REVIEW

# The study of nevi in children: Principles learned and implications for melanoma diagnosis

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Melanocytic nevi are a strong phenotypic marker of cutaneous melanoma risk. Changes in nevi during childhood and adolescence make these prime periods for studying nevogenesis. Insights gained by the study of nevi in childhood have implications for melanoma detection in both adults and children. A more comprehensive understanding of the morphologic characteristics of nevi in different anatomic locations, in association with the patient's age and pigmentary phenotype may aid in the identification of melanomas. When monitoring melanocytic lesions over time, it is essential to differentiate normal from abnormal change. This review summarizes the rapidly expanding body of literature relevant to nevus phenotype, particularly in the context of our experience with the Study of Nevi in Children (SONIC) Project. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.03.027.)

***Key words:*** adolescence; childhood; dermoscopy; detection; melanoma; nevi; nevogenesis.

## INTRODUCTION

In 2010, >49,000 individuals were estimated to have died from melanoma worldwide.[1] Nevi are among the strongest phenotypic markers of melanoma risk.[2] Diagnosis often relies on differentiating a melanoma from the patient's many nevi. This can be challenging because nevi are heterogeneous and their morphology varies depending on the patient's age, pigmentary phenotype, ultraviolet radiation exposure, and genotype, as well as the anatomic location and potential for change.[3-14] While current aids for melanoma detection rely on morphology to distinguish nevi from melanomas, such as ABCDE criteria (*a*symmetry, *b*order irregularity, *c*olor variegation, *d*iameter> 6 mm, and *e*volving) and dermoscopy,[15-19] patient-related factors are not included in diagnostic algorithms. A more comprehensive understanding of the natural history of nevi and variations in their patterns is needed to improve melanoma detection.[20]

The first 2 decades of life are notable for appearance and growth of nevi, making this an important

*Abbreviations used:*

| | |
|---|---|
| CI: | confidence interval |
| Mc1R: | melanocortin-1 receptor |
| OR: | odds ratio |
| RHC: | red hair color |
| SONIC: | Study of Nevi in Children |

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period for studying nevogenesis.[21-23] Insights gained by the study of nevi in childhood have implications for melanoma detection in both adults and children. The Study of Nevi in Children (SONIC), a cohort in Framingham, Massachusetts,[11-13,24-36] is a population-based study that documents the dermoscopic and clinical evolution of nevi in childhood and adolescence over time. Herein, we summarize a rapidly expanding body of literature, particularly in the context of our experience with SONIC, regarding patient-related factors that contribute to nevus phenotype and their implications for melanoma diagnosis.

**CAPSULE SUMMARY**

- Melanocytic nevi are strong risk markers for melanoma.
- We summarize recent insights regarding the natural history of nevi and patient-related factors that contribute to nevus phenotype, such as age, anatomic site, and skin color.
- Insights gained from studies of benign nevi can aid in the identification of potential melanomas.

## Age-related prevalence of dermoscopic patterns of nevi

The predominant dermoscopic pattern can be predicted based on a patient's age. In early childhood, a globular nevus pattern is most prevalent, while in adulthood, a reticular pattern predominates (Table I).[10] In the SONIC cohort, we observed a gradual decline in the percentage of globular nevi and an increase in that of reticular nevi during the second decade of life.[12,31,37] A similar trend was observed in a pediatric cohort study from Italy.[38] Cross-sectional analysis of the dermoscopic patterns of nevi on the trunk by age is consistent with these longitudinal observations (Table I).

Another dermoscopic pattern with an age-dependent prevalence is the peripheral globular pattern. This nevus morphology is associated with growth,[39] with large junctional nests at the periphery on examination by histopathology and reflectance confocal microscopy.[40] Among SONIC participants aged 14 (n = 345), this pattern was observed in approximately 3% of back nevi (n = 1152) but was rare (<0.5%) in leg nevi (n = 290; unpublished data). Zalaudek et al[10] noted the relative frequency of nevi with peripheral globules on the trunk among patients seen in pigmented lesion clinics to be 9% in the first decade, 5% in the second decade, 4% in the third decade, and 1.5% in the fourth decade of life, after which the frequency became <1%.

**Implications for clinical practice.** A new globular nevus is less common with advanced age (Fig 1). Recently, a subtype of melanoma termed "nested melanoma of the elderly" was reported.[41-44] These melanomas have irregularly distributed globules on dermoscopic examination, corresponding to a "clod" pattern of large compact nests on confocal microscopy, and to large intraepidermal nests on histopathologic examination.[41-44] Early recognition is important given the observation of Beer et al[45] that melanomas harboring a predominantly globular pattern, with large nests and aggregates on histopathology, grow faster than melanomas that show a predominantly reticular pattern, with lentiginous or small-nested pattern on histopathology.

The age-dependent prevalence of nevi with peripheral globules has clinical implications (Fig 2). In the second to third decades of life,[10] patients with nevi with a peripheral rim of globules do not require specific intervention. In patients >30 years of age, nevi with a peripheral rim of globules without any other melanoma-specific criteria should be digitally monitored to ensure symmetric enlargement. The growth rate of nevi with peripheral globules is comparable to the growth rate of some melanomas.[33,45] Unlike melanoma, nevi with peripheral globules grow symmetrically and do not develop any new structures or colors as they grow, lack melanoma-specific structures, and the peripheral globules become smaller and eventually disappear once nevus growth ceases. In patients >50 years of age, nevi with peripheral globules are rare, the incidence of melanoma among new or changing lesions is relatively high, and this dermoscopic pattern should prompt a clinician to consider obtaining a biopsy specimen of the lesion.[10,46]

## Anatomic site–related prevalence of dermoscopic patterns of nevi

In SONIC, we observed that globular-patterned nevi occur more frequently on the upper part of the body, where they tend to be larger in diameter; on the lower trunk and extremities, the predominant nevus pattern becomes increasingly reticular and nevi tend to be smaller.[12,31] At 11 years of age, nevi were more likely to be globular on the upper than on the lower back (odds ratio [OR] = 2 [95% confidence interval {CI}, 1.6-2.6]; $P < .001$).[12] At 14 years of age, compared to referent homogeneous nevi, globular nevi were more commonly observed on the back than the legs (OR = 29.4 [95% CI, 9.5-90.7]; $P < .001$), whereas reticular nevi were less likely to be observed on the back than the legs (OR = 0.7 [95% CI, 0.5-0.8]; $P = .001$).[31,37] Similarly, congenital melanocytic nevi

**Table I.** Prevalence of dermoscopic pattern of nevi by age

| Study, y | Design | No. of nevi (no. of patients) | Patient age, y | Prevalence of dermoscopic pattern by age | |
|---|---|---|---|---|---|
| | | | | Globular, n (%) | Reticular, n (%) |
| Scope et al,[12] 2008 | Cross-sectional | 1198 (443) | 11 | 449 (37) | 155 (13) |
| Fonsesca et al,[31] 2015 | Cross-sectional | 2320 (509) | 14 | 357 (15) | 868 (38) |
| Fortina et al,[38] 2012 | Longitudinal | 717 (160) | Baseline 3-16; ≤7 y follow-up | Baseline, 144 (20) Follow-up, 80 (11) | Baseline, 336 (47) Follow-up, 374 (52) |
| Zalaudek et al,[10] 2011 | Cross-sectional | 5481 (480) | | | |
| | | 363 | 3-10 | 212 (58) | 58 (16) |
| | | 902 | 11-20 | 380 (42) | 318 (35) |
| | | 1019 | 21-30 | 325 (32) | 501 (32) |
| | | 1057 | 31-40 | 215 (20) | 646 (61) |
| | | 832 | 41-50 | 182 (22) | 498 (60) |
| | | 677 | 51-60 | 120 (18) | 461 (68) |
| | | 446 | 61-75 | 64 (14) | 318 (71) |
| | | 185 | >75 | 14 (8) | 133 (72) |

with a globular pattern are observed more commonly on the trunk than on the extremities.[47,48] These findings are consistent with histopathologic data that bulkier, predominantly dermal nevi—which correlate dermoscopically with globular-patterned nevi—are more common in cephalad than in caudal locations.[49] Based on the distribution of globular nevi by anatomic site, which is compatible with the embryonic cephalad-to-caudal and axial-to-peripheral melanoblast migration sequence, we and others[9,12] speculate that nevi showing a globular dermoscopic pattern may be congenital in origin. This hypothesis is supported by the observation that globular nevi are more likely to appear in children than later in life.

**Implications for clinical practice.** A pigmented lesion showing a globular pattern on the lower extremities in adults is concerning in the absence of a history of long-standing stability (Fig 3). Although the prevalence of melanomas displaying a predominantly globular pattern at diagnosis is unknown (but likely uncommon), most melanomas will show a multicomponent pattern often with atypical dots or globules.[50] The subtype of melanoma termed "nested melanoma of the elderly"[41-44] is uniquely characterized by a globular pattern on dermoscopic examination. Of 24 melanomas reported with this pattern, 15 (63%) have occurred on the extremities.[41-44]

A solitary pigmented lesion that breaks the cephalad-to-caudal size and pattern gradient should be closely examined. For example, an acquired reticular-patterned melanocytic lesion located on the upper torso and significantly larger than the patient's other nevi is an "ugly duckling"[51-54] that should be carefully analyzed with dermoscopy for melanoma-specific criteria (Fig 4), such as those seen in melanomas on sun-damaged skin.[55]

## Pigment phenotype–related prevalence of dermoscopic patterns of nevi

There is a predictable association between a patient's skin color, and the dermoscopic pattern and size of nevi. In SONIC, we observed that at age 11, a darker pigment phenotype was associated with the presence of reticular nevi ($P < .0001$) and smaller nevus size ($P < .0001$ for trend).[12] Similarly, at age 14, reticular-patterned nevi were twice as likely to be associated with darker than with lighter skin color ($P < .001$).[31] Globular, homogeneous, and complex dermoscopic patterns were more frequently observed in nevi of children with a lighter pigment phenotype.[12] In 680 white adult patients, Zalaudek et al[5] found that the frequency of reticular patterned nevi on dermoscopy increased with darker pigment phenotype (OR = 2.8 for Fitzpatrick skin type IV vs. type I; $P = .03$).[5] Skin color has been associated with variation in the melanocortin-1 receptor (Mc1R).[56] Quint et al[57] tested the association of dermoscopic patterns and structures by the number of Mc1R red hair color (RHC) variants, the premise being that the more variants one has, the lighter the pigmentary phenotype of that individual: in 876 clinically atypical nevi from 111 patients, they found that pigment network and dark brown color were more frequently observed in atypical nevi from individuals without RHC variants, while structureless areas were more often seen in individuals with 2 RHC variants.[57]

**Implications for clinical practice.** Melanoma presents as an "ugly duckling"[51-54] when it deviates from the expected dermoscopic pattern of the patient's other nevi,[53,58] based on pigmentary

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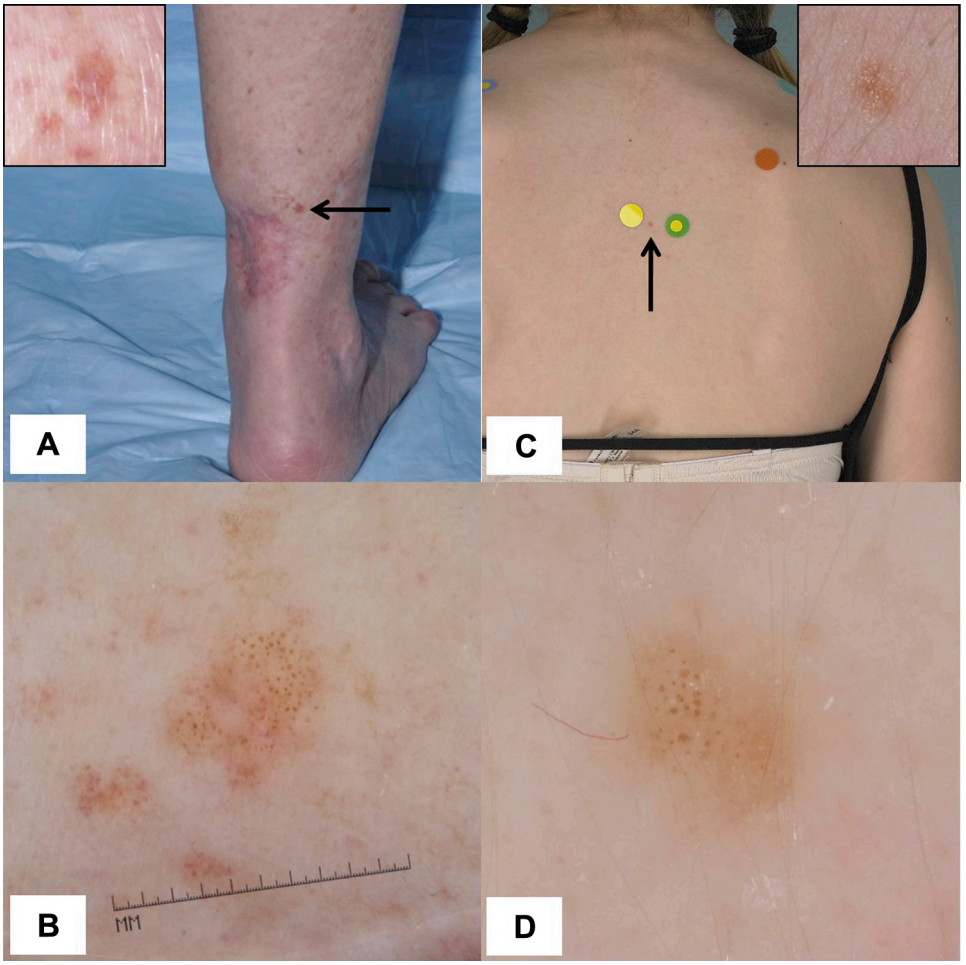



**Fig 1.** Melanoma and nevus. Age-dependent evaluation of globular lesions. **A**, An 84-year-old woman with history of 3 melanomas presented with a 6-mm light brown flat papule adjacent to a previous melanoma scar on the leg. **B**, On dermoscopy, the lesion presented a diffuse globular pattern. While banal-appearing, a new globular-patterned nevus in an older individual is unlikely. The lesion was excised and diagnosed as melanoma 0.8 mm in thickness. **C**, Clinical image of a nevus presenting as a 4-mm macule on the upper aspect of the back of a 14-year-old. **D**, On dermoscopy, this nevus showed a globular pattern. Despite the morphologic resemblance of the nevus to the melanoma shown in *B*, the young age and anatomic location are typical for a globular nevus.

phenotype. Therefore, a darkly pigmented lesion with dermoscopic criteria for melanocytic neoplasia and without a long-standing history of stability in an individual with fair skin should be examined carefully (Fig 5). The converse is similarly true: a new, nonpigmented papule in a patient with Fitzpatrick skin type ≥ III may be concerning for amelanotic melanoma. Puig et al[59] found that early melanomas from patients with 2 MC1R RHC variants may be difficult to diagnose because they harbor few dermoscopic colors and structures. They recommended sequential dermoscopic monitoring in patients with this genotype, with particular attention to the presence of subtle atypical vessels.

## Changes in nevi during childhood and adolescence

Cross-sectional and longitudinal studies have shown that nevus counts increase during childhood and adolescence.[60-65] A 3-year prospective study of 164 white children (87 aged 6-7 years; 77 aged 9-10 years) living in Vancouver, British Columbia, Canada found that median whole-body nevus counts increased from 68 to 96 nevi; however, a few children were noted to have a lower nevus count at follow-up.[60] Among SONIC participants, many new nevi appeared, but existing nevi also decreased in size, faded, or completely disappeared. Among 366 children followed from ages

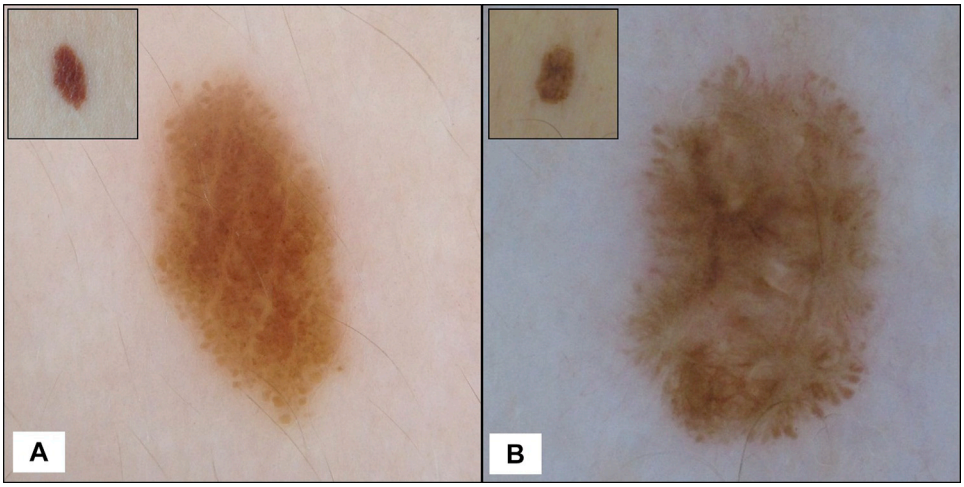



**Fig 2.** Nevus and melanoma. Age-dependent evaluation of lesions with peripheral globules. **A**, A growing nevus on the back of a 17-year-old female whose family has a history of melanoma. The dermoscopic pattern, showing a symmetrical rim of peripheral globules, is commonly encountered in growing nevi in young patients. **B**, A 5-mm brown macule on the right upper abdomen of a 60-year-old man without a personal or family history of melanoma. Dermoscopy revealed a reticular pattern with peripheral globules and streaks, and although these are distributed around the entire perimeter, the pattern indicated a growing melanocytic neoplasm in an individual >50 years of age. The lesion was excised and was diagnosed as melanoma (0.5 mm in thickness).

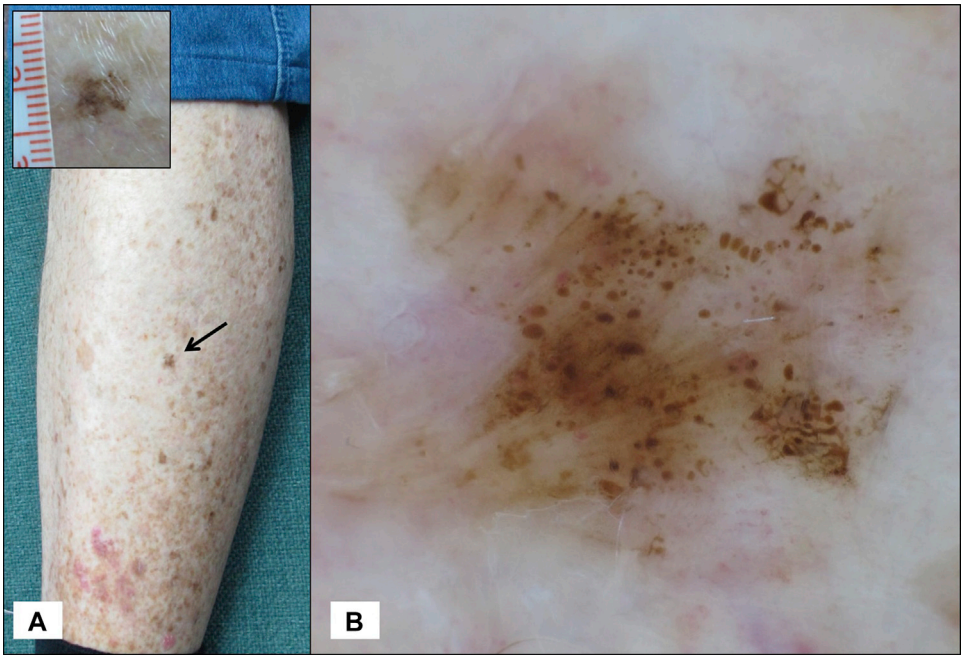



**Fig 3.** Melanoma. Anatomic site–dependent evaluation of a globular lesion. **A**, A 77-year-old man with 2 previous melanomas had a 5-mm brown macule on his leg. **B**, Dermoscopy revealed a globular pattern with globules that were nonuniform in shape and spacing. A globular patterned lesion on the leg of an older individual without a history of long-standing stability is highly suspicious; indeed, the lesion proved to be melanoma (0.1 mm in thickness).

11 to 14, 75% developed new nevi, with an average increase in a back nevus count of 2; 28% of participants had ≥1 nevus that disappeared in this time period.[11] These findings of dynamic turnover among melanocytic nevi in early life are supported by a longitudinal study of facial and neck nevi in 20

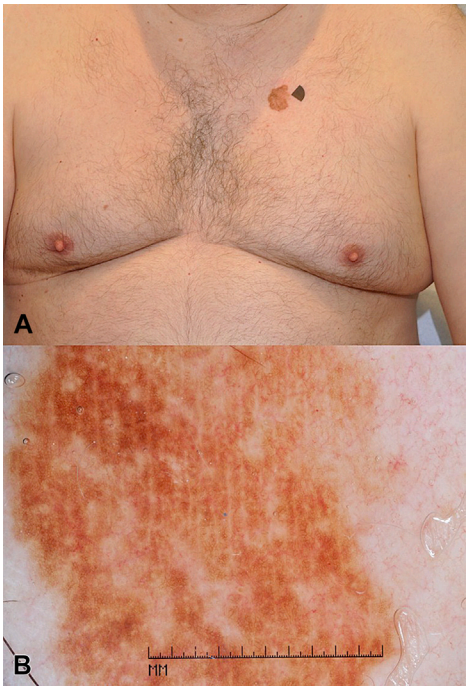



**Fig 4.** Melanoma. A solitary lesion "breaking" the cephalad-caudal distribution gradient of nevi. **A**, A 74-year-old man without a personal or family history of melanoma had a >20-mm brown patch on his chest. The patient denied having this lesion from childhood and noticed this growing lesion on his chest for many years. **B**, Dermoscopy revealed a seemingly uniform reticular pattern, but without criteria for the diagnosis of solar lentigo. A solitary, large, acquired reticular-patterned melanocytic neoplasm on the torso of an adult is suspicious for melanoma, and indeed, the lesion proved to be melanoma (0.15 mm in maximal thickness).

adolescents 12 to 14 years of age in Queensland, Australia.[61] After 3 years, 190 new nevi were observed and 61 of the 230 baseline nevi (26.5%) had disappeared.[61]

In SONIC, a majority of new nevi detected at age 14 and followed through age 17 (n = 121) either increased in size (43%), showed no change (50%), disappeared (5%), or decreased in size (2%).[66] Children with the highest baseline nevus counts were those with the highest nevus volatility (ie, a proclivity for new and disappearing nevi).[11,13] Sunburns were associated with an increase in nevus counts in these children. Among 936 nevi followed over a 3-year period (age 11-14), nearly 31% of nevi had a change in global dermoscopic pattern.[11] The most frequent change was from a patterned (ie, reticular, globular, or complex) nevus to a homogenous nevus and vice versa; this type of pattern volatility was most frequent among children with a light pigmentary phenotype and a tendency to sunburn.[11]

Change in size of nevi in adolescence was common in the SONIC cohort. Of 404 back nevi followed from ages 11 to 17, >70% changed in surface area by ≥50%; 59% increased, 3% decreased, and 10% disappeared.[66] Nevus growth differed by global dermoscopic pattern: compared to reticular nevi, globular nevi were significantly more likely to increase in size (65% vs. 52%), and less likely to decrease (7% vs. 18%; $P = .02$ for both).[66] This growth characteristic difference by dermoscopic pattern was most pronounced for nevi with the greatest surface area at baseline ($P = .001$).[66]

In SONIC, we observed that the vast majority of disappearing nevi in childhood had no evidence of a clinical halo phenomenon or dermoscopic regression structures (ie, white scar-like areas and multiple blue-grey granules). Among 936 back nevi followed from ages 11 to 14 (n = 366 participants), 9 (1%) were noted to completely disappear without displaying a halo or regression structures in preceding images.[11] Preliminary analysis of 945 nevi from the back and legs followed from age 14 to 17 (n = 213 participants) showed that 22 nevi (2.3%) completely disappeared; all but 1 disappeared without a halo or regression (Fig 6; unpublished data). In 1 nevus, a clinical halo and dermoscopic blue-grey granularity were distributed symmetrically around and throughout the entire nevus, respectively. Disappearance of nevi was more common among children with higher nevus counts, suggesting that volatility may have clinical implications for melanoma risk.[13]

**Implications for clinical practice in children and risk of pediatric melanoma.** The use of total body photography in children and adolescents to identify new or changing nevi, and surgical removal based on change, are likely to have poor specificity given the volatility of nevi in this age group (Fig 7). Recent estimates in the United States and Europe suggest that between 594 and 982 benign nevi are removed for every 1 melanoma detected in individuals ≤19 years of age.[67,68] Banky et al[46] have shown that the likelihood of melanoma detection among new or changing lesions identified with total body photography is age-dependent, ranging from 0.4% of new lesions at <50 years of age to 30% of new lesions at >50 years of age. Similarly, Menzies et al[69] found that dermoscopic change in melanocytic lesions undergoing short-term follow-up (2.5-4.5 months) had poor specificity for the diagnosis of melanoma in children and adolescents.

Pediatric melanomas often fail to exhibit conventional ABCDE criteria, but change remains an important diagnostic clue despite its poor specificity. Change was present in nearly 100% of cases

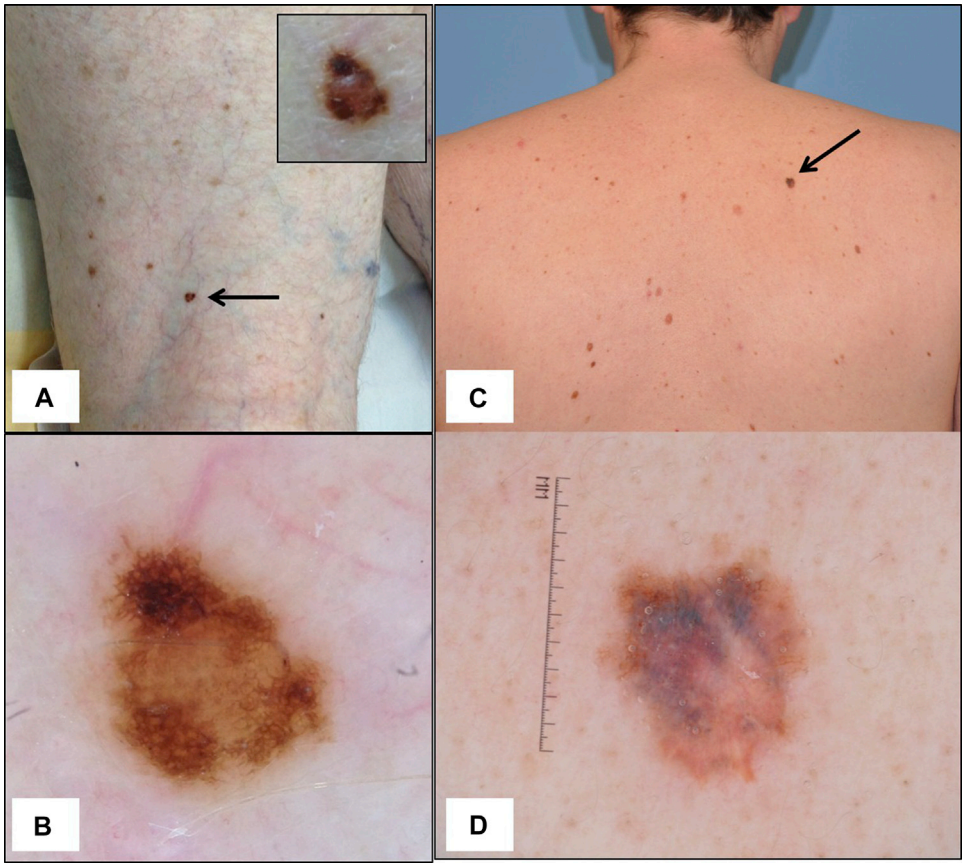



**Fig 5.** Melanoma. Lesions "too dark" for the patient's pigmentary phenotype. **A**, An 80-year-old man presented with multiple nevi, blue eyes, and Fitzpatrick skin phototype II, and reported blonde hair in his youth. A 5-mm papule (*arrow*) stands out as an ugly duckling based on its dark brown color. **B**, Dermoscopy reveals a central homogenous peripheral reticular pattern with a focal thickened network. This was a melanoma (0.45 mm in thickness). **C**, A 43-year-old man with multiple atypical nevi and without a history of melanoma presented for routine examination. A 9-mm macule (*arrow*) stands out as an ugly duckling based on its dark brown color. **D**, Dermoscopy reveals a multicomponent reticular pattern with variegate colors. This was a melanoma (0.95 mm in thickness).

from a recent pediatric melanoma cohort[70] (n = 70); therefore, a changing lesion that differs from a child's other nevi (ie, an ugly duckling) should be carefully examined, with the understanding that childhood melanoma may present alternate ABCDE features[70] (*a*melanosis, *b*leeding or *b*umps, uniform *c*olor, small *d*iameter or *d*e novo, and *e*volution). However, the clinical features described as ABCDE for pediatric melanoma are not specific for melanoma and could have a low predictive value. To avoid unnecessarily obtaining a biopsy specimen of common benign conditions in children with a similar description (eg, arthropod bite), lesions without clinical or dermoscopic features suggestive of melanoma could be closely observed. Because pediatric melanomas can be amelanotic, subtle dermoscopic clues in blood vessels may be pertinent. Menzies et al[71] evaluated 497 amelanotic and hypomelanotic skin lesions and identified predominantly central vessels, hairpin vessels, milky red-pink areas, >1 shade of pink, a combination of dotted and linear irregular vessels, and a predominance of linear irregular vessels, as the most important clues to the diagnosis of melanoma.

Disappearance and fading of nevi are not rare in childhood and adolescence and should not trigger alarm. Most of these nevi will disappear via gradual global fading of pigmentation, with transition of dermoscopic appearance from patterned to homogenous to eventual complete disappearance (Fig 6).

Additional research is required to develop useful criteria for recognizing high-risk lesions, to more clearly identify normal patterns of change in nevi during childhood and adolescence, and to determine how noninvasive technologies, such as sequential

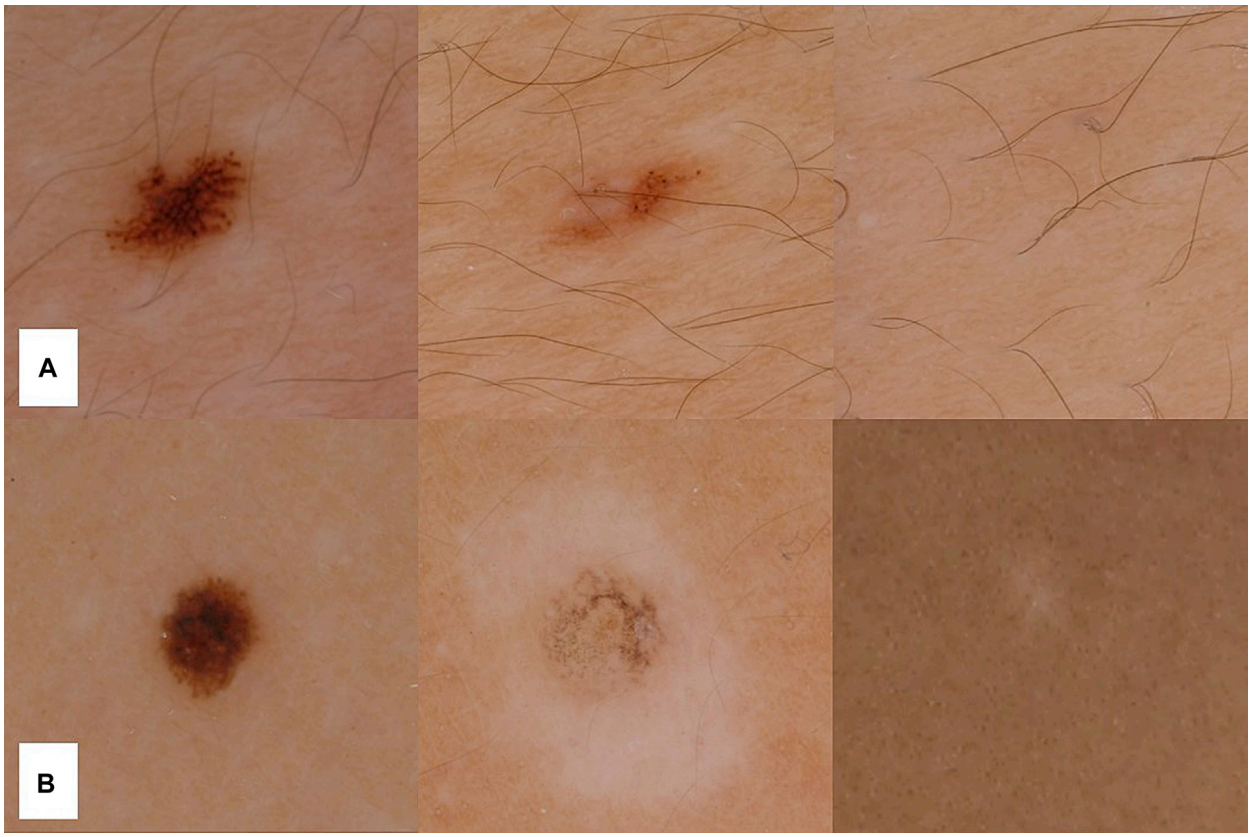



**Fig 6.** Nevi. Patterns of nevus disappearance in childhood. Among Study of Nevi in Children participants we noted 2 patterns of disappearance of nevi. The overwhelming majority of disappearing nevi showed only gradual fading of pigmentation pattern (**A**, upper panel), in contrast to the halo nevus phenomenon with blue-grey granularity (**B**, lower panel), which was infrequently seen.

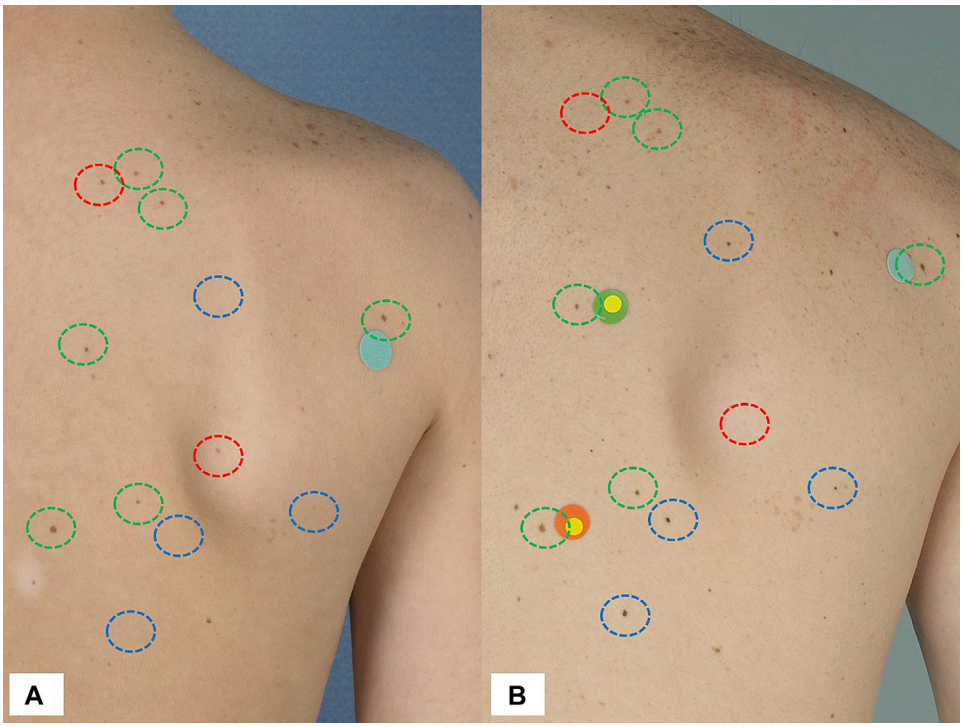



**Fig 7.** Nevi. Nevus volatility in childhood. Overview images of the back at (**A**) 11 years of age and (**B**) 17 years of age showing multiple new (*blue circles*), disappearing/fading (*red circles*), and stable nevi (*green circles*).

digital dermoscopic imaging, can be used to improve diagnostic accuracy in this age range.

In conclusion, the SONIC project has contributed to a more comprehensive understanding of the distribution, morphology, and host associations of melanocytic nevi. This knowledge may help in the detection of melanomas that are difficult to diagnose from appearance alone, based on their deviation from what is expected in benign nevi. Conversely, familiarity with the morphologic variations of nevi may reduce obtaining unnecessary biopsy specimens in children and adolescents. With advances in noninvasive imaging technologies and molecular studies, future studies will better define which nevi are stronger markers of melanoma risk, the effects of genetic–environmental interactions in nevogenesis, and the role of prevention strategies.

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