Distribution of congenital melanocytic naevi and congenital naevus-like naevi in a survey of 3406 Italian schoolchildren

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Summary

Background Scanty information is available on the prevalence of congenital melanocytic naevi (CMN) and congenital naevus-like naevi (CNLN), particularly the small ones.

Objectives To estimate the prevalence of CMN/CNLN in Italian schoolchildren, and to assess variations according to potential risk factors for melanoma.

Methods We conducted a survey in 13 Italian areas on 3406 schoolchildren aged 12–17 years. Children were examined by dermatologists who assessed pigmentary traits and made a count of small (6–15 mm in diameter) and medium/large (> 15 mm) CMN/CNLN on 19 anatomical areas.

Results Overall, 592 children (17·4%) had one or more CMN/CNLN. Prevalence of small CMN/CNLN was 16·1%, and that of medium/large CMN/CNLN was 1·8%. There was no difference between age groups and sexes. CMN/CNLN were more frequent in children with a higher number of common melanocytic naevi (multivariate odds ratio, OR = 7·1 for the highest vs. the lowest quartile), consistent in small (OR = 7·2) and medium/large CMN/CNLN (OR = 6·0). Family history of malignant melanoma (OR = 1·4) and personal history of diabetes (OR = 4·4) appeared to be directly, and sun exposure inversely associated with CMN/CNLN. No relation was evident between CMN/CNLN and pigmentary traits, anthropometric characteristics, dietary habits, freckles, sunburns, sunscreen use or history of selected diseases.

Conclusions The association with family history of melanoma, the strong association with acquired melanocytic naevi, and the lack of association with pigmentary traits and sunburns suggest that CMN/CNLN may act as an independent risk marker for subjects at increased risk for cutaneous melanoma later in life.

Congenital melanocytic naevi (CMN) represent pigment cell malformations that are visible at or shortly after birth.[1] CMN are generally classified according to the size of their largest estimated diameter, which varies from < 1 cm to lesions covering a large part of the skin (i.e. > 20 cm in diameter).[1] The classification of CMN in literature is variable; however, the one most used considers small (< 1·5 cm in diameter), medium (1·5–19·9 cm) and large or giant CMN (≥ 20 cm, or covering a substantial part – more than 30% – of the entire body surface).[2–4]

Whereas large CMN are rare (one in 20 000),[3,4] scanty information is available on the prevalence of small and medium CMN. In a recent study from southern Italy on 23 354 boys aged 18 years, the prevalence of medium/large CMN was 0·67% (0·54% had medium-sized CMN and 0·13% large-sized CMN).[2,5] Another study on 601 patients reported a prevalence of medium-sized CMN of 2·5%.[6]

Some studies in newborns found a prevalence of CMN, including small ones, ranging between 0·2% and 6%.[2,7–9] At least three studies considered CMN defined as moles with a diameter of 10 mm or larger present since birth: in a survey from Sweden on 524 children aged 8–9 years, CMN were found in 15 subjects (3%);[10] in another study from Canada on 1145 caucasian schoolchildren aged 6–18 years, CMN occurred in 1·7% of subjects;[11] in a study from Estonia, 39 of 549 children aged 9 years (7%) had one or more CMN at birth.[12]

Whereas medium and large CMN are always present at birth, some children develop early-onset naevi, usually small and visible by age 2 years, with both the clinical and histological characteristics of CMN, sometimes referred to as

'congenital naevus-like naevi' (CNLN).[3,13] The term CNLN has also been employed to identify lesions with clinical features of CMN when the information on onset is lacking or not reliable. CNLN may be considerably more common than CMN, and may affect 6–20% of adolescents and adults.[3,6,14] In a study of 939 children aged 8–16 years from Switzerland, CMN/CNLN were observed in 5·9% of children.[15] In another study on 1123 white Australian schoolchildren aged 6–15 years, the prevalence of medium-sized CNLN, usually > 15 mm, was 4·4%.[14] A study from Lithuania, on 484 children aged 1–15 years, found CMN on 3% of subjects,[16] and another one from Spain, on 1265 children aged 1–14 years, found CMN on 1·8% of subjects, mainly on the trunk.[17]

Patients with large CMN are at higher risk of neurocutaneous melanocytosis, a rare congenital syndrome consisting of multiple cutaneous naevi and abnormal melanocytosis of the central nervous system.[4,18,19] More importantly, there is substantial evidence that subjects with large or giant CMN have an increased risk – apparently greater during early childhood – of malignant melanoma (MM).[3,4,20] Subjects with large naevi have a 5–15% lifetime risk of MM.[3] However, for the rarity of the lesion, large CMN account for a small proportion of all MM.[3,4]

Scanty and controversial information is available on the role of small/medium CMN on MM risk.[2,3,7,20] In various clinical series or assemblages of case reports a high percentage of small CMN/CNLN was found to be associated with MM.[21–23] Therefore, the presence of small CMN or CNLN has been considered as a MM precursor by some authors.[6,14,21–24] However, to our knowledge, no epidemiological study analysing the association between small CMN/CNLN and risk of MM has so far been conducted.

In order to estimate the prevalence of small and medium-sized CMN/CNLN, and their association with other potential MM risk factors, we considered data from a large survey of schoolchildren from the North, Centre and South of Italy.

Materials and methods

During the spring of 1997, we conducted a multicentre study among schoolchildren attending the third class of a number of secondary schools in Italy. The methods of the study have already been described.[25,26] Briefly, we considered a total of 3406 European caucasian children (1746 boys and 1660 girls) aged 12–17 years, from 13 provinces of northern, central and southern Italy. Parents of the children filled in a questionnaire, including information about parents' education, family residence, children's anthropometric characteristics, personal history of selected diseases, family history of MM, dietary habits, use of sunscreen, lifetime sun exposure, pattern of reaction to sun exposure, and lifetime history of sunburns.

Children were examined individually by trained dermatologists in the school infirmary. Besides skin examination with an assessment of pigmentary traits, dermatologists counted different types of melanocytic naevi at 19 predefined anatomical sites.[26] An atlas was developed for the recognition of pigmentary lesions, and a naevometer was used to determine the size of the lesions. For each anatomical site considered, dermatologists counted, besides the number of acquired melanocytic naevi > 2 mm, the total number of acquired naevi > 6 mm, and, among these, the number of atypical naevi, also the total number of CMN 6–15 mm and number of CMN > 15 mm in diameter. CMN were either lesions for which an unambiguous documentation was provided that the naevus was present at birth (i.e. clinical documentation and/or photographs), or a lesion with clinical features of a CNLN, i.e. a well-circumscribed, palpable pigmentary lesion, with at least one hair shaft emerging from its surface.[6]

Unconditional multiple logistic regression models after adjustment for number of common acquired naevi, geographical area and total holiday sun exposure were fitted to obtain the odds ratios (ORs) of presence of total, small and medium/large CMN/CNLN, and the corresponding 95% confidence intervals (CIs). A backward stepwise selection analysis was performed to select which characteristics [among age, sex, geographical area, eye, hair and skin colour, number of common naevi, total holiday sun exposure and body mass index (BMI)] could influence the results. Variables excluded by the model (age, sex, eye, hair and skin colour, and BMI) were those whose corresponding χ^2 test did not reach 95% significance.

Table 1 Distribution of Italian schoolchildren by the presence of one or more congenital melanocytic naevi/congenital naevus-like naevi (CMN/CNLN) ≥ 6 mm, according to sex, age, geographical area and body mass index (BMI). Corresponding odds ratios[a] (ORs) and 95% confidence intervals (CIs)

Covariates	Total number of children, n	Children with one or more CMN/CNLN, n (%)	OR (95% CI)
Total	3406	592 (17·4)	
Sex			
Males	1746	309 (17·7)	1·00[b]
Females	1660	283 (17·0)	1·06 (0·88–1·28)
Age (years)			
12–13	2321	408 (17·6)	1·00[b]
14–17	785	158 (20·1)	1·18 (0·95–1·46)
Geographical area			
North	2043	379 (18·6)	1·00[b]
Centre	600	110 (18·3)	1·15 (0·90–1·47)
South	763	103 (13·5)	0·59 (0·46–0·76)
BMI (kg m^{-2})			
< 18·7	1132	204 (18·0)	1·00[b]
18·7–21·0	1129	208 (18·4)	0·99 (0·80–1·24)
≥ 21·1	1136	178 (15·7)	0·90 (0·71–1·13)

[a]Estimated by unconditional multiple logistic regression models after adjustment for number of common acquired naevi, geographical area and total holiday sun exposure. [b]Reference category.

Results

Of 3406 children, 592 (17·4%) had one or more CMN/CNLN: 443 children (13·0%) had one, 104 (3·1%) two, 24 (0·7%) three, and 21 (0·6%) four to nine CMN/CNLN. Prevalence of small CMN/CNLN was 16·1%, and that of medium/large CMN was 1·8%. There was no difference between sexes. Sixteen subjects (0·5%) had both small and medium/large CMN/CNLN.

Overall, 2·8% had small and 0·1% had medium/large CMN/CNLN on the head and neck. Corresponding percentages for upper limbs were 2·2% and 0·4%, for lower limbs 4·2% and 0·6%, for anterior trunk 4·8% and 0·4%, and for posterior trunk 5·1% and 0·6%, respectively.

Prevalence of CMN/CNLN was similar in strata of sex (multivariate OR = 1·06 for girls vs. boys) and age (OR = 1·18 for ≥ 14 vs. < 14 years), and they appeared to be less frequent in children residing in southern compared with northern Italy (OR = 0·59) (Table 1). No significant association was shown for BMI (OR = 0·90 for the third vs. the first tertile), body surface area (OR = 0·93), weight (OR = 0·98) or height (OR = 1·12). CMN/CNLN were more frequent in children with a higher number of common melanocytic naevi (OR = 7·13 for the highest vs. the lowest level). Conversely, CMN/CNLN did not appear to be related to pigmentary traits including eye, hair and skin colour and freckles (Table 2), sunburns or sunscreen use. An inverse association was found between CMN/CNLN and a proxy of sun exposure (OR = 0·75 for ≥ 1500 vs. < 500 h of lifetime holiday sun exposure) (Table 3).

Children residing in southern compared with northern Italy had less frequently small (OR = 0·50), but more frequently medium/large CMN/CNLN (OR = 2·61). The association with common melanocytic naevi was consistent in small (OR = 7·23 for the highest vs. the lowest level) and medium/large CMN/CNLN (OR = 6·00) (Table 4).

Of 140 children with family history of MM, 34 (24·3%) had one or more CMN/CNLN corresponding to a multivariate OR of 1·44 (95% CI 0·95–2·19). The corresponding estimate for small CMN/CNLN was 1·39 (95% CI 0·91–2·14)

Table 2 Distribution of Italian schoolchildren by the presence of one or more congenital melanocytic naevi/congenital naevus-like naevi (CMN/CNLN) ≥ 6 mm, according to selected pigmentary traits and lesions. Corresponding odds ratios[a] (ORs) and 95% confidence intervals (CIs)

Covariates	Total number of children, n	Children with one or more CMN/CNLN, n (%)	OR (95% CI)
Eye colour			
Black/brown	1463	226 (15·4)	1·00[b]
Hazel	699	135 (19·3)	1·12 (0·88–1·43)
Brown/grey	390	74 (19·0)	1·02 (0·75–1·37)
Green/grey	451	71 (15·7)	0·83 (0·61–1·12)
Blue	403	86 (21·3)	1·12 (0·84–1·50)
Hair colour			
Black	322	44 (13·7)	1·00[b]
Dark/medium brown	1615	261 (16·2)	1·13 (0·79–1·62)
Light brown	1077	209 (19·4)	1·27 (0·88–1·83)
Blond/red	392	78 (19·9)	1·20 (0·79–1·82)
Skin complexion			
Dark	467	67 (14·3)	1·00[b]
Medium	1941	335 (17·3)	0·95 (0·71–1·28)
Fair	989	189 (19·1)	0·89 (0·65–1·23)
Number of naevi > 2 mm			
< 5	781	48 (6·1)	1·00[b]
5–10	854	108 (12·6)	2·15 (1·51–3·08)
11–21	880	169 (19·2)	3·61 (2·57–5·06)
≥ 22	891	267 (30·0)	7·13 (5·13–9·91)
Freckles (at least one site)			
1 (none)	2665	453 (17·0)	1·00[b]
2–3 (low)	545	105 (19·3)	0·82 (0·64–1·06)
4–6 (high)	196	34 (17·3)	0·80 (0·53–1·19)

[a]Estimated by unconditional multiple logistic regression models after adjustment for number of common acquired naevi, geographical area and total holiday sun exposure. [b]Reference category.

Table 3 Distribution of Italian schoolchildren by the presence of one or more congenital melanocytic naevi/congenital naevus-like naevi (CMN/CNLN) ≥ 6 mm, according to lifetime sun exposure, pattern of reaction to sun exposure, lifetime history of sunburns, and use of sunscreen. Corresponding odds ratios[a] (ORs) and 95% confidence intervals (CIs)

Covariates	Total number of children, n	Children with one or more CMN/CNLN, n (%)	OR (95% CI)
Lifetime holiday sun exposure (h)			
< 500	1239	221 (17·8)	1·00[b]
500–1499	993	178 (17·9)	0·85 (0·68–1·07)
≥ 1500	1174	193 (16·4)	0·75 (0·60–0·94)
Burn			
Never	628	94 (15·0)	1·00[b]
Seldom	1279	237 (18·5)	1·14 (0·87–1·49)
Sometimes	908	155 (17·1)	0·91 (0·68–1·21)
Always	500	97 (19·4)	1·08 (0·78–1·50)
Tan			
Dark	1906	321 (16·8)	1·00[b]
Medium/no	1424	259 (18·2)	0·91 (0·75–1·10)
Sunburns			
None	1411	257 (18·2)	1·00[b]
1	868	136 (15·7)	0·73 (0·58–0·93)
≥ 2	1029	187 (18·2)	0·82 (0·66–1·01)
Sunscreen use			
Never	438	73 (16·7)	1·00[b]
Sometimes	1547	266 (17·2)	0·90 (0·67–1·21)
Always	1370	244 (17·8)	0·85 (0·63–1·14)

[a]Estimated by unconditional multiple logistic regression models after adjustment for number of common acquired naevi, geographical area and total holiday sun exposure. [b]Reference category.

Covariates	Children with one or more small CMN/CNLN		Children with one or more medium/large CMN/CNLN	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Total	547 (16·1)		61 (1·8)	
Sex				
Males	284 (16·3)	1·00[b]	35 (2·0)	1·00[b]
Females	263 (15·8)	1·08 (0·89–1·31)	26 (1·6)	0·82 (0·49–1·38)
Age (years)				
12–13	379 (16·3)	1·00[b]	41 (1·8)	1·00[b]
14–17	145 (18·5)	1·15 (0·92–1·43)	16 (2·0)	1·29 (0·71–2·33)
Geographical area				
North	364 (17·8)	1·00[b]	23 (1·1)	1·00[b]
Centre	97 (16·2)	1·03 (0·80–1·33)	14 (2·3)	2·50 (1·27–4·94)
South	86 (11·3)	0·50 (0·38–0·65)	24 (3·1)	2·61 (1·45–4·72)
BMI (kg m^{-2})				
< 18·7	192 (17·0)	1·00[b]	18 (1·6)	1·00[b]
18·7–21·0	192 (17·0)	0·97 (0·77–1·22)	20 (1·8)	1·01 (0·53–1·94)
≥ 21·1	161 (14·2)	0·87 (0·69–1·10)	23 (2·0)	1·16 (0·62–2·18)
Number of naevi ≥ 2 mm				
< 5	43 (5·5)	1·00[b]	5 (0·6)	1·00[b]
5–10	95 (11·1)	2·07 (1·42–3·01)	15 (1·8)	2·98 (1·07–8·27)
11–21	162 (18·4)	3·82 (2·68–5·44)	8 (0·9)	1·53 (0·49–4·71)
≥ 22	247 (27·7)	7·23 (5·12–10·2)	33 (3·7)	6·00 (2·31–15·6)
Freckles (at least one site)				
None	413 (15·5)	1·00[b]	52 (2·0)	1·00[b]
Low	101 (18·5)	0·85 (0·66–1·10)	7 (1·3)	0·70 (0·30–1·63)
High	33 (16·8)	0·86 (0·57–1·29)	2 (1·0)	0·52 (0·12–2·22)

Table 4 Distribution of Italian schoolchildren by the presence of one or more small (6–15 mm) or medium/large (> 15 mm) congenital melanocytic naevi/congenital naevus-like naevi (CMN/CNLN), according to sex, age, geographical area, body mass index (BMI) and pigmentary lesions. Corresponding odds ratios[a] (ORs) and 95% confidence intervals (CIs)

[a]Estimated by unconditional multiple logistic regression models after adjustment for number of common acquired naevi, geographical area and total holiday sun exposure. [b]Reference category.

and for medium/large CMN/CNLN was 2·25 (95% CI 0·87–5·82). Among the diseases investigated, diabetes was the only one associated with CMN/CNLN (OR = 4·39; 95% CI 1·55–12·4), consistent for small (OR = 3·74; 95% CI 1·28–10·9) and medium/large CMN/CNLN (OR = 3·91; 95% CI 0·49–31·5). Conversely, a history of thyroid diseases (OR = 1·51), asthma (OR = 0·96), hepatitis (OR = 1·31), psoriasis (OR = 0·90) or vitiligo (OR = 0·92) was not associated with CMN/CNLN.

None of the dietary items investigated was associated with CMN/CNLN, the OR for the highest vs. the lowest consumption level being 1·13 for milk, 0·85 for meat, 1·01 for liver, 0·99 for carrots, 0·89 for vegetables, 1·19 for tomatoes, 0·99 for fruit, 0·87 for eggs, 0·78 for processed meat, 0·88 for fish and 0·87 for cheese.

Discussion

In the present large study, we found that 17·4% of schoolchildren had one or more CMN/CNLN. This is the highest prevalence of CMN/CNLN found so far. The large differences with previous studies considering small CMN/CNLN, whose prevalence ranged between 0·2% and 7%,[2,7,12] are mainly due to the discrepancies in the definition of CMN/CNLN. We considered all CMN/CNLN of 6 mm or larger, in contrast with some studies counting among small CMN/CNLN only those with a diameter ≥ 1 cm.[10–12] We grouped together CMN and CNLN, as we were interested in naevi with features of CMN, while the presence at birth especially for small naevi was difficult to obtain retrospectively in a reliable way. The relatively high prevalence could also be due to the detailed dermatological visit, as dermatologists counted both small and medium/large CMN/CNLN in 19 different anatomical areas.[26] Finally, difficulties in diagnosing CMN/CNLN may contribute to the discrepancies we found. The prevalence of medium/large CMN/CNLN was in broad agreement with the findings of another study.[6]

We confirm that CMN/CNLN affect preferentially the trunk,[15,17] while the head and neck and upper limbs are spared. This notion remained valid when surface area of various body sites was taken into account.

We found no significant association between CMN/CNLN and sex. This finding is apparently in contrast with some studies showing a higher prevalence of large CMN in females,[1,27–30] but is in agreement with some other studies on small CMN/CNLN.[11,14,15] In our population, CMN/CNLN did not vary with age, confirming the suggestion that congenital naevi develop early in life.[14]

The strong association found between CMN/CNLN and common naevi (the most important risk factor for MM),[31]

consistent among naevus sizes (small and medium/large naevi), is in broad agreement with some[15,24] but not all studies.[10–12]

We did not find any association between CMN/CNLN and pigmentary traits, including hair, eye and skin colour, in contrast with some, but not all,[11] studies that showed that CMN/CNLN occurred more frequently in dark types of skin complexion.[9,14,15] We found no relation between CMN/CNLN and freckles, in agreement with two previous studies,[11,14] or with propensity to sunburn, in agreement with one study,[11] but in contrast with another one, which showed a lower prevalence of CMN/CNLN in subjects who burn first.[14] We found a direct association between CMN/CNLN and family history of MM, consistent in small and medium/large naevi, although the estimates did not reach statistical significance due to the relatively small number of children with a family history of MM. This was in apparent contrast with a study on 420 newborns, where all 19 babies with a family history of MM had no CMN.[9]

To our knowledge, this is the first study providing data on the association between CMN/CNLN and anthropometric characteristics, dietary habits, sunscreen use and personal history of selected diseases. History of diabetes was associated with CMN/CNLN, although the estimates were based on a small number of children with CMN/CNLN and diabetes.

The association with sun exposure is difficult to explain, but gives further assurance that acquired melanocytic naevi were not assigned to CMN/CNLN. However, given the large number of estimates provided by the present study, some significant associations, including the direct one with diabetes and the inverse one with sun exposure, could be given by chance due to the lack of consideration of multiple testing in the present analyses. Among the other weaknesses of the present study there is the impossibility to compare our findings with those of other investigations defining small CMN as naevi with a diameter > 1 cm,[10–12] to derive estimates separately for medium and large CMN/CNLN, considered as major risk factors for MM,[1,3] and to verify whether the CNLN were present at birth.

Among the strengths of the study there is the uniquely large number of participants, the multicentre design, the fact that children were examined by dermatologists who counted various pigmentary lesions, including CMN/CNLN, and made judgements on pigmentary traits, the large number of different body areas considered, and the possibility to allow in the models for several covariates.

This is one of the few studies providing data on small CMN/CNLN, and adds further relevant information on the prevalence and the anatomical distribution of CMN/CNLN, and their relationship with other factors. The association found with family history of MM, the strong association with acquired melanocytic naevi, and the lack of association with pigmentary traits and sun exposure, suggest that the presence of (small) CMN/CNLN selects a population at higher risk of MM. Thus, future observational epidemiological investigations should consider CMN/CNLN, to clarify and quantify their role on the risk of MM.

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