



PIGMENTED SKIN LESIONS IN CHILDREN: CONGENITAL MELANOCYTIC NEVUS, PEDIATRIC LONGITUDINAL MELANONYCHIA, AND PEDIATRIC MELANOMA

Citation

Tsai, Serena Yun-Chen. 2024. PIGMENTED SKIN LESIONS IN CHILDREN: CONGENITAL MELANOCYTIC NEVUS, PEDIATRIC LONGITUDINAL MELANONYCHIA, AND PEDIATRIC MELANOMA. Master's thesis, Harvard Medical School.

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PIGMENTED SKIN LESIONS IN CHILDREN: CONGENITAL MELANOCYTIC NEVUS,
PEDIATRIC LONGITUDINAL MELANONYCHIA, AND PEDIATRIC MELANOMA

By

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A Dissertation Submitted to the Faculty of Harvard Medical School

in Partial Fulfillment of

the Requirements for the Degree of Master of Medical Sciences in Clinical Investigation

(MMSCI)

Harvard University

Boston, Massachusetts

March, 2024

Area of Concentration: Dermatology/Pediatrics

Project Advisor: Dr. Elena B. Hawryluk

I have reviewed this thesis. It represents work done by the author under my
guidance/supervision.

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Acknowledgements

I wish to express my sincere appreciation to the leadership team of the Master of Medical Science in Clinical Investigation (MMSCI) at Harvard Medical School, including **Dr. Ajay Singh, Dr. Finnian McCausland, Dr. Martina McGrath, Dr. Rosalyn Adam, and Dr. Lourdes Perez-Chada**. I am deeply grateful for the privilege of participating in this two-year program and for all of their unwavering support in facilitating my research training from the program.

I wish to express my deepest gratitude to my primary mentor, **Dr. Elena B. Hawryluk**, for her professional guidance and unconditional support all the time. Thank you for being my mentor as I navigate the journey toward a clinical and research career in the United States. It has been my great pleasure and honor to work with you for the past two years. My sincerest thanks for having my back, not just in the medical world but in all the twists and turns of life.

I would like to thank **Dr. Sophia Delano, Dr. Jonathan Cunningham, and Dr. Tina Ho**, for serving as the members of my Thesis Defense Committee. Thank you so much for dedicating your time to review my work and for your presence in every thesis committee meeting and the final defense.

I would like to thank **all collaborators** for their time and commitment to enhance our research. Without your invaluable assistance, the accomplishments herein would not have been possible.

Ultimately, I am eternally thankful to my cherished **family and friends** for their incredible support throughout every stage of my life and career; without your presence, I would not be where I am today.

Chapter 1: Background

Pigmented skin lesions are among the most common exam findings in children, resulting from the proliferation of melanocytes or increased melanin production. (1) Three questions have often been raised in managing these lesions: (1) Is biopsy necessary? (2) Do they exhibit a neoplastic nature, i.e., what is the risk of malignant transformation, namely melanoma? (3) Could they impact other systems or impose any burdens?

While pediatric melanoma may be exceedingly rare, its risk factors, melanocytic nevi, are nearly ubiquitous, with more than 90% of Caucasian children having at least one nevus during their early childhood. (2,3) Various types of nevi are differentiated, including congenital melanocytic nevi (CMN), acquired melanocytic nevi (AMN), blue nevi, and Spitz nevi. CMN typically presents at birth or during infancy, affecting around 1% of newborns. (4) As for AMN, development usually begins in early childhood and continues through mid-adolescence. (5) Nevi in different anatomic locations have distinctive characteristics, variations in natural evolution, and varying levels of associated malignant risks. Anatomic locations classified as “special sites” include scalp, ear, breast, genitalia, acral locations (hands, feet, and nails), and conjunctiva, which have unique histopathologic features based on the site of origin.

Some specific-site nevi are posited to be present more commonly in children and adolescents. (6) One particular special site that causes stress for children and their caretakers is the nail unit. In children, a nail matrix nevus constitutes the main cause of melanonychia, a brown or black pigmentation of the nail plate, followed by other diagnoses, including melanocyte activation, lentigo, and subungual melanoma. (7) Subungual melanoma is an uncommon entity of cutaneous melanoma, notorious for its poor prognosis. (8) Certain red-flag signs in melanonychia indicate a higher likelihood of subungual melanoma, prompting the need for a biopsy. However, pediatric longitudinal melanonychia can exhibit atypical

features that mimic red-flag signs for subungual melanoma in adults, leading to diagnostic uncertainty. (9)

The gold standard for diagnosis of subungual melanoma is a nail unit biopsy, a procedure involving the removal of the entire nail plate and the excision of the lesion with stitches, with risks of scarring and nail plate deformity. While biopsy is generally less favored in pediatric patients due to considerations such as pain, anxiety, anesthesia risks, and potential iatrogenic trauma to the nails, understanding the clinical features of pediatric melanonychia is the crucial step to building a risk stratification and deciding whether biopsy is needed. (10) Although individual studies have described the clinical features of pediatric melanonychia, these studies are limited by small sample sizes and inconsistent findings, hindering the reliability and generalizability of reported prevalence rates. Therefore, there remains a need to integrate this existing data to better inform clinical decision-making. Our hypothesis is that pediatric melanonychia exhibits higher percentages of atypical characteristics, such as dark color, multi-colored bands, broad bandwidth, irregular dermoscopy patterns, nail dystrophy, Hutchinson sign, and triangular sign, despite their benign nature. The features of melanonychia differ between adults and children.

Beyond the increased lifetime risk of melanoma, nevi can be associated with other comorbid conditions. These associations are thought to be typified by the longstanding and often largest CMN. Complications linked with CMN (particularly those of large and giant size) include extracutaneous melanoma, central nervous system (CNS) abnormalities, clinical neurologic symptoms, and psychological burdens; sporadic observations in the literature also suggested possible associations with child development and puberty. (11,12) AMN, on the other hand, are more strongly associated with the development of malignancy, although their relationship with other diagnoses are seldom investigated. (13) Considering childhood is a prime period for nevogenesis, it is intriguing to explore whether melanocytic nevi in early

childhood are associated with other diagnoses or issues commonly seen in the pediatric population, especially neurological and developmental disorders. Our hypothesis is that, given the ectodermal origin of melanocytes and neural tissues, congenital or early-onset nevi might be associated with neurological and developmental disorders later in life. As such, a population-based study is warranted to identify potential signals.

Chapter 2: Paper 1

Tsai SY, Hamilton CE, Mologousis MA, Hawryluk EB. Melanoma-like features in pediatric longitudinal melanonychia: A systematic review and meta-analysis. *Pediatr Dermatol*.

Published online March 18, 2024. doi:10.1111/pde.15597

Article Type: Original Article

Title: Melanoma-like features in pediatric longitudinal melanonychia: a systematic review and meta-analysis

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Statement of contribution: ST and EBH conceived of the project. ST and CEH performed data collection and analysis. ST and MAM drafted the manuscript under the supervision of EBH with the support and input of all other authors. EBH and CEH provided critical feedback on the manuscript and all authors approved its final version.

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Key words: longitudinal melanonychia, pigmented lesions, acral lentiginous melanoma, pediatric dermatology

Main text words: 1999

Figures: 2

Tables: 2

References: 37

Supplementary Figures: 1

Supplementary Tables: 3

This study was presented at Massachusetts General Hospital Scientific Advisory Committee (SAC) 2023 Virtual Poster Session and International Societies for Investigative Dermatology (ISID) meeting 2023 Poster Session.

Acknowledgements: EBH receives funding from the Pediatric Dermatology Research Alliance Career Bridge Award.

Conflicts of interest: EBH reports disclosures of UpToDate (author, reviewer) and Skin Analytics (consultant), DermTech (research materials).

Abstract

Background: Pediatric longitudinal melanonychia (LM) can exhibit atypical features that mimic red-flag signs for subungual melanoma in adults and lead to diagnostic uncertainty. Nail biopsy may be unnecessary if clinical inspection and dermoscopy suggest a benign nature.

Methods: We searched PubMed and Embase from inception to February 2023 for studies of any design reporting either the number or proportion of clinical and dermoscopic features in at least five children (≤ 18 years) with LM. Non-English articles, reviews, and abstracts were excluded. We performed a systematic review and meta-analysis to collate all existing data.

Results: A total of 1,218 articles were screened and 24 studies with 1,391 pediatric patients were included. Nevus was the most common diagnosis (86.3%). The most prevalent sites were fingernails (76.2%) and first digits (45.4%). Pooled proportions of common features were: dark-color bands (69.8%), multi-colored bands (47.6%), broad bandwidth (41.1%), pseudo-Hutchinson sign (41.0%), irregular patterns (38.1%), Hutchinson sign (23.7%), dots and globules (22.5%), nail dystrophy (18.2%), and triangular sign (10.9%). Outcomes included progression (widening or darkening, 29.9%), stability (23.3%), and spontaneous regression (narrowing or fading, 19.9%). Only 8 cases of subungual melanoma in situ were reported, and no invasive melanomas were identified.

Conclusion: Although atypical characteristics are common in pediatric LM, the probability of malignant transformation is exceedingly low. Appropriate evaluation and management of pediatric LM includes careful clinical and dermoscopic inspection with attention to benign features followed by long-term interval follow-up.

Introduction

Longitudinal melanonychia (LM) describes a pigmented band within the nail plate from increased melanin deposition. It is observed in both children and adults and results from melanocytic activation (in response to infection, systemic disease, medication, or trauma) or proliferation (as is observed in a subungual nevus, lentigo, or melanoma) of melanocytes in the nail matrix, where they usually remain quiescent or dormant but can start producing melanin or increase in number when stimulated.^{1,2}

The differentiation of benign from malignant cases of LM is crucial given the poor prognosis of advanced subungual melanoma (SUM). In adults, clinical features concerning SUM have been well characterized and include broad bandwidth, rapid or sudden growth, pigment variegation, Hutchinson sign, and nail dystrophy.³ Nail matrix biopsy is the gold standard with histopathologic examination for diagnosis and appropriate management for adult LM that displays atypical features.^{4,5}

Conversely, pediatric LM may exhibit classical clinical features of adult SUM but rarely represent SUM in situ and, even less frequently, invasive SUM.^{6,7} Despite these low risks, atypical clinical features in pediatric LM raises diagnostic uncertainty. The uncertainty also exists in cases of pediatric SUM, as the veracity of the diagnosis has been questioned. The melanocyte counts in the nail matrix are lower (around 200 melanocytes per millimeter) when compared to the normal skin (around 1000 to 1500 melanocytes per millimeter).⁸ Unlike adults, where melanocyte counts in the nail unit have been fully examined, there has been no assessment in children.⁹ The nature of the lower number of melanocytes in the nail matrix and the absence of pediatric data make the determination of cytological changes, such as atypia or proliferation, more difficult and subjective. In many case reports, pediatric SUM either resembled nevus or atypical hyperplasia, or lacked a clear clinical course compatible with malignancy.¹⁰ Furthermore, slight dysplasia or nuclear atypia in melanocytes or a mild

degree of transepithelial melanocytic migration can be seen in benign conditions, such as acral melanocytic nevi and Spitz nevi, rendering these atypical architectural traits insufficient to signal malignancy.¹¹ Although a biopsy can confirm the diagnosis, considerations include the scar, stress, cost of a procedure, anesthesia risk, and complications (particularly with poor technique or infrequent practice) that include pain or deformity. These challenges have complicated the clinical diagnosis of pediatric LM, increased anxiety among parents and clinicians, and interjected uncertainty in the decision-making process. A non-invasive diagnostic approach based on clinical features and dermoscopy should be prioritized in diagnosing pediatric LM.

Although prior studies have described clinical features of pediatric LM, they have been limited by small sample sizes and inconsistent findings, which may hinder the reliability and generalizability of the reported prevalence rates. Therefore, there remains a need to integrate this existing data to support clinical decision-making. This study evaluates the pooled prevalence of clinical features in pediatric LM reported in the literature and analyzes the difference in manifestations between children and adults among studies reporting both. We hypothesize that while most pediatric melanonychia may exhibit higher percentages of atypical characteristics compared to those of adult melanonychia, the nature of these lesions remains benign. As such, the features of melanonychia may differ between adults and children, with childhood longitudinal melanonychia being more likely to exhibit red-flag signs such as Hutchinson sign when compared to adults.

Methods

Search strategy

This systematic review and meta-analysis was registered on PROSPERO (CRD 42023390874) and followed the Preferred Reporting Items for Systematic Reviews and Meta-

analyses (PRISMA) guidelines.¹² We searched PubMed and Embase using the search terms synonymous to “pediatrics” (e.g., child or adolescent) and “melanonychia” (e.g., subungual hyperpigmentation or nail hyperpigmentation). The last search was run on February 21, 2023. No search filters were applied. The complete search strategy is outlined in Supplementary Table 1. The search results were imported to Covidence, a web-based collaboration platform for systematic reviews.¹³ Duplicates were automatically removed by the software.

Study selection

Two reviewers (Y.C.T. and C.E.H.) selected the eligible studies independently by conducting the title and abstract screening and the full-text review in Covidence. Disagreements were resolved by conferring with a third reviewer (E.B.H.). We included studies reporting either the number or proportion of clinical and/or dermoscopic features of LM in at least five children (< 18 years of age). We excluded articles published in non-English languages, reviews, case reports, and abstracts. We also excluded studies that reported data on both adults and children but did not provide extractable pediatric data. The selection process is illustrated in Figure 1.

Data extraction

Data were extracted by one of the reviewers (Y.C.T.) and reviewed by coauthors. The following data were retrieved from each included study: first author, country, publication year, study design, sample source, sample size, age, gender, race, Fitzpatrick skin type, number of cases presenting with each feature of pediatric LM, diagnosis, management, and follow-ups. In addition to pediatric LM, we also collected data on adult LM from studies that reported LM in both age groups. We assessed the quality and risk of bias using the Joanna Briggs Institute (JBI) critical appraisal tools.¹⁴ A score of 7 or more was high quality, a score

of 5-7 was medium quality, and a score of less than 5 was considered low quality.

Disagreements were settled through discussion among authors. All studies were included regardless of their appraisal score.

Statistical analysis

Statistical analyses were performed in RStudio, Version 1.4.1106, using a meta-package. The raw numbers of events were imported, and the pooled prevalence with a 95% confidential interval (CI) of each feature in pediatric LM was calculated. Separate meta-analyses were computed using the generalized linear mixed-effects model with the logit link function.^{15,16}

Among studies that reported both pediatric and adult LM, we calculated the pooled odds ratios (ORs) using random-effects models with the Cochran-Mantel-Haenszel method to compare the occurrence of each feature between children and adults. ORs greater than 1 indicate that the feature is more likely to be observed in children than adults. I^2 and Q tests were measured for between-study heterogeneity when $P < 0.05$ implied significant heterogeneity rather than chance. I^2 values of 0% to 40% represent low heterogeneity; 40% to 75% may imply substantial heterogeneity, and 75% to 100% may indicate considerable heterogeneity. Potential publication bias was evaluated using a funnel plot and Egger's test. Egger's test with $P > 0.05$ indicates there is no evidence of publication bias.

Results

Study characteristics

A total of 1632 studies were identified from the electronic databases. Eighty-five were eligible for full-text review. After exclusion for study type, population, language, outcome measures, and incomplete data, 24 studies were eventually included in this systemic review and meta-analysis. The studies were published between 1996 and 2023 and were conducted

in the following regions: Asia (n = 13),^{6,17–28} Europe (n = 6),^{29–34} North America (n = 3),^{35–37} and South America (n = 1).³⁸ One of the studies was conducted internationally and collected cases from 30 different countries.³⁹ A total of 1391 pediatric cases with LM were included. Of the 1367 cases in which gender was reported, 716 (52%) were male. The mean age at diagnosis ranged from 5.3 to 13.3 years. The characteristics of the studies are outlined in Supplementary Table 2. According to the JBI critical appraisal, the overall risk of bias is low, with a mean JBI score of 8.7 (Supplementary Table 3). No studies were of low quality (i.e., JBI < 5).

Prevalence of the clinical and dermoscopic features of pediatric longitudinal melanonychia

Table 1 outlines the pooled prevalence of each clinical and dermoscopic feature of LM reported among pediatric cases. Of the 731 lesions in which diagnosis was provided (402 lesions [55.0%] were diagnosed based on histopathologic evidence, and 329 lesions [45.0%] were diagnosed based only on clinical and dermoscopic criteria), nevus was the most common diagnosis (86.3%, Figure 2), followed by lentigo (3.0%) and melanocytic activation (1.3%). Only 8 cases were diagnosed as subungual melanoma in situ, and no invasive melanomas were identified. The most prevalent sites of lesions were fingernails (76.2%), most commonly on first digits (thumb or hallux) (45.4%).

The following features were observed either grossly or with dermoscopy: dark-colored bands (69.8%), multi-colored bands (47.6%), broad bandwidth (41.1%), pseudo-Hutchinson sign (41.0%), irregular patterns (38.1%), Hutchinson sign (23.7%), dots and globules (22.5%), nail dystrophy (18.2%), and triangular sign (10.9%). During longitudinal clinical course (15 out of 24 [62.5%] included articles reported the follow-up data), most lesions remained stable (23.3%) or underwent spontaneous regression (19.9%). While 29.9% of cases continued to

evolve (with changes in width or color over time), none of the benign cases in the studies developed into malignancies. Mean follow-up time ranged from 1 to 5.5 years in the studies that reported this data. Of note, certain features displayed high heterogeneity (I^2 values > 75%). Nevertheless, the funnel plots and Egger's test revealed no publication bias ($p = 0.0717$) (Supplementary Figure 1).

Comparison of the prevalence of clinical and dermoscopic features of longitudinal melanonychia between children and adults

Six studies reported both pediatric and adult LM, with 238 cases in children and 233 in adults.^{18,23–25,27,32} No pediatric SUM was identified, while 27 adult cases were diagnosed as SUM. Table 2 provides pooled OR estimates indicating which clinical and dermoscopic features were more common in pediatric LM versus adult LM. Among the atypical features that may suggest SUM, children had a higher likelihood of multi-colored bands (OR, 3.07; 95% CI, 1.55-6.07) and Hutchinson sign (OR, 1.86; 95% CI, 1.03-3.34). Other features, including broad bandwidth (OR, 0.83; 95% CI, 0.54-1.29) and nail dystrophy (OR, 1.70; 95% CI, 0.94-3.09), did not show a preference for either age group. Some studies included in this part of the review provided data on additional characteristics in both children and adults, but there was insufficient data for comparison in the forest plots.

Clinical and dermoscopic features of confirmed pediatric SUM in the literature

There are 25 cases of pediatric SUM in the literature dating back to 1989 with 24 subungual melanomas in situ (SMIS) and only 1 invasive SUM (Supplementary Table 4). Most cases showed broad bandwidth (14/25, 56%), dark color (17/25, 68%), variegated colors (11/25, 44%), irregular lines and thickness (9/25, 36%), Hutchinson sign (9/25, 36%), nail dystrophy (4/25, 16%), and evolution in width or color (21/25, 84%). It is important to note that cases

that either reported the absence of the feature or did not describe the feature were viewed as negative in each of the calculative data above. The time from the onset of LM to the diagnosis varied, ranging from 6 months to 13 years.

Discussion

This analysis highlights that pediatric LM primarily involves a benign nail matrix nevus (NMN) diagnosis, accounting for 86.3% of cases with a histopathologic diagnosis; notably, around 45% of cases were not confirmed histopathologically. The literature supports that SUM often arises *de novo*.⁴⁰ It is worth noting that the high prevalence of NMN may be overstated, as some studies only recruited LM with NMN cases and excluded other causes. The finding is in concordance with a previous scoping review, which concluded that the leading causes of LM differed between adults and children, with nevi (48%-94%) being the most common cause in children and melanocyte activation (73%) in adults.⁴¹ The difference presents as well when speaking of malignancy: in adults, the incidence of SUM in adults arising from LM ranges from 4.3% to 19.8%,⁴¹ whereas in children, the prevalence is more rare. Only 25 cases of pediatric SUM have been reported in the literature so far.

Atypical signs in LM are red flags for melanoma that usually warrant a nail unit biopsy, considering their high prevalence in SUM. For instance, irregular lines with color variegation were observed in 70% of SUM, nail dystrophy in 43%, Hutchinson sign in 25%, and triangular shape in 5%.⁴² However, a high proportion of benign pediatric LM in our study also share these atypical features, including dark-colored bands (prevalence 69.8%), multi-colored bands (47.6%), broad bandwidth (41.1%), pseudo-Hutchinson sign (41.0%), irregular patterns (38.1%), Hutchinson sign (23.7%), nail dystrophy (18.2%), and triangular sign (10.9%). When comparing atypical signs between adults and children with LM, data pertaining to the proportions of each feature in adult LM is lacking. Therefore, we reviewed

studies that provide both adult and pediatric data. A cohort study employing a predictive scoring model revealed that pediatric subungual melanoma in situ exhibited significantly higher odds of asymmetry (OR = 34.00), border fading (OR = 9.33), multicolor (OR = 11.59), width of at least 3 mm (OR = 5.31), and Hutchinson sign (OR = 18.18) compared to adult-onset LM. Differences in the triangular pattern, dots or globules, and nail plate dystrophy between the two groups were not statistically significant.⁴³ In our analysis, multi-colored bands (OR = 2.98) and Hutchinson sign (OR = 1.86) were more prevalent in children, even if some SUM cases were included in the adult cohort. Although the prevalence of other atypical features, such as broad bandwidth and nail atrophy, did not demonstrate a significant difference between children and adults, previous studies have suggested that pediatric NMNs were wider and exhibited more nail dystrophies²³ or were darker, multicolored, and displayed more triangular signs.²⁷ When comparing the prevalence of these atypical features between pediatric LM and SUM, we found similar occurrences (LM vs SUM): broad bandwidth (41.1% vs 56.0%), dark-colored bands (69.8% vs 68.0%), multi-colored bands (47.6% vs 44.0%), Hutchinson sign (23.7% vs 36.0%), and nail dystrophy (18.2% vs 16.0%). On the contrary, the clinical courses presented differently. While most SUM cases (84.0%) experienced expansion, darkening, or changes in pattern, only 29.9% of LM cases experienced such changes. Therefore, the presence of these atypical signs should not be considered as an arbitrary criterion for biopsy.

Importantly, this analysis highlights the prevalence of benign features among pediatric LM. Features such as dots/globules or pseudo-Hutchinson's sign, which can occur secondarily to benign conditions, were either more or equally prevalent compared to atypical features, consistent with the literature.^{27,41} The frequency of benign features may be underappreciated, as benign lesions are less often examined and reported in detail. This nuance may impact the clinical impression of these lesions.

In the pivotal clinical decision of whether to biopsy a child with longitudinal melanonychia, perhaps with features that would require a prompt biopsy in an adult, this study provides data to support the option of clinical monitoring. Observation is a reasonable approach given a low baseline risk of malignancy in this population, even in the setting of atypical features. Most pediatric LM were stable or underwent regression during interval follow-up, consistent with prior work that reported a 10% complete regression rate of LM lesions during an approximately 10-year period.⁶ However, it has been observed that the melanocytic behavior of LM remains indolent in childhood, and the growth of SUM is often slow, resulting in late diagnosis.^{25,44} Therefore, shared decision-making regarding risks, counseling, photography, and a clear follow-up plan are essential components of management. When both benign and atypical signs are present, clinicians should evaluate whether the evolution is consistent with a natural indolent course, and any changes that exceed expectations are important to recognize and biopsy. Ultimately, the decision to pursue a nail matrix biopsy should carefully weigh the likelihood of malignancy with procedural risks, and shared decision making is key to individual management decisions.

Currently, there is no consensus or validation of criteria for predicting SUM. The ABCDEF rule, adapted from cutaneous melanoma, was once proposed but found to be insufficient and with unstable consistency for diagnosing SUM. In a study examining the validity of the ABCDEF rule among patients with LM, including SUM and benign cases, only greater width signified SUM, and thus re-examination of the rule was suggested; more concerning features other than those described in the ABCDEF rule (age, race, bandwidth, border, color, change, digit, extension, and family history), such as nonhomogeneous pigmentation and triangular sign, were recommended to be introduced in the future modified diagnostic rule.⁴⁵ However, these aforementioned features are quite conspicuous in pediatric LM, and make less reliable criteria for biopsy decisions in children. Drawing from our

clinical experience and based on the findings of our study, if reassuring features are present in a pediatric LM lesion, biopsy can be avoided. Even in cases where worrisome features manifest, regular clinical surveillance over an extended period (i.e., every 3-6 months until stable) is often the preferred option, as benign LM may either regress or remain stable. Parental photography and interval telemedicine are options for patients who can send adequate photographs to demonstrate stability; any concerning or evolving features are best evaluated in clinic with dermoscopy. Discussion of a biopsy is warranted for lesions that are quickly changing or growing sustainably.

Future studies should provide more detailed descriptions of dermoscopic patterns observed in pediatric LM. Additionally, since nail apparatus melanomas can be amelanotic and the etiology of the disease is not well-understood, a better understanding of risk factors, clinical manifestations, pathology and prognosis of SUM is required.⁹

Limitations

Most studies were conducted in Asia, and there are limited available data stratified by skin type; LM in the white population might not be adequately represented. Case reports, which typically include 3 or fewer patients, were not included in our review due to our eligibility criteria. These case reports predominantly focused on single features, manifestation in a specific systemic disease, or treatment approaches. Given their limited number relative to the total cases in our study, their exclusion is unlikely to impact the outcomes significantly. Study data were limited by inconsistent reporting of LM features and a lack of some key features, such as multiple-digit involvement and blurred edge.

Conclusions

Given the high prevalence of atypical features in benign pediatric LM, it is crucial to appreciate the benign features and natural evolution of NMNs using dermoscopy and to monitor as appropriate. A nail unit biopsy is not mandatory for every case, including those showing changes in width or color over time. Clinical monitoring is a reasonable management strategy.

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Table 1. Clinical manifestations and dermoscopic features of LM in children

Variable (in n cases)	Pooled proportion (95% CI)	I ²	p value*
Diagnosis (n = 731)			
Nevus	86.3 (48.8 – 97.6)	53.9%	0.0015 0.0012
Lentigo	3.0 (0.6 – 13.7)	54.4%	0.8345 0.8649
Melanocytic activation	1.3 (0.2 – 9.4)	0.0%	
Atypical melanocytic hyperplasia	0.0 (0.0 – 17.3)	0.0%	
Site of lesion			
Fingernail (n = 1488)	76.2 (71.6 – 80.2)	25.9%	0.1305
Toenail (n = 1488)	24.5 (20.5 – 29.0)	24.4%	0.1465
Thumb or hallux (n = 1464)	45.4 (40.3 – 50.6)	56.5%	0.0008
Broad bandwidth ^a (n = 1470)	41.1 (27.6 – 56.1)	89%	< 0.0001
Color (n = 1561)			
Light color ^b	30.2 (21.6 – 40.4)	76.1%	< 0.0001
Dark color ^c	69.8 (59.6 – 78.5)	76.1%	< 0.0001
Multi-colored band (n = 1234)	47.6 (32.8 – 62.9)	91.2%	< 0.0001
Irregular pattern (n = 827)	38.1 (14.7 – 68.8)	94.8%	< 0.0001
Dots and globules (n = 825)	22.5 (14.2 – 33.7)	88.3%	< 0.0001
Hutchinson sign ^d (n = 1430)	23.7 (12.9 – 39.4)	89.6%	< 0.0001
Pseudo-Hutchinson sign (n = 1081)	41.0 (24.4 – 59.9)	93.3%	< 0.0001
Triangular sign (n = 815)	10.9 (6.2 – 18.4)	73.7%	0.0004
Nail dystrophy ^e (n = 1254)	18.2 (11.2 – 28.0)	71.9%	< 0.0001
Clinical course (n = 928)			
Stable	23.3 (8.8 – 48.7)	64.5%	0.0062
Evolving	29.9 (13.9 – 53.2)	90.8%	< 0.0001
Regression ^f	19.9 (8.1 – 41.2)	65.9%	0.0018

*Test of heterogeneity (Wald-type test).

^a Defined as bandwidth greater than or equal to 50% or 3 mm, or more than two-thirds of nail plates.

^b Gray and light brown.

^c Brown, dark brown, and black.

^d Signs were observed either grossly or with dermoscopy (micro-Hutchinson sign).

^e Included cases which reported nail atrophies, crumbling, and splitting.

^f Only cases which reported spontaneous regression were counted.

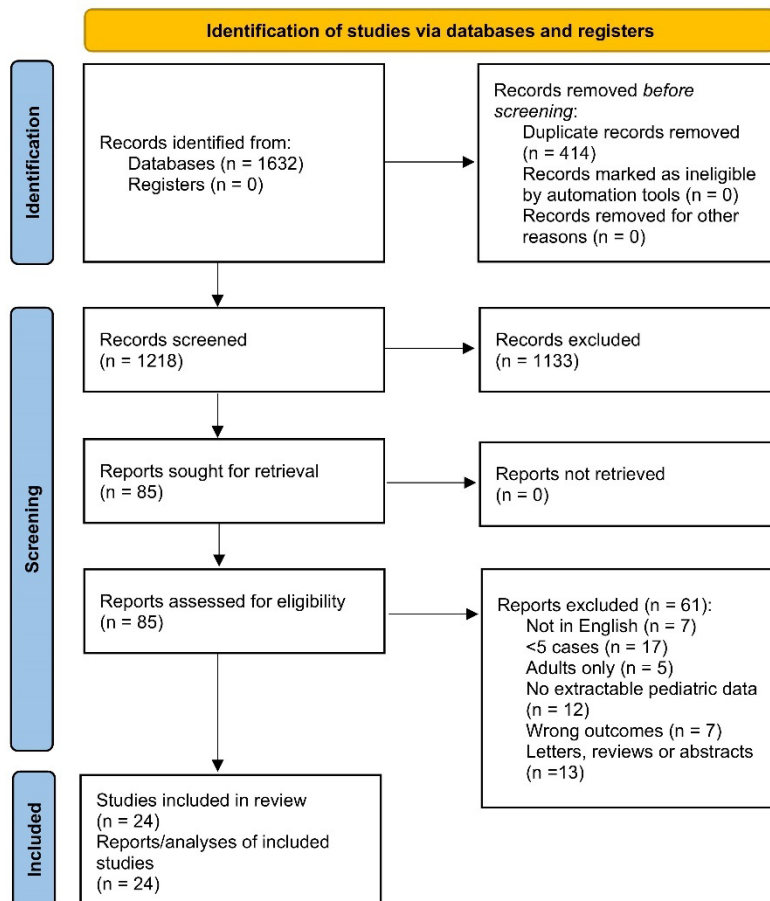
Table 2. Comparison of clinical and dermoscopic features in children and adults

Clinical manifestations	Pooled odds ratio (95% CI)	I ²	Outcome
Multi-colored band	3.07 (1.55 - 6.07)	78.1%	More common in children
Hutchinson sign	1.86 (1.03 – 3.34)	39.2%	More common in children
Broad bandwidth	0.83 (0.54 – 1.29)	77.5%	Inconclusive
Nail dystrophy	1.70 (0.94 – 3.09)	17.0%	Inconclusive

1 Figure Legends

2 Figure 1. PRISMA flow diagram.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

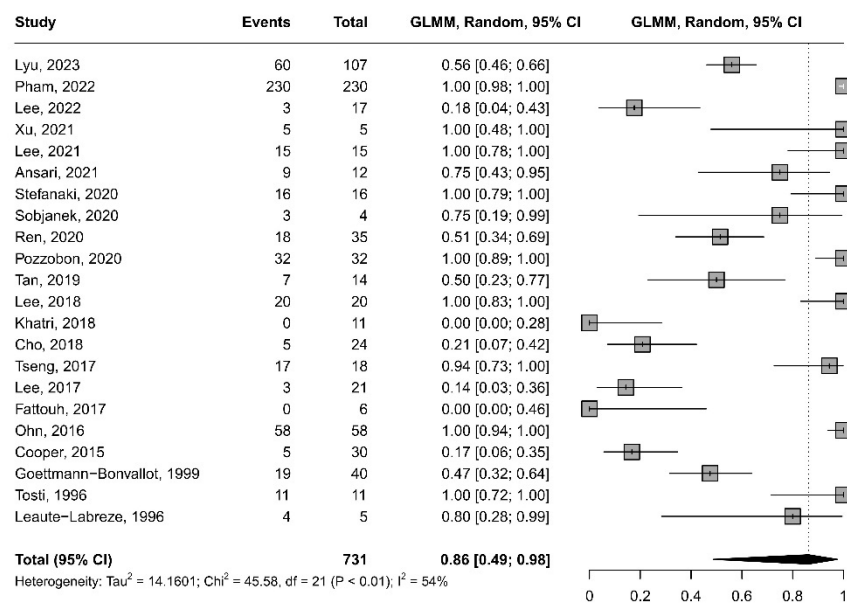


From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

4 Figure 2. Pooled prevalence of nail matrix nevus in melanonychia.

5 GLMM, generalized linear mixed models



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15 Supplementary materials

16 Table 1. Search terms

17 1a. PubMed

#	Searches
1	melanonychia[tiab] OR (("Nails"[Mesh] OR nail*[tiab] OR ungual[tiab] OR subungual[tiab]) AND ("Pigmentation"[Mesh] OR pigmentation*[tiab] OR "Hyperpigmentation"[Mesh] OR hyperpigmentation*[tiab] OR hypermelanos*[tiab] OR "pigmented"[tiab] OR "Nevus"[Mesh] OR nevus[tiab] OR nevi[tiab] OR naev*[tiab] OR "melanocytic"[tiab]))
2	"Pediatrics"[Mesh] OR pediatric* OR paediatric* OR "Child"[Mesh] OR child* OR newborn* OR neonat* OR infan* OR adolescen* OR teen*
3	1 AND 2

18

19 1b. Embase

#	Searches
1	'melanonychia' OR 'nail pigmentation'/exp OR (('nail'/exp OR nail*:ab,ti,kw OR subungual:ab,ti,kw OR ungual:ab,ti,kw) AND ('pigmentation'/exp OR pigmentation*:ab,ti,kw OR 'hyperpigmentation'/exp OR hyperpigmentation*:ab,ti,kw OR hypermelanos*:ab,ti,kw OR 'nevus'/exp OR nevus:ab,ti,kw OR nevi:ab,ti,kw OR naev*:ab,ti,kw OR 'pigmented nevus'/exp OR 'pigmented':ab,ti,kw OR 'melanocytic':ab,ti,kw))
2	'pediatric'/exp OR pediatric* OR 'paediatric'/exp OR paediatric* OR 'child'/exp OR child* OR 'newborn'/exp OR newborn* OR neonat* OR 'infant'/exp OR infant* OR 'adolescent'/exp OR teen*
3	1 AND 2

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22 Table 2. Study characteristics

Study	Country	Period	Study design	Population	Race of pediatric cases	Diagnosis confirmed by biopsy, n of pediatric lesions ^a					Follow-up (mean)
						NMN	Lentigo	Melanocytic activation	Atypical hyperplasia	SUM	
Lyu, 2023	China	2018-2021	Retrospective cohort study	106 children 66 adults	All Chinese	60	6	41	0	0	1.2 years
Pham, 2022	France	2009-2019	Prospective cohort study	230 children	International; from 30 countries	230	0	0	0	0	NA
Park, 2022	United States	2010-2021	Retrospective cohort study	204 children	49% Hispanic, 17% Asian, 13% White, 8% Black	20 benign appearing biopsies			2	0	NA
Lee, 2022	South Korea	2001-2021	Retrospective cohort study	381 children	All Koreans	3	2	7	5	0	2.6 years
Xu, 2021	China	2013-2020	Case series	5 children 3 adults	NA	5	0	0	0	0	NA
Lee, 2021	South Korea	2014-2019	Case series	15 children	NA	15	0	0	0	0	1.9 years
Ansari, 2021	Iran	NA	Prospective cohort study	35 children 73 adults	NA	9	0	3	0	0	1 year
Stefanaki, 2020	Greece	2016-2019	Prospective cohort study	16 children	FST II: 1, III-IV: 15	16	0	0	0	0	1.8 years

Sobjanek, 2020	Poland	2010-2016	Case series	8 children	Central and Eastern European descents; FST II: 5, III-IV: 3	3	1	0	0	0	NA
Ren, 2020	China	2013-2019	Retrospective cohort study	35 children	All Chinese	18	17	0	0	0	3.2 years
Pozzobon, 2020	Colombia	2008-2018	Retrospective cohort study	32 children	All Colombians; FST II: 4, III-IV: 28	32	0	0	0	0	1.1 years
Tan, 2019	Singapore	2005-2015	Retrospective cohort study	62 children	All Asian descents	7	5	1	1	0	5.5 months (median)
Lee, 2018	South Korea	2012-2015	Retrospective cohort study	20 children 8 adults	All Asian descents	20	0	0	0	0	1.1 years
Khatri, 2018	United States	1990-2017	Retrospective cohort study	11 children	4 Asians, 2 Whites, 2 Blacks	0	0	0	9	2	1.6 years
Cho, 2018	South Korea	2010-2016	Retrospective cohort study	24 children 68 adults	All Koreans with FST III	5	8	11	0	0	NA
Tseng, 2017	Taiwan	1996-2017	Retrospective cohort study	18 children 45 adults	NA	17	0	1	0	0	NA
Lee, 2017	South	2010-	Retrospective	21 children	All Koreans	3	8	10	0	0	4.1 years

	Korea	2015	cohort study		with FST III						
Fattouh, 2017	France	2012-2016	Retrospective cohort study	6 children 24 adults	FST I: 1, III-VI: 29	0	0	0	0	6	NA
Ohn, 2016	South Korea	2005-2014	Retrospective cohort study	56 children 34 adults	NA	58	0	0	0	0	2.1 years
Cooper, 2015	United States	NA	Retrospective cohort study	30 children	NA	5	20	0	5	0	1.5 years
Murata, 2012	Japan	1998-2008	Retrospective cohort study	15 children	All Japanese	NA					4.5 years
Goettmann-Bonvallot, 1999	France	1993-1996	Retrospective cohort study	40 children	International; FST V-VI: 7	19	12	9	0	0	NA
Tosti, 1996	Italy	1989-1994	Retrospective cohort study	11 children 11 adults	All Whites	11	0	0	0	0	NA
Leaute-Labreze, 1996	France	NA	Case series	8 children	NA	4	1	0	0	0	5.5 years

NA, not available

^a There may be more than one lesion in a patient.

26 Table 3. Risk of bias assessment for included studies

	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Score
Lyu, 2023	1	1	1	1	1	1	1	1	1	1	10
Pham, 2022	1	1	1	1	1	1	1	1	1	1	10
Park, 2022	1	1	1	1	1	1	1	0	1	0	8
Lee, 2022	1	1	1	1	1	1	1	1	1	1	10
Xu, 2021	1	1	1	1	1	1	1	1	1	0	9
Lee, 2021	0	1	1	1	0	1	1	1	0	0	7
Ansari, 2021	1	1	1	1	1	1	1	1	0	1	9
Stefanaki, 2020	1	1	1	1	1	1	1	1	1	0	9
Sobjanek, 2020	0	1	1	1	0	1	1	1	1	0	7
Ren, 2020	1	1	1	1	1	1	1	1	1	1	10
Pozzobon, 2020	1	1	1	1	0	1	1	1	1	0	8
Tan, 2019	1	1	1	1	1	1	1	1	1	0	9
Lee, 2018	1	1	1	1	1	1	1	1	1	1	10
Khatri, 2018	1	1	1	1	1	1	1	1	1	0	9
Cho, 2018	1	1	1	1	1	1	1	0	1	0	8
Tseng, 2017	1	1	1	1	1	1	1	1	1	1	10
Lee, 2017	1	1	1	1	1	1	1	1	1	0	9
Fattouh, 2017	0	1	1	1	0	1	1	1	1	0	7
Ohn, 2016	1	1	1	1	1	1	1	1	1	1	10
Cooper, 2015	1	1	1	0	0	1	1	1	1	0	7
Murata, 2012	1	1	1	1	1	1	1	1	1	1	10
Goettmann-Bonvallot, 1999	1	1	1	1	1	1	1	1	1	0	9
Tosti, 1996	1	1	1	1	0	1	1	1	1	0	8
Leaute-Labreze, 1996	0	1	1	0	0	1	1	1	0	0	5

27 1: if the answer is yes.

28 0: if the answer is no, unclear, or not applicable.

29 Q1: Were there clear criteria for inclusion in the case series?

30 Q2: Was the condition measured in a standard, reliable way for all participants included in the case series?

31 Q3: Were valid methods used for identification of the condition for all participants included in the case series?

32 Q4: Did the case series have consecutive inclusion of participants?

33 Q5: Did the case series have complete inclusion of participants?

34 Q6: Was there clear reporting of the demographics of the participants in the study?

35 Q7: Was there clear reporting of clinical information of the participants?

36 Q8: Were the outcomes or follow-up results of cases clearly reported?

37 Q9: Was there clear reporting of the presenting sites'/clinics' demographic information?

38 Q10: Was statistical analysis appropriate

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42 Table 4. Reported cases of confirmed pediatric subungual melanoma in situ (n=24) and subungual melanoma (n=1) in the literature

No.	First author	Age at onset/diagnosis	Location	Clinical description (including dermoscopy if available)
1	Kato, 1989 ¹	1, 4	3 rd LF	1 mm wide to the entire nail, brown pigmented macule spreading into the proximal nail fold
2		1.5, 2	2 nd RF	2 mm wide and continue to increase in size, combination of colors ranging from dark brown to black
3		0.5, 1	1 st RT	Developed rapidly over 6 months and changed its color from dark brown to brownish black
4	Kiryu, 1998 ²	3, 5	5 th LF	Longitudinal single line to the entire nail plate, dark-brown in color, Hutchinson sign, gradually increased in width and in darkness of color
5	Antonovich, 2005 ³	NA, 7	4 th LF	Narrow pigmented streak to the entire nail plate, dark-brown, streaky, and irregular pigmentation, increased pigmentation in the proximal nailfold, thinner and brittle nail, expanded laterally
6	Motta, 2007 ⁴	3, 12	1 st RF	Entire nail plate, dark-brown macule and brown and black longitudinal streaks, Hutchinson sign, had extended eccentrically and become darker
7	Iorrizzo, 2008 ⁵	1, 14	3 rd RF	Half of the nail plate, dark-brown to gray color with irregular parallel lines, irregular margins, ill-defined edges, pigmentation of the proximal nail fold, gradually enlarged and darkened
8		5.5, 6	1 st RT	Pigmented spot in the middle of the nail plate to a broad band, light to dark-brown color with ill-defined edges, irregular lines, pigmentation in the proximal nail fold

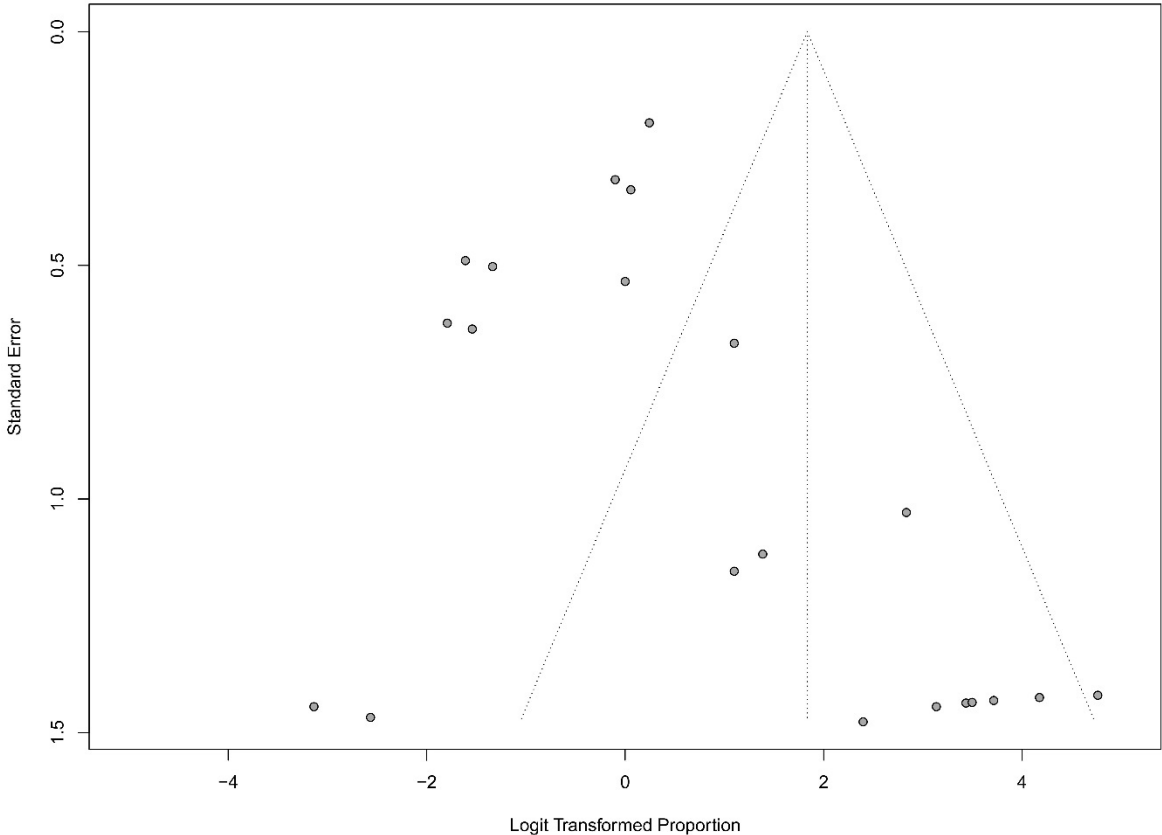
9	Bilemjian, 2009 ⁶	7, 13	1 st RF	9 mm wide (half of the nail), light and dark brown color pigmentation, micro-Hutchinson sign, change in pattern
10	Tosti, 2012 ⁷	Brith, 0.5	1 st RT	Triangular shape to rectangular shape with parallel margins, deep brown with a pale central part and darker peripheral lines, nail splitting and fissuring, pseudo-Hutchinson sign
11		1, 11	2 nd RT	Most of the nail, pale brown in color with lines of irregular coloration and thickness, enlargement of the band and development of new black longitudinal lines
12	Bonamonte, 2004 ⁸	2, 9	5 th LF	A single longitudinal streak to a diffuse pigmentation of the nail plate, light to deeper brown, irregularly spaced and variably thick bands, Hutchinson sign
13	Woo, 2016 ⁹	11, 18	1 st RF	A longitudinal pigmented band to total melanonychia, black discoloration of the nail plate, Hutchinson sign, nail splitting and fissuring, widened and darkened over time
14	Fattouh, 2017 ¹⁰	7, 12	1 st F	Progressive enlargement
15		9, 15	4 th F	NA
16		8, 14	5 th F	Change of color
17		3, 10	1 st F	NA
18		10, 11	1 st F	Progressive enlargement
19		13, 15	3 rd F	Change of color

20	Knackstedt, 2017 ¹¹	NA, 9	1 st LT	3.5 mm wide, light-brown pigmentation with central darker brown yet regular streak
21	Khatri, 2018 ¹²	2, 4	2 nd LF	6 mm wide (80% of the nail plate), black color, change in streak
22		2, 6	1 st LT	6 mm wide, brown color, change in streak
23	Sgubbi, 2019 ¹³	NA, 12	NA	NA
24	Akay, 2020 ¹⁴	5 months before the diagnosis, 16	4 th LF	Brown background with triangular bands, irregular lines and thickness, nail splitting and fissuring, rapid change within 3 months
25 Subungual melanoma	Yan, 2020 ¹⁵	9, 13	1 st LF	1 mm wide to 8 mm (70% of the nail plate) wide black macule, hypomelanotic area on the proximal nail plate, pigmentation extended to the hyponychium

43 Table 4. Reported cases of confirmed pediatric subungual melanoma in situ (n=24) and subungual melanoma (n=1) in the literature, including reports published after 1989 with
44 full text available for review. Cases 14-19, 21, 22, and 25 were included in the meta-analysis, having come from cohorts that met criteria for inclusion in this analysis. Case
45 25 is the only subungual melanoma; the other cases are reported as in situ. NA, not available.

Supplementary Figure Legends

Supplementary Figure 1. Funnel plot for prevalence of nail matrix nevus.



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119 **Chapter 3: Paper 2**

120 Tsai SYC, Ma KSK, Hawryluk EB. Long-term clinical outcomes associated with
121 melanocytic nevi in early childhood. Pediatrics (under review).

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**Long-term neurological and developmental outcomes associated with melanocytic
nevi in early childhood**

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Short title: A population-based study

Conflict of Interest Disclosures (includes financial disclosures): EBH reports
disclosures of UpToDate (author, reviewer) and Skin Analytics (consultant), DermTech
(research materials). The other authors have no conflicts of interest to disclose.

Funding/Support: No funding was secured for this study.

Abbreviations: MN, melanocytic nevi; CMN, congenital melanocytic nevi

Contributors Statement Page

Dr Elena B. Hawryluk and Dr Serena Yun-Chen Tsai conceptualized and designed the study, drafted the initial manuscript, and critically reviewed and revised the manuscript.

Dr Serena Yun-Chen Tsai and Dr Kevin Sheng-Kai Ma designed the data collection instruments, collected data, carried out the initial analyses, and critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Background: Congenital melanocytic nevi (CMN) are pigmented birthmarks which may be associated with the central nervous system and other anomalies.

Methods: This was a population-based cohort study utilizing a United States claims database. Pediatric patients (under 18 years) with at least 1 diagnosis of CMN before 3 years of age were included. Unexposed controls were individuals who had encountered health services before 3 years of age without any recording of the aforementioned diagnosis; these were matched for demographics using a 1:1 propensity score matching method. Primary composite outcome was the incidence of subsequently documented neurological and developmental diagnoses, including CNS cancers, seizures, hydrocephalus, cerebral palsy, developmental (speech/learning/motor) delay, attention-deficit hyperactivity disorder, autism spectrum disorder, and intellectual disability. The secondary outcomes included individual components of the primary composite outcome.

Results: A total of 30,021 patients with CMN and 2,113,232 unexposed controls were identified, with 30,005 participants after matching in both groups. Individuals with early-onset melanocytic nevi exhibited significantly higher risks of new-onset neurological and developmental diagnoses (HR = 1.43; 95% CI = 1.39-1.48; $p < 0.001$).

Conclusion: These findings underscore the significance of addressing neurobehavioral impact in pediatric patients with CMN.

INTRODUCTION

Melanocytic nevi, or moles, are ubiquitous in almost every child and constitute a common reason for consultations at pediatric dermatology clinics: they may be present from birth “congenital,” or “acquired.”¹ In general, melanocytic nevi are benign growths on the skin formed by a proliferation of melanocytes. They are usually round with a discretely defined border, uniform in pigment, and flat or raised. Congenital melanocytic nevi (CMN), as the name implies, are those evident at birth or during infancy.² The appearance of CMN can vary in size, color, and morphology. Based on the projected adult size of their maximal diameter, CMN are classified into small (<1.5 cm), medium (1.5-19.9 cm), and large or giant (≥ 20 or 40 cm, respectively); the color is predominantly brown, with occasional shades of tan, dark brown, grey, and blue; in terms of morphology, CMN often begin as flat, pigmented patches but may later grow into plaques with papules and/or nodules and hypertrichosis.³ Not all CMN persist over time, some fade with age. On the contrary, acquired melanocytic nevi (AMN) increase in number and size by age, with average nevus counts up to 80 nevi by 16 years of age; nevus development usually begins in early childhood and increases through mid-adolescence.⁴ However, the associations of nevi with diseases other than melanoma have not been fully described. While distinguishing the nature of melanocytic nevus can be challenging even by histopathology, those occurring in early childhood are often considered more likely to be congenital type, as most diagnoses relied on medical histories.⁵

When considering the developmental origin of melanocytes, the skin and nevi are derivatives of neural crest cells, which originate from the ectoderm in the neural fold. The neural crest cells not only give rise to melanocytes, but also the neurons and glia of the peripheral nervous system, smooth muscle cells, odontoblasts, and neuroendocrine cells.⁶

As a result, melanocytes (and melanin) can be found not only in the skin but also extracutaneous sites, including eyes, ears, brain, heart, adipose tissue, and lungs.⁷ Their roles differ based on their locations. For instance, melanocytes in brain tissues are involved in neuroendocrine function and detoxification.⁸ The differentiation and specification of melanocyte precursors rely on the coordinated interplay of cellular and molecular mechanisms taking place during their cellular migration. Any interruption or disorganization in the embryogenic development of these cells can result in various pigment or skin disorders, neurological abnormalities, and tumors, traditionally termed neurocutaneous melanosis.^{9,10} The incidence of neurocutaneous melanosis ranges from 10% to 33% in children with multiple CMN, independent of size and site of the largest nevus.¹⁰ The abnormal neurodevelopment includes abnormal radiological findings on magnetic resonance imaging (MRI), seizures, hydrocephalus, brain tumors, central nervous system (CNS) malformations, hearing loss, and visual impairment.¹¹

We hypothesize that given the embryologic development and ectodermal origin of the skin and neural tissues, along with the clues provided to us by more dramatic presentation of neurocutaneous melanosis, that nevi with onset in early childhood may be associated with neurologic and developmental disorders.¹² There is a lack of long-term follow-up studies reporting the risk of these disorders in individuals with congenital or early-onset melanocytic nevi in the literature, with most studies providing data in case reports or small case series. Additionally, due to the rarity of their nature, it would be challenging to investigate their relationships at single center. As such, we aimed to explore the risk of long-term neurological and developmental outcomes among melanocytic nevi diagnosed in infancy and early-childhood using a large dataset from a US Collaborative research network.

METHODS

Study design, population, and data collection

This population-based cohort study used the TriNetX Network to retrieve deidentified electronic health records from 80 health care organizations (HCOs) across the United States. The participating HCOs in the networks are hospitals, primary care, and specialist providers who contribute data from uninsured and insured patients. Since the study used deidentified patient records, it was exempted from the Institutional Review Board.

We used coding systems from the International Classification of Diseases, Tenth Revision (ICD-10) codes to determine diagnoses for this study. Detailed codes are provided in Supplemental Table S. Exposure was defined by a diagnosis of melanocytic nevus (ICD 10 code D22) in early childhood (under 3 years of age) between January 1st, 2013 and December 31th, 2023. Unexposed controls were those who underwent routine child health examinations without abnormal findings (ICD-10: Z00.129) and without the diagnosis of melanocytic nevus by the same age. We specified the age at diagnosis under 3 years of age since there is no specific code for CMN. Whereas the nature of nevi cannot be confirmed by coding, we considered nevi diagnosed in the early childhood more likely to be congenital type, as acquired type is usually associated to accumulated sun exposure and start its development after 2 or 3 years of age. According to the literature, the prevalence of AMN is only 1% at age 4-5 years.¹³ All participants with a history of malignancies, including melanoma in situ, were excluded. The flowchart of study sample selection is illustrated in Figure 1.

The index date was the first diagnosis of nevus in the exposed group or the encounter of health examinations in the unexposed groups.

Baseline characteristics, including age, sex, race and ethnicity, low socioeconomic status, preterm birth, low birth weight, congenital comorbidities (congenital malformations and deformations of eye, ear, face and neck, the nervous system, the musculoskeletal system, and chromosomal abnormalities), other types of birthmarks or skin malformations (hemangioma, congenital skin malformations, and other disorders of pigmentation), and prior healthcare history (hospitalization and emergency visit), were recorded. The baseline characteristics (except for age, sex, and race) were evaluated using anytime data prior to the index date (excluding index date).

The primary outcome was the composite outcome of neurological and developmental diagnoses reported to be associated with congenital or early-onset nevi in the literature, including CNS cancers, seizures, hydrocephalus, cerebral palsy, developmental (speech/learning/motor) delay, attention-deficit hyperactivity disorder, autism spectrum disorder, and intellectual disability. The secondary outcomes were the individual components of the primary composite outcome. The follow-up period was ten years after the index date. Patients were censored at the occurrence of each of the prespecified outcome, on the day after the last fact in their record, or end of the follow-up period.

Statistical analysis

All statistical analyses were conducted using the built-in Advanced Analytics on TriNetX research platform and in RStudio (Version: 2023.12.1+402). No imputations were performed for missing data; the complete cases analyses were performed. The distribution of baseline characteristics was compared between the two groups, with a standardized mean difference of greater than 0.1 indicating imbalance. Propensity scores based on baseline characteristics, including age, sex, race, socioeconomic status, health utilization,

gestational status, and congenital comorbidities, were derived from logistic regression. Two cohorts were then propensity-score matched using 1:1 greedy nearest-neighbor method. The matching procedure aimed to ensure that the matched variables would be distributed equally across cohorts; the process is graphically depicted in Figure 2. Only new-onset events of prespecified outcomes were counted, for which individuals with the outcome prior to baseline were excluded from the analysis. We investigated each outcome separately; for instance, in the analysis of the risk of seizure, we excluded individuals with prior history of seizure for this specific analysis but did not exclude other outcomes of interest (e.g., brain tumors and vision impairments). Time to occurrence of prespecified outcomes within ten years from the baseline were investigated. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional hazards regression model. The proportional hazard assumption was tested using the generalized Schoenfeld approach. A 2-tailed log-rank test $p < 0.05$ was considered statistically significant. To mitigate the inflation of type I error rates, or false discovery rates (FDR), arising from with multiple comparisons, we applied the Benjamini-Hochberg (B-H) procedure to correct for p values of 9 prespecified outcomes simultaneously tested in the analysis. A significance threshold was set at an FDR-adjusted p-value of less than 0.05 to denote statistical significance. In subgroup analyses, we stratified cohorts by sex (male and female).

RESULTS

A total of 30,021 cases and 2,113,232 controls were identified. Early melanocytic nevi were most frequently diagnosed in White patients (56%), and patients who are more likely to have higher body mass index, low socioeconomic status (3.3%), more frequent emergency visits in the prior healthcare history (15.4%), and congenital malformations

including those of the eye, ear, face, and neck (2.4%), and musculoskeletal system (7.5%), when compared to those without the nevus diagnosis. In addition, individuals with melanocytic nevi were more likely to coexist with other types of birthmarks or skin malformations, including hemangioma (4.0%), congenital skin malformations such as capillary malformations and dermal melanocytosis (8.9%), and other disorders of pigmentations such as café au lait spots (3.9%). Each group had 30,005 participants after matching (Table 1).

When compared to individuals without a diagnosis of melanocytic nevi in early childhood, individuals with early-onset melanocytic nevi exhibited significantly higher risks of new-onset the primary composite outcome, neurological and developmental diagnoses (HR = 1.43; 95% CI = 1.39-1.48; $p < 0.001$); secondary outcomes, including hydrocephalus (HR = 1.50; 95% CI = 1.07-2.11; $p = 0.019$), developmental speech/learning/motor delay (HR = 1.59; 95% CI = 1.31-1.92; $p < 0.001$), autism spectrum disorder (HR = 1.13; 95% CI = 1.02-1.25; $p = 0.016$), and intellectual disability (HR = 1.31; 95% CI = 1.02-1.68; $p = 0.034$). After B-H correction, primary composite outcome, hydrocephalus, developmental speech/learning/motor delay, and autism spectrum disorder remained statistically significant (Table 2). Most primary and secondary outcomes revealed no sex differences in the sex-stratified subgroup analyses, except that the risk of hydrocephalus did not elevate or decrease in both sex groups and intellectual disability only increased in males (Table 3).

DISCUSSION

This is the first study utilizing a large patient database to examine the associations early-onset melanocytic nevi with long-term neurological and developmental outcomes in children.¹² Since melanin depositions can occur at extracutaneous sites such as brain

parenchyma, leptomeninges, and retinal pigment epithelium, many of the pigmentary skin disorders are associated with similar pigmentary abnormalities in these organs, resulting in seizure, hydrocephalus, central nervous system tumors, and vision impairment.^{11,14} We found an increase in a variety of neurological and developmental diagnoses, hydrocephalus, developmental speech/learning/motor delay, and autism spectrum disorder in the melanocytic nevus cohort, suggesting a potential association of melanocytic nevus with neurological, cognitive, and behavioral functions.

Melanocytic nevi vary in sizes, locations, and numbers, especially in the early stage of development. In pediatric dermatology clinics, children chaperoned by their caregivers with the chief complaints of melanocytic nevi usually present with visible or multiple nevi, requiring a comprehensive skin evaluation by dermatologists. Although the main concern has been the potential of malignant changes, as numbers and distribution of melanocytic nevi in childhood are major indicators of the melanoma risk, other concerns including neurobehavioral sequelae, developmental, and psychological burdens may arise.¹⁵ According to the previous meta-analysis including 2,339 patients with CMN of all sizes, the prevalence of neurological signs and symptoms was 7.04 (95% CI 4.47-10.93%).¹¹ In a retrospective review of 46 children diagnosed with CMN undergoing an MRI of brain and/or spine for a reason related to their CMN, 12 patients (26.1%) had abnormal MRI imaging, 15 patients with neurodevelopmental problems (e.g., developmental delay, autism spectrum disorder, speech delay or disorder, learning disability, attention-deficit disorder, and motor problem) (32.6%), 7 with seizures (15.2%), and 2 hydrocephalus (4.3%) requiring ventriculoperitoneal shunting.¹⁶ In our primary analysis, we found a rise of all neurological and developmental diseases in the melanocytic nevi group. We also discovered that the presence of early-onset melanocytic nevi was associated with a

significantly higher risk of new-onset hydrocephalus in our study, albeit with extremely low incidences and without significance in sex-based subgroup analyses. It is noteworthy that hydrocephalus may be underreported in children, as the disease can be asymptomatic or spontaneously arrested and resolved.¹⁷ Other neurological abnormalities, including CNS tumor, seizure, and cerebral palsy, were not significantly increased or decreased in individuals with melanocytic nevi.

The risk of subsequent developmental speech/learning/motor delay, autism, and intellectual disability were significantly increased in individuals diagnosed with early-onset nevi in our study. While the exact mechanism underlying the association remains largely unknown, it is postulated that the relationship may be related to RAS gene mutations. Most congenital melanocytic nevi harbor NRAS mutations, with only a few cases harboring BRAF mutations.¹⁸ The mutations in RAS/mitogen-activated protein kinases (RAS/MAPK) pathway has been shown to result in developmental disorders, such as developmental delay and neurocognitive deficits.¹⁹ Intellectual disability and autism spectrum disorders are a group of co-occurring neurodevelopmental disorders that share similar pathophysiological pathways and are highly correlated with abnormal brain development with regards to genetic and environmental processes, which consequently often coexist with each other.²⁰ Previous translational studies also indicate the association between RAS-MAPK mutation and autism spectrum disorder as well as intellectual disability.^{21,22} The findings that the risk of intellectual disability was significantly increased in the male subgroup but not the female subgroup may be related to the disease nature and epidemiology, as males are more likely to be diagnosed with intellectual disability in general.²³

The major strength of our study is the size of the database, which provides significant statistical power relative to limited data. There are several limitations in this

study. First, this study relied on ICD-10 codes to identify exposures and outcomes, introducing the possibility of misclassification, which limits the validity of our findings. Second, there is a lack of distinct codes for differentiating the nature (congenital or acquired nevi) and the size of melanocytic nevus. Third, although propensity score matching was utilized to alleviate most confounders between the groups, residual unmeasured confounding, particularly those that cannot be captured using ICD-10 codes (such as Fitzpatrick skin type, sun exposure, history of sunburns, genetic mutations, and family history of melanoma), may still exist. Given the potential for unobserved confounding or reverse causation bias in observational studies, conducting an instrumental variable study in the future would enhance the evidence regarding the association between melanocytic nevi and neurological and developmental outcomes. Finally, the large percentage of missing data in race/ethnicity cannot be ignored, as race/ethnicity plays an important role in the prevalence and etiology of melanocytic nevi.²⁴ Due to the limitation of the data source, we did not perform multiple imputations; the complete cases analysis performed in the study may result in selection bias.

CONCLUSION

In conclusion, we found an increased in long-term neurological and developmental outcomes in individuals with melanocytic nevus diagnosed under three years of age. Further research is required to elucidate the mechanisms that underlie these associations.

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Table 1. Baseline demographics of children with diagnosis of melanocytic nevi in early childhood compared to children without melanocytic nevi

	Before propensity score matching			After propensity score matching		
	Melanocytic nevus (n = 30,005)	Unexposed controls (n = 2,113,232)	SMD	Melanocytic nevus (n = 30,005)	Unexposed controls (n = 30,005)	SMD
Age, mean $\pm$ SD						
Age at index	1.2 $\pm$ 1.2	0.6 $\pm$ 1.0	0.490	1.2 $\pm$ 1.2	1.2 $\pm$ 1.2	0.003
Sex, n (%)						
Female	13,918 (46.4)	944,736 (44.7)	0.024	13,910 (46.4)	13,934 (46.4)	0.002
BMI (kg/m ²)	16.6 $\pm$ 2.6	15.9 $\pm$ 2.9	0.261	16.5 $\pm$ 2.6	16.2 $\pm$ 2.7	0.113
Race and ethnicity, n (%)						
White	16,737 (55.8)	944,092 (44.7)	0.226	16,721 (55.7)	16,733 (55.8)	0.001
Black or African American	3,349 (11.2)	410,298 (19.4)	0.245	3,349 (11.2)	3,341 (11.1)	0.001
Asian	1,474 (4.9)	83,697 (4.0)	0.045	1,474 (4.9)	1,450 (4.8)	0.004
Unknown	8,445 (28.1)	675,145 (31.9)	NA	8,461 (28.2)	8,481 (28.3)	NA
Hispanic or Latino	5,637 (18.8)	402,523 (19.0)	0.013	5,635 (18.8)	5,666 (18.9)	0.003
Not Hispanic or Latino	19,267 (64.2)	1,193,637 (56.5)	0.156	19,252 (64.2)	19,226 (64.1)	0.002
Unknown	5,101 (17.0)	517,072 (24.5)	NA	5,118 (17.1)	5,113 (17.0)	NA
Socioeconomic status, n (%)						
Low socioeconomic status	983 (3.3)	17,068 (0.8)	0.179	978 (3.3)	978 (3.3)	<0.001
Neonatal conditions and prior healthcare history, n (%)						
Preterm and low birth weight	937 (3.1)	35,453 (1.7)	0.096	934 (3.1)	946 (3.2)	0.002
Hospitalization	308 (1.0)	12,122 (0.6)	0.060	308 (1.0)	319 (1.1)	0.004
Emergency visit	4,631 (15.4)	144,626 (6.8)	0.281	4,626 (15.4)	4,599 (15.3)	0.003
Congenital malformations, n (%)						
Nervous system	239 (0.8)	6,233 (0.3)	0.069	238 (0.8)	250 (0.8)	0.005
Eye, ear, face and neck	709 (2.4)	10,398 (0.5)	0.162	706 (2.4)	725 (2.4)	0.004
Musculoskeletal system	2,255 (7.5)	32,881 (1.6)	0.297	2,251 (7.5)	2,299 (7.7)	0.006
Chromosomal abnormalities	170 (0.6)	5,028 (0.2)	0.053	169 (0.6)	172 (0.6)	0.001
Other types of birthmarks or skin malformations, n (%)						
Hemangioma	1,212 (4.0)	8,163 (0.4)	0.257	1,205 (4.0)	1,210 (4.0)	0.001
Congenital skin malformations ^a	2,659 (8.9)	12,492 (0.6)	0.405	2,652 (8.8)	2,681 (8.9)	0.004
Other disorders of pigmentation ^b	1,184 (3.9)	3,977 (0.2)	0.274	1,169 (3.9)	1,130 (3.8)	0.007

NA, not assessed; SD, standard difference; SMD, standardized mean difference. Bold font represents imbalance (SMD > 0.1).

^a Congenital skin malformations include capillary malformations, such as port-wine stains and strawberry nevus, dermal melanocytosis (Mongolian spot), incontinentia pigmenti, and other skin disorders present at birth.

^b Other disorders of pigmentation include dyspigmentation, such as café au lait spots and pigmentary mosaicism.

Table 2. Comparison of outcomes in children with diagnosis of melanocytic nevi in early childhood compared to children without melanocytic nevi

	Melanocytic nevus (n = 30,005)	Unexposed controls (n = 30,005)	HR	95% CI	P-value (log- rank) *	BH- adjusted p- value**
Outcomes	Events (%)	Events (%)				
Primary composite outcome						
Neurological and developmental diseases	5,931 (21.2)	4336 (16.2)	1.43	(1.39, 1.48)	<0.001*	<0.001**
Secondary outcomes						
Central nervous system cancers	32 (0.1)	27 (0.1)	1.61	(0.96, 2.70)	0.070	0.105
Seizure	1,330 (4.6)	985 (3.5)	1.02	(0.94, 1.11)	0.618	0.695
Hydrocephalus	73 (0.2)	63 (0.2)	1.50	(1.07, 2.11)	0.019*	0.043**
Cerebral palsy	105 (0.4)	72 (0.3)	0.95	(0.70, 1.29)	0.741	0.741
Developmental speech/learning/motor delay	3,997 (13.3)	3,211 (10.7)	1.59	(1.31, 1.92)	<0.001*	<0.001**
Attention-deficit hyperactivity disorder	1,521 (5.1)	888 (3.0)	1.04	(0.96, 1.13)	0.377	0.485
Autism spectrum disorder	882 (3.0)	718 (2.4)	1.13	(1.02, 1.25)	0.016*	0.043**
Intellectual disability	145 (0.5)	117 (0.4)	1.31	(1.02, 1.68)	0.034*	0.061

BH, Benjamini-Hochberg; CI, confidence interval; HR, hazard ratio.

* denotes nominally significant values (unadjusted $p < .05$).

** denotes statistical significance following Benjamini-Hochberg procedure for multiple comparisons (adjusted $p < .05$).

Table 3. Sex-stratified subgroup analyses of outcomes in children with diagnosis of melanocytic nevi in early childhood compared to children without melanocytic nevi

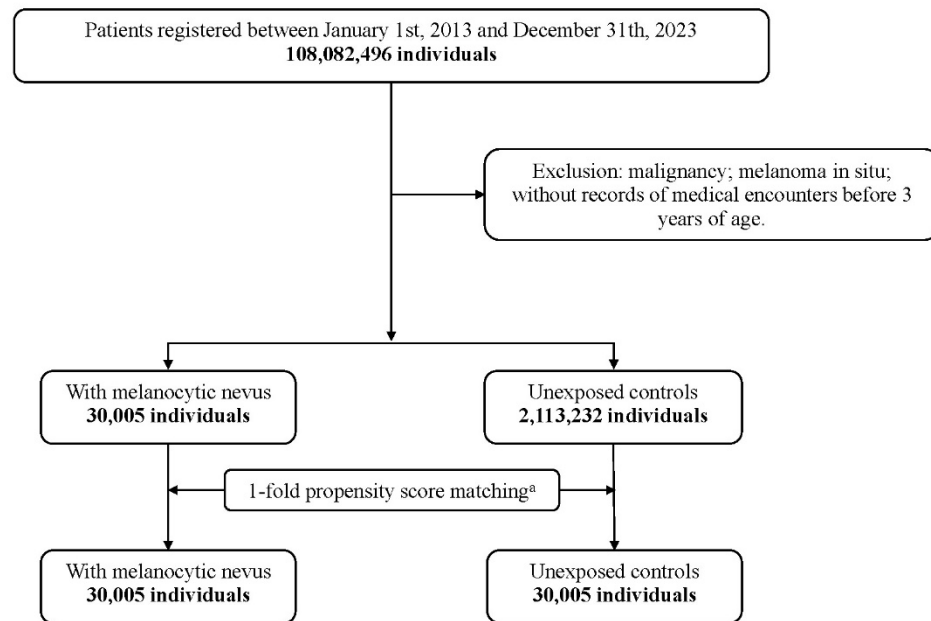
	Male						Female					
	Melanocytic nevus (n = 15,306)	Unexposed controls (n = 15,306)	HR	95% CI	P-value (log- rank)*	BH-adjusted p- value**	Melanocytic nevus (n = 15,166)	Unexposed controls (n = 15,166)	HR	95% CI	P-value (log- rank)	BH-adjusted p- value**
Outcomes	Events (%)	Events (%)					Events (%)	Events (%)				
Neurological and developmental diseases	3,061 (20.1)	2,510 (16.4)	1.41	(1.35, 1.46)	<0.001*	<0.001**	2,903 (19.2)	2,284 (15.1)	1.39	(1.33, 1.45)	<0.001*	<0.001**
Central nervous system cancers	21 (0.1)	19 (0.1)	1.45	(0.77, 2.71)	0.246	0.416	11 (0.1)	10 (0.1)	2.01	(0.80, 5.06)	0.133	0.286
Seizure	727 (4.9)	529 (3.8)	1.00	(0.90, 1.13)	0.928	0.967	624 (4.2)	465 (3.2)	1.04	(0.92, 1.17)	0.541	0.553
Hydrocephalus	45 (0.4)	36 (0.2)	1.00	(0.65, 1.57)	0.967	0.967	37 (0.2)	33 (0.2)	1.40	(0.87, 2.25)	0.159	0.286
Cerebral palsy	102 (0.7)	78 (0.5)	0.96	(0.72, 1.30)	0.802	0.967	69 (0.46)	45 (0.3)	0.83	(0.57, 1.21)	0.334	0.429
Developmental speech/learning/motor delay	2,173 (14.2)	1,638 (11.1)	1.30	(1.19, 1.42)	<0.001*	<0.001**	2,077 (13.7)	1,592 (10.5)	1.14	(1.03, 1.25)	0.007*	0.032**
Attention-deficit hyperactivity disorder	1,122 (7.3)	622 (4.0)	0.95	(0.86, 1.04)	0.277	0.416	537 (3.5)	309 (2.0)	1.10	(0.95, 1.27)	0.200	0.300
Autism spectrum disorder	732 (4.8)	607 (4.0)	1.12	(1.01, 1.25)	0.037*	0.083	274 (1.8)	247 (1.6)	1.22	(1.03, 1.46)	0.022*	0.066
Intellectual disability	87 (0.6)	80 (0.5)	1.51	(1.11, 2.06)	0.009*	0.027**	71 (0.5)	48 (0.3)	1.12	(0.77, 1.63)	0.553	0.553

BH, Benjamini-Hochberg; CI, confidence interval; HR, hazard ratio.

* denotes nominally significant values (unadjusted $p < .05$).

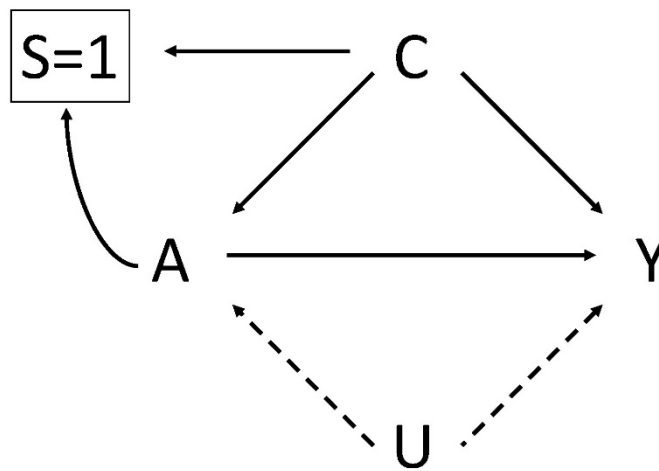
** denotes statistical significance following Benjamini-Hochberg procedure for multiple comparisons (adjusted $p < .05$).

Figure 1. Study sample selection



^a1-fold propensity score matching based on age, sex, race, socioeconomic status, health utilization, gestational status, and congenital comorbidities.

Figure 2. Causal directed acyclic graph of the study.



A denotes an exposure, Y denotes an outcome, C denotes confounders and matching variables, and U denotes unobserved confounders; S indicates whether an individual in the source population is selected in the matched cohorts (1: selected, 0: not selected).

Supplemental Methods

Table S. List of ICD-10 codes for defining exposures, baseline characteristics, and outcomes

	ICD-10 codes
Exposure	
Melanocytic nevus	D22
Routine child health examinations without abnormal findings	Z00.12
Malignancies	C00-C96
Melanoma in situ	D03
Baseline characteristics	
Low socioeconomic status	Z55-Z65
Preterm birth	P05
Low birth weight	P07
Congenital malformations and deformations of eye, ear, face and neck	Q10-Q18
Congenital malformations and deformations of the nervous system	Q00-Q07
Congenital malformations and deformations of the musculoskeletal system	Q65-Q79
Chromosomal abnormalities	Q90-Q99
Hemangioma	D18.0
Congenital skin malformations	Q82
Other disorders of pigmentation	L81
Outcomes	
Neurological and developmental diseases (central nervous system cancers, seizure, hydrocephalus, cerebral palsy, developmental speech/learning/motor delay, attention-deficit hyperactivity disorder, autism spectrum disorder, and intellectual disability)	C70-C72, G40, G80, G91, R56, F70-79, F80-82, F84.0, F90
Central nervous system cancers	C70-C72
Seizure	G40, R56
Hydrocephalus	G91
Cerebral palsy	G80
Developmental speech/learning/motor delay	F80-F82
Attention-deficit hyperactivity disorder	F90
Autism spectrum disorder	F84.0
Intellectual disability	F70-F79

Chapter 4: Summary of Conclusions

Paper 1

The high pooled prevalence of atypical characteristics in pediatric melanonychia, such as dark-colored bands, multi-colored bands, broad bandwidth, Hutchinson sign, and irregular patterns, aligns with the data in the literature and supports the prevalence of these atypical features in pediatric patients with melanonychia. In addition, numerous cases of pediatric melanonychia undergo evolution or progression during the disease course. Despite the common occurrence of these atypical characteristics in pediatric melanonychia, the likelihood of malignant transformation is exceedingly low.

Paper 2

Melanocytic nevi, or moles, are ubiquitous in almost every child but not found to be a worrisome diagnosis. Their association with other diseases remains largely unknown. In this retrospective cohort study, we retrieved deidentified electronic health records from 80 U.S. health care organizations and studied 30,005 children with melanocytic nevi in early childhood (defined as less than 3 years of age). Those patients with early childhood nevi presented with a significantly higher risk of neurologic and developmental diseases, hydrocephalus, developmental delay, autism, and intellectual disabilities, when compared to matched controls.

Chapter 5: Discussion and Perspectives

Paper 1

For pediatric melanonychia, it is crucial to appreciate the benign features and natural evolution of nail matrix nevi using dermoscopy and to monitor as appropriate. A nail unit biopsy is not mandatory for every case, even those that are evolving, but long-term interval follow-up is required to confirm the benign clinical features of nail matrix nevi.

There were some limitations in this systemic review and meta-analysis. Most studies were conducted in Asia, and there is a lack of available data that is stratified by skin type. Melanonychia is commonly encountered in skin phototypes IV–VI, and the incidence was approximately 1% in Whites, 10–20% in Asians, and 77–100% in African Americans. As such, melanonychia in a non-Asian population might not be adequately represented. Further, study data was limited by inconsistent reporting of melanonychia features, a lack of some key features, and a lack of histopathological confirmation of diagnoses in most cases. Certain features also displayed high heterogeneity, and the funnel plots revealed substantial publication bias in some variables.

Future studies should provide more detailed descriptions of dermoscopic patterns observed in pediatric melanonychia, as biopsy may serve as the last resort of diagnosis. Additionally, a better understanding of the correlation between subungual melanoma and nail matrix nevi is required, particularly in relation to congenital and acquired types.

Paper 2

Our findings identify an association of neurologic and developmental disease and the diagnosis of nevi in early childhood (before age 3 years). This provides new information regarding potential comorbid diagnoses, rationale for screening in clinical practice, and

important signals for further study.

Limitations include the validity of diagnostic coding; a lack of distinct codes for congenital-type and acquired-type nevi, which may result in misclassification bias; and residual confounding resulting from variables that cannot be measured or coded, such as sun exposure and the family history of melanoma.

The large cohort size and the potential impact of these associated diagnoses merit further study. While a retrospective cohort study is the first step in validating our hypotheses, a prospective study is necessary in the future, especially investigating the correlation between early-onset nevi and child development, neurobehavioral sequelae, and psychological impacts.

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