (Table III), the 3 groups were different for anemia, with the first class displaying observed frequencies greater than class 3 (adjusted standardized residuals: 3.8 vs –3.6). No other differences were found.

Discussion

In this study, we identified 3 profiles based on the common presentations of insomnia in children, namely difficulty in falling asleep, difficulty in falling asleep with restlessness, nocturnal restlessness, multiple night awakenings, and early morning awakenings. These 3 groups represent distinct phenotypes, where parents may seek advice from the primary pediatrician: class 1: insomnia with restlessness; class 2: insomnia with prevalent early morning awakenings; and class 3: insomnia with multiple night awakenings and difficulties falling asleep. Combining the 3 groups with personal and family history, we hypothesize that these 3 insomnia subtypes may have different underlying mechanistic causes and pathophysiology. More specifically, insomnia with motor restlessness characterizes children with a family and clinical history of restless legs syndrome, iron deficiency anemia, and growing pains that might indicate a dopaminergic dysfunction. Evaluation for anemia may be warranted. This clinical presentation resembles the cases of restless legs syndrome reported by Picchietti and Stevens[36] that in early infancy showed chronic sleep-onset and sleep-maintenance problems. A recent study showed that, in children with suspected restless leg syndrome, the most striking single symptom was awakening after 1-3 hours of sleep followed by screaming, crying, kicking, and slapping the legs or by verbally expressing that the legs "hurt" with a seemingly comforting effect of massage performed by parents.[37] Similarly, we

Table III. Means and SDs on child sleep variables and frequencies (percentages) of familiar history for sleep problems and child disturbances for each class

	Class 1 n = 58		Class 2 n = 71		Class 3 n = 209				
Sleep variables	**Mean**	**SD**	**Mean**	**SD**	**M**	**SD**	**F**	***P***	**Partial η^2**
Bedtime, hour:min	9:40 p.m.	1:04	9:47 p.m.	0:49	9:38 p.m.	0:52	0.600	.55	
Wake-time, hour:min	6:59 a.m.	0:53	7:14 a.m.	1:01	7:13 a.m.	0:54	1.305	.27	.01
Sleep latency, min	45_a	24	33_b	29	28_b	20	12.608	<.001	.09
	n (%)		**n (%)**		**n (%)**		**χ^2**	***P***	**χ^2 post-hoc analysis**
Family history									
Insomnia	12 (20.7)		20 (28.2)		70 (33.5)		3.799	.15	
Parasomnias	8 (13.8)		6 (8.5)		15 (7.2)		2.501	.29	
Headache/migraine	14 (24.1)		28 (39.4)		60 (28.7)		4.060	.13	
Depression/mood disorders	7 (12.1)		45 (63.4)		41 (19.6)		58.972	<.001	Class 2 > 1 and 3
Anemia	32 (55.2)		11 (15.5)		37 (17.7)		38.390	<.001	Class 1 > 3
Restless legs syndrome	24 (41.4)		6 (8.5)		12 (5.7)		55.356	<.001	Class 1 > 3
Allergies/food intolerance	22 (37.9)		16 (22.5)		106 (50.7)		18.138	<.001	Class 3 > 2
Child medical complaints									
Colic	30 (51.7)		29 (40.8)		102 (48.8)		1.816	.40	
Allergies/food intolerance	14 (24.1)		11 (15.5)		33 (15.8)		2.402	.30	
Dermatitis	12 (20.7)		9 (12.7)		20 (9.6)		5.292	.07	
Gastroesophageal reflux	19 (32.8)		13 (18.3)		57 (27.3)		3.686	.16	
Anemia	9 (15.5)		5 (7.0)		4 (1.9)		17.189	<.001	Class 1 > 3

For sleep latency, different subscripts indicate significant mean differences between the classes; class 1 had longer sleep latency vs class 2 and 3.

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described the case of a toddler with severe insomnia associated with bedtime and nocturnal restlessness, accompanied by leg kicking and rubbing, and highly suggestive of restless legs syndrome.[38]

Insomnia characterized by no particular difficulties in falling asleep but prolonged early morning awakenings and a family and clinical history of insomnia, parasomnias, headache/migraine, depression, and mood disorders may represent a serotonergic dysfunction. This kind of insomnia might be comparable with insomnia in depression, characterized by no trouble falling asleep but prolonged midnight awakening with difficulty returning to sleep. Some researchers have shown a relationship between sleep difficulties in childhood and depression in mid-adolescence[39] as well as in adulthood.[40] It has also been demonstrated that the administration of 5HT2A receptor antagonists improves slow-wave sleep, reduces rapid eye movement sleep, and increases sleep continuity.[41] No studies have been carried out with tricyclic antidepressants or selective serotonin reuptake inhibitors in children with insomnia. There are some reports of the use of L-5-hydroxytryptophan (precursor of serotonin), which does not have opioid-like effects and does not limit cognitive performance or inhibit arousal from sleep.[42-46]

Insomnia with multiple night awakenings and difficulties falling asleep often characterizes infants who also have food intolerance, milk allergy, or atopic dermatitis and with a high prevalence of allergies in the family history. This kind of insomnia might reveal a histaminergic dysfunction. Several studies have been published on the first generation of antihistamines with high affinity for the H1 receptor.[47-52] The histaminergic system in the brain is localized within the posterior hypothalamus with projections to almost all the major regions of the central nervous system. Administration of histamine or H1 receptor agonists affects wakefulness, whereas administration of H1 receptor antagonists induces sleep. The first generation of antihistamines easily penetrates the blood–brain barrier and leads to drowsiness and sedation. Most of these antihistamines, including the nonselective H1 receptor antagonists from the phenothiazine class and over-the-counter diphenhydramine, have a positive impact on sleep continuity as well as on subjective and objective indices of nocturnal sleep in healthy human subjects.[53] If these speculative pathways are confirmed, characterizing insomnia in these 3 subtypes might have therapeutic implications, allowing the clinician to personalize pharmacologic treatment.

In this study, we also attempted to add information derived from the family and personal history to evaluate the presence of symptoms that could be associated with the hypothesized categorization of insomnia. This approach is of high relevance because recent studies emphasized the role of genetic factors on the development of insomnia during childhood. Research has demonstrated that heritability may explain 30.8% of nocturnal sleep duration, 36.3% of diurnal sleep duration, and 35.3% of child night awakenings.[24] Moreover, other researchers observed that variance in consolidated nighttime sleep duration was explained by genetic factors, with a strong heritability (71%) for the short-persistent (<10 hours) nighttime sleep duration trajectory.[25]

LeBlanc et al underlined that family history was the second strongest predictive factor in patients with insomnia, suggesting a familial predisposition and, thus, a vulnerable phenotype.[54] Bastien and Morin reported that 35% of patients with insomnia have a first- or second-degree relative with a current or past sleep difficulty and the mother was the most commonly affected family member.[55]

Moreover, studies in families and twins highlight that genetic predisposing factors of individual vulnerability might impact on the onset of insomnia. Studies on twins have found a strong concordance in slow-wave sleep, suggesting about 50% heritability, as well as similarities in sleep onset latency and in sleep disruption, that are not solely explained by environmental influences.[56,57] Speculatively, these studies suggest that certain subtypes of insomnia may have different etiologies.

However, although the current literature suggests that insomnia is heritable and related to anxiety, depression, and stress-reactivity, several epigenetic factors seem to be involved in the development of insomnia. Among these factors, stressful experiences during prenatal/early life development may impact on changes in stress reactivity that may persist during adulthood. If epigenetic factors are potentially reversible via environmental or pharmacologic treatments, it might be hypothesized that either cognitive behavioral therapy or pharmacologic interventions for insomnia might impact the epigenetic modifications of insomnia.[58]

Due to the partial overlap between genetic, epigenetic, and behavioral mechanisms of insomnia in childhood, ineffectiveness of some behavioral treatments[59,60] may not solely be due to parental resistance to apply the behavioral interventions but also to genetic conditions that may influence the expression of chronic insomnia. If biological factors are overlooked, they could limit the efficacy of cognitive behavioral therapy and explain its unsuccessfulness in several cases. If diverse pathophysiologic mechanisms are confirmed, both behavioral and pharmacologic treatment might be needed.

This study should be interpreted in the context of several limitations. First, because this is a referred population, there may be a selection bias, because the cohort might exclude those for whom parents felt behavioral or pharmacologic therapy helpful, those patients with no previous treatment, and others not seeking care from a sleep specialist. Therefore, our sample may be different from the broader pediatric insomnia population in this age group. Future directions include the need to investigate subtyping in the broader population to be able to generalize the results. Second, all data are by parent report without corroborating objective data. Third, we lacked objective measures that could differentiate the 3 groups and, therefore, we do not know whether the proposed clinical categorization is related to different objective sleep patterns. The implementation of randomized studies with objective measures is highly advised, to evaluate the correct classification. Once confirmed, studies evaluating the efficacy of different pharmacologic approaches in subtypes of pediatric insomnia may be needed.

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Pediatric insomnia seems to occur with different subtypes implying several pathophysiologic mechanisms, linked to clinical characteristics of the child and of the family and to specific sleep complaints. Therefore, insomnia in childhood should not be considered exclusively as a behavioral disorder but may reflect genetic and epigenetic influences as well. In agreement with Benjamins et al, we suggest that different subtypes of insomnia exist, each with its own multivariate profile of clinical presentation and specific child and family history linked to genetic traits.[61] Future studies should confirm our preliminary classification aiming at its accurate definition and discrimination.

A further issue to be studied is the stability of phenotypes over time: a study in adults showed that approximately 60% of persistent insomnia cases reported the same symptom profile at 1-year follow-up as they did at baseline.[62] A retrospective study in children showed that, although the majority of children will outgrow their problems once they reach late adolescence, sleep problems are likely to become chronic for 1 in every 3 children with a sleep problem early in life.[63] Given the many negative consequences of insomnia in adulthood, these findings call for an increased awareness of childhood sleep problems as a public health concern and likely, early and effective treatment (either behavioral and/or pharmacological) with an aim to prevent persistence of insomnia. In addition, simple screening tools may be developed to facilitate accurate diagnosis and personalized treatment approaches. ■

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Appendix

Semistructured Interview for Insomnia

Name: _____ Age:_____

Bedtime hour:	_____	
Sleep latency:	_____	
Wake up time:	_____	
How does your child fall asleep?	_____	
Mean number of night awakenings	_____	
Time spent in sleep during the night?	Hour _____ Minutes _____	
Daytime naps	_____	
Your child is or was affected by:	Colic	☐
	Leg or arm pain	☐
	Allergies	☐
	Food intolerance	☐
	Atopic dermatitis	☐
	Gastroesophageal reflux	☐
	Anemia or iron deficiency	☐
	Other _____	
Your child insomnia in characterized by:	Difficulties in falling asleep	☐
	Difficulties in falling asleep with restlessness	☐
	Nocturnal restlessness	☐
	Early morning or midnight awakenings	☐
	Multiple night awakenings (all night)	☐

Family health problems:	*Mother*	*Father*	*Grandparents*	*Second-degree relatives*
Insomnia	☐	☐	☐	☐
Parasomnias	☐	☐	☐	☐
Headache/migraine	☐	☐	☐	☐
Depression or symptoms of depression	☐	☐	☐	☐
Mood disorders	☐	☐	☐	☐
Anemia or iron deficiency	☐	☐	☐	☐
Legs discomfort or pain, need to move	☐	☐	☐	☐
Allergies/food intolerance	☐	☐	☐	☐

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