Dermatol Ther (Heidelb) (2022) 12:2453–2488
https://doi.org/10.1007/s13555-022-00806-x

REVIEW

Body Site Distribution of Acquired Melanocytic Naevi and Associated Characteristics in the General Population of Caucasian Adults: A Scoping Review

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Received: July 19, 2022 / Accepted: August 30, 2022 / Published online: September 30, 2022
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ABSTRACT

The number of melanocytic naevi is a major risk factor for melanoma. The divergent pathway hypothesis proposes that the propensity for naevus proliferation and malignant transformation may differ by body site and exposure to ultraviolet (UV) radiation. This scoping review aimed to summarise the evidence on the number and distribution of naevi (≥ 2 mm) on the body overall and by individual anatomical sites in Caucasian adults, and to assess whether studies used the International Agency for Research on Cancer (IARC) protocol to guide naevus counting processes. Systematic searches of Embase and PubMed identified 661 potentially relevant studies, and 12 remained eligible after full-text review. Studies varied widely in their counting protocols, reporting of naevus counts overall and by body sites, and used counting personnel with differing qualifications. Only one study used the IARC protocol. Studies reported that the highest number of naevi was on the trunk in males and on the arms in females. Body sites which receive intermittent exposure to UV radiation had higher density of naevi. Larger naevi (≥ 5 mm) were detected mostly on body sites intermittently exposed to UV radiation, and smaller naevi (< 5 mm) on chronically exposed sites. Studies reported that environmental and behavioural aspects related to UV radiation exposure, as well as genetic factors, all impact body site and size distribution of naevi. This review

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Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-022-00806-x.

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found that to overcome limitations of the current evidence, future studies should use consistent naevus counting protocols. Skin surface imaging could improve the reliability of findings. An updated IARC protocol is required that integrates these emerging standards and technologies to guide reliable and reproducible naevus counting in the future.

Keywords: Body site distribution; Melanocytic naevi; Melanoma; Melanoma risk; Moles; Population-based adults

Key Summary Points

Melanocytic naevi are benign pigmented lesions resulting from melanocytic proliferation. Having many naevi indicates melanoma risk profile, and up to 30% of melanomas may directly arise from a naevus.

It is important to study the body site-specific distribution of naevi to better understand the apparent regional variation in their susceptibility for malignant transformation. Hence, body site distribution of naevi has been a subject of research in dermatology for many years, and is summarised in this review.

The existing studies on site distribution of melanocytic naevi vary widely in their naevus counting and reporting methodology, and how they aggregated body sites and naevus sizes for analysis and reporting.

Research shows that environmental and behavioural aspects related to ultraviolet (UV) radiation exposure, as well as genetic factors, all impact the number, site distribution and size of melanocytic naevi.

Given the important role that naevi play in the development and understanding of melanoma, future studies should use large population-based samples and standardised naevus counting protocols. Comparable studies using non-white populations and people of colour are lacking.

INTRODUCTION

Melanocytic naevi are benign pigmented skin lesions that start to appear on the skin in childhood. Besides skin, hair and eye colour, the number of common and atypical naevi constitutes the most important phenotypic risk factor for cutaneous melanoma [1]. Naevi were considered to be an obligatory precursor for the majority of cutaneous melanomas [2–4]. However, more recent studies found low associations between site-specific naevus distribution and naevus-related melanomas (ratio on face 1:6, back 1:2) [5], suggesting that the proportion of melanomas arising from melanocytic naevi was likely overestimated [2, 6, 7]. Remnants of naevus tissue are only found in approximately 30% of melanoma histopathology specimens [8], and studies suggest that melanomas arising from naevi and other melanomas follow divergent body site distribution and pathways [9].

Several studies reported that the density of melanocytes differs by anatomical location [10–13]. This supports the hypothesis that different body sites may differ in their susceptibility for melanocytic proliferation and malignant transformation [14, 15]. The location of a particular melanocyte may also affect its likelihood of being exposed to ultraviolet (UV) radiation [5]. Whiteman et al. proposed the divergent pathway hypothesis [16] that acute and chronic UV radiation exposure give rise to melanoma in different ways. This hypothesis suggests that people with inherently low propensity for melanocytic proliferation (and therefore often low naevus counts) require chronic UV exposure to stimulate the development of melanoma. In contrast, individuals

with an inherently high propensity for melanocytic proliferation (and often high naevus count) only need a low dose of UV radiation exposure to promote the onset of melanoma. For these people, melanoma more often occurs at a younger age, and in body areas most covered by clothing such as the back [16, 17]. Given their important role in melanoma risk prediction, multiple studies recommended detailed assessment of naevus counts and body site distribution [1, 18–20].

In 1990, the International Agency for Research on Cancer (IARC) developed a standard protocol for identifying, counting and reporting naevi [21]. This protocol provides guidelines for differentiating a naevus from other skin lesions, definitions and boundaries of anatomical body sites, and how to categorise anatomical sites for naevus reporting. Despite this, it is unknown how many studies have followed the IARC protocol, what other naevus identification and counting methods were used, and what influence this may have on estimated naevus counts by anatomical site [22].

This scoping review summarises the evidence on the distribution of melanocytic naevi (referred to as naevi henceforth) by anatomical sites in the general population of Caucasian adults, reports on factors associated with body site distribution, and identifies whether studies used the IARC protocol to guide their naevus counting processes.

METHODS

This review followed guidelines by Arksey and O'Malley [23] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses—Extension for Scoping Reviews (PRISMA-ScR) [24], and is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Eligibility Criteria

Studies reporting the prevalence of naevi $\geq$ 2 mm in diameter by specific body sites in population-based samples of the adult general population (majority of participants $\geq$ 18 years) from any country, written in English, were eligible. Cross-sectional or longitudinal population-based studies were included, as well as control groups from melanoma case-control studies. Clinical studies were only eligible if conducted outside dermatology settings, as people attending dermatology clinics may have higher risk for melanoma or skin cancer. Reviews [25], abstracts and pooled analyses [14] were excluded. Studies concerned solely with naevus-related syndromes (e.g. familial dysplastic naevus syndrome, giant congenital melanocytic naevi), considered only a specific type of naevus (e.g. halo naevus, blue naevus), reported self-counted naevi or counted naevi on only a specific part of the body (e.g. arm) or focussed on children or adolescents were also excluded.

Information Sources and Search Strategy

PubMed and Embase databases were searched in May 2021 using a combination of keywords and Medical Subject Heading (MeSH) terms (Appendix 1). Additional studies were identified by manually screening the references and citations of the search results.

Selection of Sources of Evidence

The web-based Covidence application [26] was used for screening of the studies. Duplicates in the combined search results were identified and removed. Relevance of the studies was assessed from the title and abstract, and the full text of potentially relevant studies were reviewed for the consideration of inclusion by one reviewer (D.J.), and conflicts were resolved by discussing with a second reviewer (M.J.).

Data Extraction and Synthesis

From each article, we extracted the following: first author, year of publication, country, study design, study objective, sample size, age range of participants, inclusion or exclusion criteria, sizes of naevi considered, who conducted the counts and their qualifications, and average

total naevus count (Table 1). We further extracted whether naevus counts or naevus density (e.g. naevus count per m^2 or naevus counts per body site), or both (where reported) were reported; body sites excluded from naevus counting; categorisation of body sites used; body surface area calculations; body site distribution of naevi and associated factors; and whether there were measures taken to address inter- and intra-observer variation (Table 2). Due to the major inconsistencies in how studies reported results, the naevus counts per body site were not able to be quantitatively summarised. Overview results are reported, with detailed results from each individual study provided in Table S1. Patterns of body site distribution of naevi were summarised across studies, in relation to participant characteristics such as sex, age and phenotype.

RESULTS

The PRISMA flow diagram (Fig. 1) summarises the search and screening results. A total of 661 articles were identified. After removal of duplicates ($n = 75$), and screening of titles and abstracts, 115 articles remained for full text review. According to the eligibility criteria, 18 articles [19, 27–43] were potentially suitable to be included. However, duplication of study samples was identified in nine studies and required further exclusions. If two studies reported on the same sample, the study focusing on body site distribution of naevi was selected for inclusion (e.g. [28] was used, while [19 and 40] were excluded). This resulted in exclusion of five publications [19, 39–42]. If a study sample was used to answer two relevant research questions and the results did not overlap, both publications were included [34, 44]. One study [43] was excluded because the majority of the participants in the sample (55%) were younger than 18 years. Therefore, a total of 12 studies remained for review.

Characteristics of Sources of Evidence

One study was from the USA [28], one from Australia [35], and 10 were from Europe [27, 29–34, 36–38] (Table 1). Study designs included one randomised control trial [37], five case-control studies [27, 28, 35, 36, 38], and five cross-sectional studies [29–33], while one study was a heritability and genome-wide association study using twins [34]. The 12 studies reported data from 9593 participants, whose age ranged from 15 to 92 years. Ten (91%) studies included only Caucasian participants [28–37]. Out of the five case-control studies, four matched the controls to cases with regards to sex and age [28, 35, 36, 38], one study [29] used visitors to patients in hospital wards, and three [28, 35, 36] used data from patients in a hospital setting other than dermatology clinics as the sample. One study [33] which recruited participants from patients in a hospital setting, included 31 people (16%) with psoriasis. Only three studies [27, 30, 32] used a general population-based sample.

Naevus Counting and Reporting

One study [33] was published before the IARC protocol was available, and of the remaining 11 studies, only one [36] explicitly mentioned that it followed the IARC protocol. The reporting of naevus size differed between studies (Table 1). For example, Richard et al. [37] used naevus categories of 2–4.99 mm and $\geq$ 5 mm, while Randi et al. [36] used 2–5.99 mm and $\geq$ 6 mm. The experience and qualification of personnel differed widely. Five studies [29, 32, 33, 36, 37] reported that counting was done only by dermatologists, two studies [28, 35] by dermatologists and other trained clinical staff, one study [27] by a doctor (not further specified), and four studies [30, 31, 34, 38] by nurses trained by dermatologists (Table 1). Four studies [27, 29, 30, 33] reported how they reduced inter- and intra-observer variation, and two studies quantified the inter-observer correlation of total naevus counts, which was $r = 0.88$ in [35] and $r > 0.75$ for intra and inter-observer correlation [36], respectively.

Most studies ($n = 10$) reported overall naevus counts, two studies [32, 37] reported naevus density by body site, based on body surface area calculations proposed by Lund and Browder

Table 1 Characteristics of the included studies

First author (year) & country	Type of study	Main objectives of the study	Sample size (female percentage)	Characteristics of the sample		Naevus counting		Average total naevus count		
						Naevus size classes considered	Counted by			
				Age range	Inclusion and exclusion criteria			Total	Male	Female
English (1988), Scotland	Cross sectional	Assessing the relationship between naevus counts at different body sites, and between site-specific naevus counts and total body counts	197 (61%)	15–84	Caucasians Recruited patients from a hospital setting (Included 31 people with psoriasis)	≥2 mm	Two trained dermatologists	12	9	14
Augustsson (1992), Sweden	Cross sectional	Assessing the influence of different UV exposure types on naevus formation through body site distribution of naevi, association between site specific naevus counts and total body naevus counts	310 (51%)	30–50	Caucasians Randomly selected from a census file of the target population	≥2 mm	One trained dermatologist	66*	69	63
Richard (1993), France	Randomised controlled trial	Assessing the role of sun exposure on naevus counts in an age-sex phenotype-controlled population	Red phenotype—150 (0%) Dark phenotype—150 (0%)	17–24	Parents or grandparents not being black, Arabic or Asiatic Randomly selected from an armed forces recruitment centre	≥2 mm but < 5 mm ≥5 mm	One experienced dermatologist	[a]	[a]	[a]
Holly (1994), USA	Case control	Determining whether naevus counts by anatomical site correlated with total body naevus counts, and to determine which body site counts best correlated with total body counts	Controls—139 (51%)	20–74	White Controls were proportionally matched to the melanoma patients by race, gender and age within 5 years from outpatient clinics in the same hospitals as cases without dermatological conditions	≥2 mm	A dermatologist and a dermatology fellow	36	[a]	[a]

Table 1 continued

First author (year) & country	Type of study	Main objectives of the study	Sample size (female percentage)	Characteristics of the sample		Naevus counting		Average total naevus count		
						Naevus size classes considered	Counted by			
				Age range	Inclusion and exclusion criteria			Total	Male	Female
Grulich (1996), Australia	Case control	Assessing the relationship between risk of cutaneous malignant melanoma and total-body and site-specific naevus counts and other host factors	Controls –276 (45%)	15–84	White Controls were proportionally matched to the melanoma patients by race, gender and age from the same hospitals as cases without dermatological conditions	≥2 mm Separately recorded ≥5 mm but < 9 mm ≥1 mm	A dermatologist and a trained medical epidemiologist	29	[a]	[a]
Dabkowski (1997), Poland	Case control	Evaluating the importance of the number of common melanocytic naevi, the presence of atypical naevi, and various pigmentary phenotypic features as risk factors for malignant melanoma	Controls—300 (57%)	21–80	A randomized sample from the population, not matched with the cases	2–5 mm (According to their definition of a naevus)	Doctor	15	19	12
Farinas-Alvarez (1999), Spain	Cross sectional	Examining the relationship between naevus numbers at different sites as predictors of total-body naevus count	146 (66%)	21–78	Caucasian In a hospital setting—Visitors to patients in wards other than dermatology, and who were without acute disease at the time of the study	≥2 mm	One dermatologist	35	36	35
Randi (2006), Italy	Case control	Assessing and quantifying the site-specific association between risk of melanoma and number of naevi	Controls—538 (57%)	15–92	Caucasian Controls were age- and gender-matched with melanoma patients from the same hospitals as cases without dermatological conditions	≥2 mm but < 6 mm ≥6 mm	Trained dermatologists (number unspecified)**	12	13	11

Table 1 continued

First author (year) & country	Type of study	Main objectives of the study	Sample size (female percentage)	Characteristics of the sample		Naevus counting		Average total naevus count		
				Age range	Inclusion and exclusion criteria	Naevus size classes considered	Counted by	Total	Male	Female
Silva Idos (2008), UK	Cross sectional	Investigating the effect of sun exposure during foreign holidays on nevus counts and skin aging among young white women living in a temperate climate	754 (100%)	18–46	White A population-based sample of female residents from age-sex registers from 3 general practices	≥2 mm	Three nurses trained by a dermatologist	58	[b]	58
Newton-Bishop (2010), UK	Case control	Investigating the risk associated with naevus phenotype in relation to patterns of sun exposure	Controls—960 ([b])	18–76	Skin types or ethnicity not reported Randomly invited family members with the same sex and within the same 5-year age group as a case	≥2 mm	3 trained research nurses	[a]	[a]	[a]
Ribero (2016), UK	(i) Cross sectional data from a twin study	Assessing the predictive value of naevus count on 17 different body sites in estimating total-body naevus count	3694 (100%)	Median 47 (IQR 37–55)	Healthy Caucasian twins of European ancestry	≥2 mm	Trained nurses (number unspecified)	32	[a]	[a]
	(ii) General population control group from a case–control study (Bataille et al. 1996)	Validating the results from the twin study by replicating in the general population control group	Controls—415 (61%)	Median 45 (Range 16–80)	Caucasian Approximate frequency matching for sex and age of the cases recruited from outpatient clinics and general practice surgeries within the same region as cases	≥2 mm	Two dermatologists	33	[a]	[a]

Table 1 continued

First author (year) & country	Type of study	Main objectives of the study	Sample size (female percentage)	Characteristics of the sample		Naevus counting		Average total naevus count		
				Age range	Inclusion and exclusion criteria	Naevus size classes considered	Counted by	Total	Male	Female
Visconti (2020), UK	Heritability study/ genome-wide association study	Investigating the association of sex, genetic and environmental factors, and common DNA variants with the site distribution of naevi	3524 (94%)	Age not reported	Healthy Caucasian twins of European ancestry	≥2 mm	Trained nurses (number unspecified)	[a]	[a]	[a]

[a]Not defined
[b]Not applicable
*Mean naevus density per unit m^2
**The IARC protocol was used to count and record naevi

[45], while one study [35] reported only naevus count categories (Table 2). Only one study [32] did not exclude any part of the body, while most studies [28, 30, 31, 33, 35, 37, 38] did not count on genitalia and breasts in females, and four studies [28, 31, 35, 36] did not include the scalp in the counting protocols. One study [27] used dermoscopy to discriminate naevi from non naevi (Table 2).

Naevus Counts

Studies reported a mean total-body naevus count ranging between 12 and 58 naevi [27–31, 33, 35, 36].

Naevus Counts and Distribution by Sex

Males had on average 9–36 naevi, while females had 14–58 naevi [27, 29, 30, 33, 36] (Table 1). Ten studies reported that naevus counts by body sites varied with sex [27–36].

Most studies ($n = 9$) reported naevus counts by specific body sites for males and females separately. Five studies reported that males had the highest number of naevi on the trunk (one study on the upper back [28], one on thorax [29], two studies on the posterior trunk [35, 36], one on trunk [27]) and one study on upper limbs [33]. In comparison, only one study reported that females had the highest naevus counts on the trunk [27], six on the arms (four on arms [29, 30, 33, 36]; two on upper arms [28, 31]) and one on legs [35].

One study reported a higher mean number of naevi in every anatomical location in males compared with females, although statistical significance was not shown [27]. According to two studies, males had more naevi on the following body sites than females: buttocks, chest and back (one study, $p < 0.01$) [32], and on the trunk (one study, $p < 0.001$) [33]. According to three studies, females had more naevi than males on the face (one study, $p < 0.01$) [32] and lower limbs or parts of lower limbs (three studies, thigh: $p = 0.05$ [29]; anterior surface of the thigh: $p < 0.01$ [32] and lower limbs: $p < 0.01$ [32, 33]).

Table 2 Description of naevus distribution by body sites and associated factors

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
English (1988)	Count	Scalp, genitalia	Upper limbs, lower limbs, trunk, face and neck, palms and soles	[a]	Age: mean total naevus count and mean naevus count of each site with extensive numbers, decreased with age Sex: higher total naevus counts for women than men in every age group. Women had a higher number of naevi on upper limbs and lower limbs, while men had greater numbers on trunk Associations between body sites: high correlation between counts on upper limbs and trunk (males: 0.71, females:0.7), lower limbs and trunk (males: 0.61, females:0.61), upper limbs and lower limbs (males: 0.55, females:0.71) which were statistically significant ($p < 0.001$)	Simultaneous examination of the subjects by the second dermatologist to improve validity

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					Association with total naevus count: greatest associations with the total naevus count were with the naevus count on the upper limbs and lower limbs in females ($r = 0.91$) and trunk in males ($r = 0.9$) ($p < 0.001$). The upper arm is the strongest predictor for the total body count (r^2 not given)	
Augustsson (1992)	Mean number of naevi per unit surface area	None	16 body sites categorized based on clothing habits and UV exposure	Number of naevi per unit surface area using the estimates of Lund and Browder with minor adjustments. Four percent of their calculated area was subtracted from the arms and added to the trunk area	Site distribution: highest mean naevus count was on the lateral arm (three times that of the expected value), followed by the back (twice as many on the back than the expected value). Low ratios between observed counts and expected counts were seen on scalp, hands (palm and back of palm) and soles	[b]

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					Sex: after adjustment of total naevi count, significantly high number of naevi on chest, back and buttocks in men, and face, anterior thighs and lower legs in females UV exposure: naevus density was higher in UV-exposed skin than areas rarely exposed. Intermittently exposed areas had a higher naevus density than chronically and rarely exposed areas ($p < 0.001$) Phenotype: there was no significant difference in regional distribution of naevi between people with type I and II, and people with type III and IV skin colour	

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					Distribution of dysplastic naevi (DN): presence of DN was highest on trunk, a few in extremities and approximately none on face or upper chest. Presence of DN had no difference on relative regional distribution of naevi. DN density was higher in UV exposed skin than areas rarely exposed. Difference of naevi counts on intermittently exposed and rarely exposed areas were higher in subjects with DN than those without ($p < 0.001$). Men had more DN on the trunk than women ($p < 0.05$).The site distribution of DN is different to that of naevus (UV may not be the major aetiological factor for the development of DN)	

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					Association with total naevus count: highly significant correlations with total naevus count and counts on anterior thigh, lateral arm and back ($p < 0.001$). The best predictor for total naevus count was the anterior thigh ($r^2 = 0.72$) and the correlation increased when it was combined with the count on lateral arm ($r^2 = 0.87$)	
Richard (1993)	Count and mean density per m^2 both	Scalp, genitalia	29 body sites	Number of naevi per unit surface area using the estimates of Lund and Browder divided by 1.78 (corresponding to the mean surface area (1.78 m^2) estimated in 17- to 24-year-old men) to calculate the mean densities in naevi per m^2	Phenotypes: in both red and dark phenotype groups, the lowest mean density of < 5 m naevi was on the buttocks. In the dark phenotype (DP) group, the highest mean density of < 5 mm naevi was on face and neck, and in the red phenotype (RP), the highest was on the neck, outer forearms and dorsum of the hand UV exposure:	[b]

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					1. Sun exposure categories on body—on upper arm and lower arm, the number of small naevi (< 5 mm) was significantly higher on outer arm than the inner arm ($p < 0.0001$ both). The mean density of < 5 mm naevi was higher on chronically exposed areas than intermittently exposed areas ($p < 0.0001$) and higher on intermittently exposed areas than rarely exposed areas ($p < 0.0001$) in both phenotype groups	

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					2. Sun burns—in the RP group, the mean number of $\geq$ 5 mm naevi was higher on chronically ($p < 0.05$) and intermittently ($p < 0.05$) exposed areas of those who experienced at least two or more severe sunburns than others. This relationship was not significant for $\geq$ 5 mm naevi on rarely exposed areas, or for small naevi in any area. No relationship was found in the DP group for any naevus size 3. No significant relationship between the number of naevi and the cumulative sun exposure during the most recent summer	

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					Size: the density of $\geq$ 5 mm naevi was higher on the trunk (especially back) than the buttocks in the RP group The mean density of $\geq$ 5 mm naevi was higher on intermittently exposed areas than chronically exposed areas ($p < 0.0001$) in both phenotypes, and was higher on chronically exposed areas than rarely exposed areas only among the dark phenotypes	

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
Holly (1994)	Count	Scalp, perineum, palms, soles	Head and neck, chest, abdomen, upper back, lower back, buttocks, upper arms, forearms, thighs, lower legs	[a]	Association with total naevus count: All sites were highly correlated with total naevus count ($p < 0.0001$), except for the buttocks in males. Chest ($r = 0.81$), upper arm ($r = 0.83$) and the upper back ($r = 0.83$) had a high correlation (> 0.8) with total naevus count among the control group men. In women, correlation was high (> 0.85) in upper back ($r = 0.92$), upper arms ($r = 0.92$) and thighs ($r = 0.89$) in controls. The correlation between total number of naevi and site-specific naevi was higher for women than men in buttocks and lower legs	[b]

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
Grulich (1996)	Count categorized into ranges	Genitalia, breasts (in women), posterior scalp	Arms, legs, anterior trunk, posterior trunk, scalp, feet, buttocks, face and neck	[a]	Sex: men had higher counts on backs than females. For females, naevus counts were higher on the legs and arms than men (but not statistically significant), and similar on head and neck	Repeatability of naevus counting was calculated from a sample of 15 patients using the Fisher's transformation, and the inter-observer correlation of the total naevus count was 0.88
Dabkowski (1997)	Count	[b]	Head and neck, trunk, lower limbs, upper limbs	[a]	Sex: men and women of the control group both had the highest number of naevi on the trunk followed by upper limbs. Men had higher mean number of naevi in all sites than women (statistical significance not given)	Dermoscopy was used to discriminate naevi with non naevi
Farinaz-Alveraz (1999)	Count	[b]	Face and neck, thorax, arms, hands, thighs, legs and feet	[a]	Sex: in both sexes, thorax and arms had the highest numbers of naevi. Men had higher mean number of naevi on the thorax ($p < 0.05$) and women had higher means in legs ($p = 0.02$) and thighs ($p = 0.05$) (two-tailed tests)	Clinical examinations were carried out in winter to minimize confounding factors such as evanescent freckles and summer tanning

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					Association with total naevus count: arms were the best predictor for all subjects (r = 0.78) and men (r = 0.87), and thighs in women (r = 0.78)	
Randi (2006)	Count	Genitalia, scalp	Face and neck, anterior trunk, posterior trunk, upper limbs, lower limbs	[a]	Sex: men had the highest mean number of naevi on the posterior trunk, while women had the highest on the upper limbs	Concordance of naevus counts was satisfactory with both intra and inter observer intraclass correlation values not less than 0.75, in two independent trials
Silva (2009)	Count	Breasts, genitalia	Head (face, scalp and neck), trunk (chest, abdomen, back and buttocks), upper limbs, lower limbs (including feet)	[a]	Sex: highest mean naevus count in females was on trunk	Observer variability was monitored at 6-month intervals, with each nurse independently counting naevi in the same five patients and reviewing their counts together with the dermatologist

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
Newton-Bishop (2010)	Count	Genitalia, breasts (in women)	18 body sites	[a]	UV exposure: relationship between holiday exposure and naevus number was significantly higher in intermittently exposed sites than in continuously exposed sites (p = 0.0005, regression coefficient = 0.2, 22% increase). Weak evidence that higher average weekend sun exposure in warmer months was associated with less naevi in continuously exposed areas (p = 0.05, regression coefficient = −0.11, 10% decrease)	[b]
Ribero (2016)	Count	Genitalia, breasts (in women), posterior scalp	17 body sites	[a]	General population twin study	[b]

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					Association with total naevus count: sites most associated with total naevus count were right arm ($r = 0.5$, $p < 0.001$), left arm ($r = 0.51$, $p < 0.001$), right leg ($r = 0.49$, $p < 0.001$) and left leg ($r = 0.48$, $p < 0.001$), where laterality did not affect correlation. The correlation between total naevus count and right arm and total and right leg were not different ($p = 0.65$), while the correlation coefficients for leg or arm were significantly different from other sites ($p < 0.001$). Correlations for other sites were as follows: chest: $r = 0.31$; back: $r = 0.43$; buttocks: $r = 0.16$ (all $p < 0.001$)	

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					The most accurate threshold of naevus counts in the right arm to predict having > 50 total naevus counts and > 100 total naevus counts is 7 (AUC_{adj} = 0.74, 95% CI: 0.71–0.76) and 11 (AUC_{adj} = 0.73, 95% CI: 0.69–0.78), respectively. For the right arm above the elbow, it was 4 for > 50 (AUC_{adj} = 0.72, 95% CI: 0.69–0.74) and 8 for > 100 (AUC_{adj} = 0.73, 95% CI: 0.68–0.77)	

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					Women with > 7 naevi on the right arm had approximately 9 times higher risk for having > 50 naevi (ORadj: 8.81, 95% CI: 7.03–11.04) compared with women with < 7 naevi. Women with > 11 naevi on the right arm had approximately 9 times higher risk for having > 100 naevi (ORadj: 9.38, 95% CI: 6.71–13.11) compared with women with < 11 naevi	
	Count	Genitalia, breasts (in women), posterior scalp	17 body sites	[a]	Replication study	[b]

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					Association with total naevus count: the most predictive site was right arm for males ($r = 0.85$), females ($r = 0.88$), and both males and females ($r = 0.86$) (all $p < 0.001$). This was particularly high in the right arm above the elbow ($r = 0.83$, $p < 0.001$). Back was strongly associated in males only ($r = 0.84$, $p < 0.001$). The correlation coefficients were significantly different in the general population twin study and replication study ($p < 0.001$)	

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					In women: the most accurate threshold of naevus counts in the right arm to predict having > 50 total naevus counts and > 100 total naevus counts is 7 (AUC_{adj} = 0.89, 95% CI: 0.85–0.94) and 11 (AUC_{adj} = 0.93, 95% CI: 0.91–0.96), respectively. For the right arm above the elbow, it was 5 for > 50 (AUC_{adj} = 0.86, 95% CI: 0.81–0.91) and 8 for > 100 (AUC_{adj} = 0.93, 95% CI: 0.86–0.99)	
Visconti (2020)	Count	[b]	Head and neck, trunk (back, abdomen and chest), upper limbs (including shoulders), lower limbs	[a]	Sex: significant sex difference in distribution of naevi on the lower limbs with females having a higher number of naevi ($p < 0.0001$), while males had a higher naevi count on trunk, though the difference was not significant ($p = 0.02$)	[b]

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					Heritability: the best fitting model for site-specific heritability of naevus count in women was the full ACE model. Fifty-nine percent of the total naevus count variance was explained by the additive genetic effects, and the other 41% explained by environmental effects. A high variability of the effect on the naevus count from environmental versus additive genetic factors was observed at individual sites, where trunk had the lowest genetic influence (A = 26%) and lower limbs had the largest (A = 69%)	

Table 2 continued

First author (year)	Counting of naevi on different body sites			Body site area calculations	Associated factors	Measures taken to address inter- and intra- observer variation
	Measured unit	Exclusions	Body sites considered for analysis			
					The best fitting model for site-specific heritability of naevus count in men was the parsimonious AE and CE models. More than 67% of the naevus count variation in every site and total count was due to additive genetic effects, except for lower limbs, where there was no genetic effect (E = 100%)	

[a]Not applicable
[b]Not disclosed

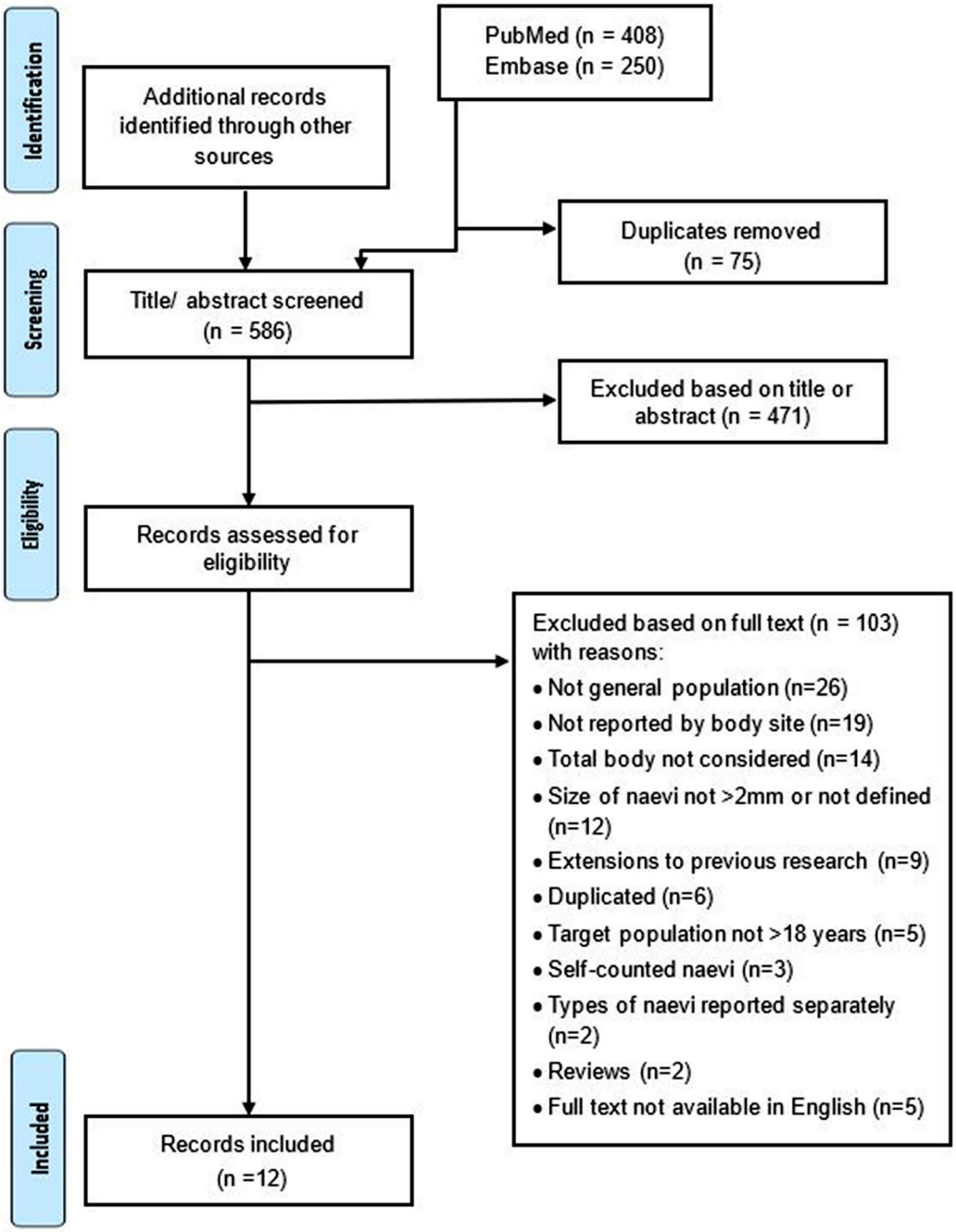
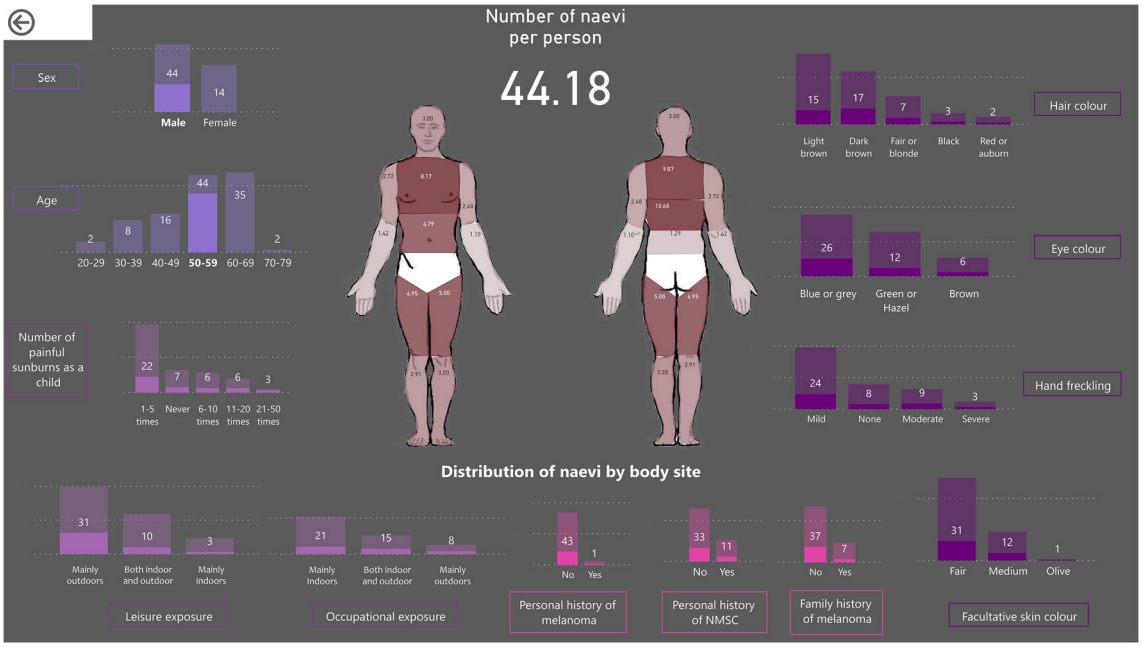


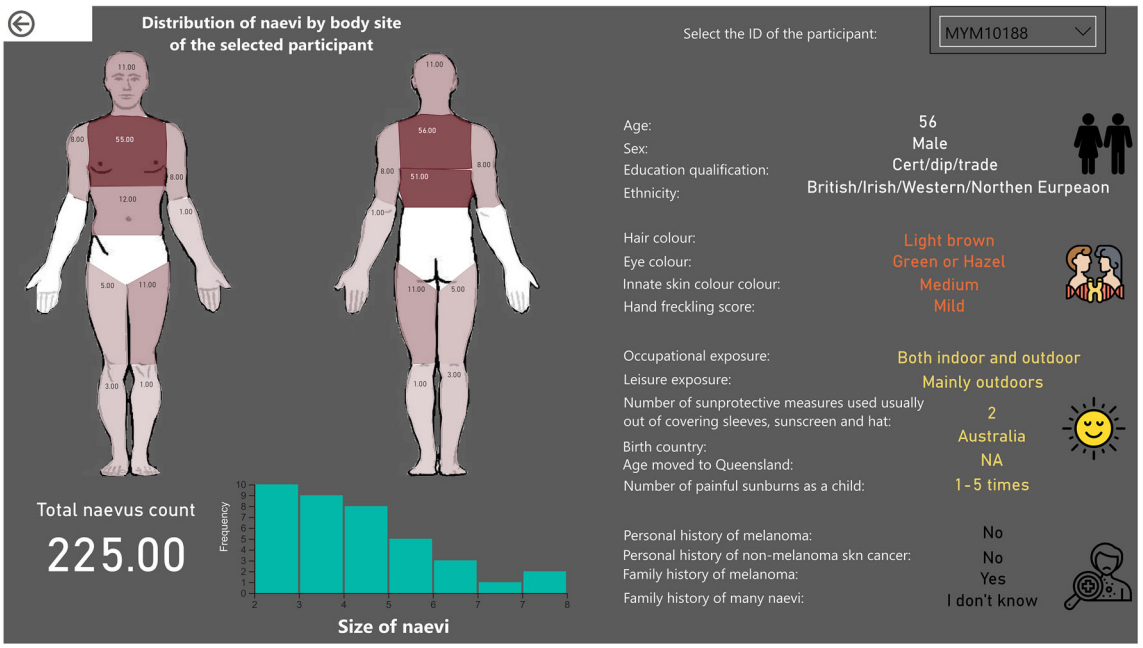
Fig. 1 PRISMA flow chart of the screening process

Naevus Density

Only two studies [32, 37] reported the overall distribution of naevi in participants without grouping them according to sex. Males and females both had the highest density per m^2 on the lateral arms, followed by the back [32] and the neck [37]. The lowest naevus density was reported on scalp, hands, soles [32] and buttocks [37].

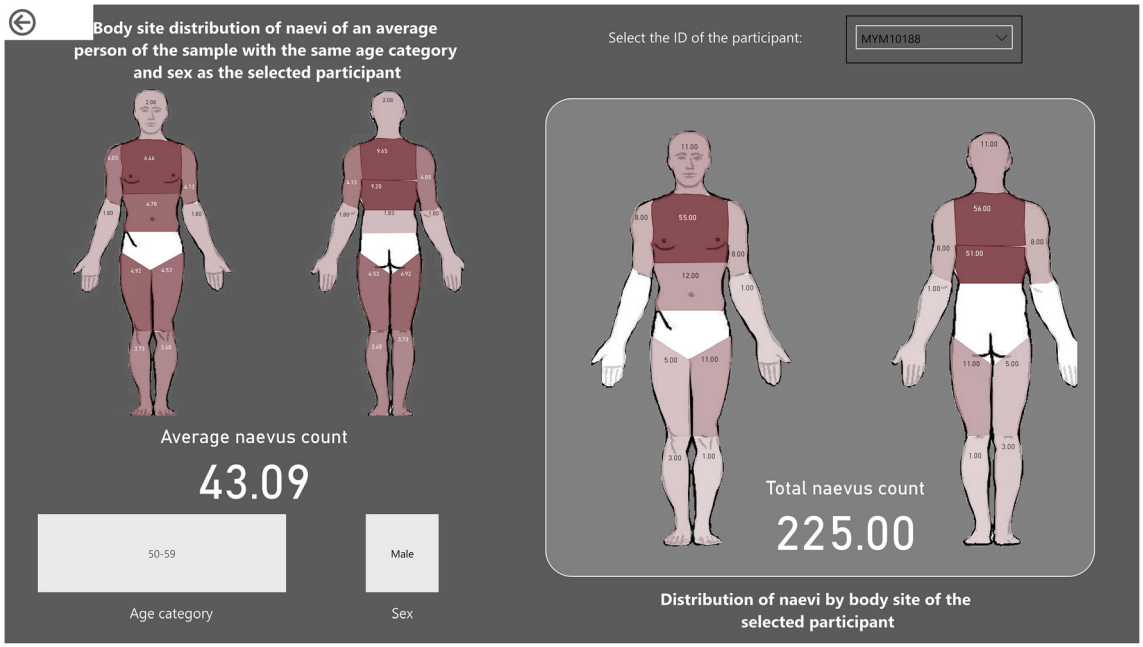


(i)



(ii)

Fig. 2 Images from an interactive dashboard using 3D total-body imaging data to visualize body site distribution of naevi and associated characteristics. (i) Body site distribution of naevi filtered for 'male' participants in the age range 50–59 years. (ii) Body site distribution of naevi and characteristics of participant 'MYM10188'. (iii) Comparison of the body site distribution of naevi of participant 'MYM10188' with participants in the sample with the same age and sex category



(iii)

Fig. 2 continued

Age

Only one study reported on the differences in naevus counts on different body sites between age groups [33], and reported that the mean naevus counts on sites with extensive number of naevi decreased in the older age groups.

Phenotype

Differences in body site distribution of naevi by participants' phenotypes were reported in two studies [32, 37]. One study found no significant difference comparing people with skin types I–II and III–IV [32]. In an age–sex–phenotype controlled study [37], the highest mean density of naevi 2–5 mm were on the face and neck in people with the 'darker phenotype' (brown or black hair, dark complexion on the inner part of the arm, absence of freckles and easy tanning without burning), while the highest naevus density was on the neck, exterior side of forearms and dorsum of the hand in people with the 'red phenotype' (red or red–blonde hair, white complexion on the inner part of the arm and inability to tan).

Exposure to Sunlight

Four studies [30, 32, 37, 38] aggregated body sites as chronically, intermittently or rarely exposed to sun. One study reported the highest density of naevi on intermittently exposed sites, followed by chronically exposed sites and rarely exposed sites [32]. When the size of naevi was considered, the same pattern was observed for ≥ 5 mm naevi [37], while for small (< 5 mm) naevi, the mean density was higher in chronically exposed sites than intermittently or rarely exposed sites ($p < 0.001$). In the same study, it was reported that the number of small naevi (< 5 mm) was significantly higher on the outer, more sun exposed arm than the inner arm ($p < 0.0001$).

Other studies showed a positive relationship between intermittently holiday sun exposed exposure sites (trunk and upper legs) and increased naevus counts [30, 38]. Fewer naevi were reported by one study in sites chronically exposed to sun [38].

Correlations between Body Site Specific and Total Naevus Count

Four studies reported correlations between site-specific and total naevus counts in different ways, as detailed in Table 2.

Two studies reported that the best predictor for total naevus count was the naevus count on the thigh [anterior thigh (r = 0.85) [32], thigh (r = 0.88 for females) [29]], while three studies reported that the best correlation with total naevus count was with the number of naevi on arms [upper arm (r not given) [33], upper right arm (r = 0.83) [31], arms (r = 0.88) [29], right arm (r = 0.86) [31]] and one study the back (only males considered r = 0.84) [31].

The UK twin study reported that people with more than 7 or 11 naevi on the arms are more likely to also have more than 50 or 100 total naevi, respectively [31].

Correlations between Body Sites

Naevus counts were reported to correlate across body sites, with correlation coefficients ranging from 0.30 to 0.70. For example, the strongest correlations were seen between upper limbs and trunk (r = 0.62–0.71), lower limbs and trunk (r = 0.49–0.61), and upper and lower limbs (r = 0.55–0.71) [30, 33].

Heritability

One study used classic additive genetic (A), common (C) and individual-specific environment (E) (ACE) twin models to estimate the contribution of genes on the body site distribution of naevi in males and females [34]. In females, it was estimated that naevus counts on the lower limbs were strongly under genetic influence (69%), while the influence of genetic disposition on naevi on the trunk was lower (26%). In males, there was only environmental effect and no genetic effect for lower limbs, while more than 67% of naevus count variation in other sites were estimated to be due to genetic influential factors [34].

DISCUSSION

This review included 12 studies that provided detailed information on the body site distribution of naevi in Caucasian adults. A meta-analysis could not be performed because the 12 studies differed widely in their naevus counting and reporting methodology. The studies also differed in how they aggregated body sites for analysis and reporting and in their naevus size categories, and only one study reported the use of the IARC protocol. Despite this, some findings were relatively consistent across most studies.

In most of the studies, males had more naevi on the trunk than females [32–35], while females had more naevi on the lower limbs than males [29, 32, 33, 35]. Females had the highest number of naevi on the arms compared with other parts of the body in most [28–31, 33, 36], but not all studies [27, 35]. This is in contrast to studies in high-risk cohorts and children, in which higher density of naevi were reported on the face and neck [46–48].

Irrespective of sun exposure in later life, genetic effects related to gender play an important role in site-specific naevus development [49]. Sex differences in body site distribution of naevi can be observed as early as 7–8 years of age [47]. In a study using Canadian Hutterite children [50], whose religious clothing protects females from UV exposure, sex differences in site distribution of naevi were observed despite low exposure to UV. Hence, the apparent differences in site distribution of naevi reported in the studies reviewed here are likely due to a combination of genetic and environmental factors [34, 49, 51, 52].

There is sufficient epidemiological evidence that exposure to UV radiation is a strong modifiable risk factor for the development of naevi [53, 54], with intermittent rather than chronic sun exposure associated with a higher density of naevi [32, 37]. One proposed reason for this suggests that chronic sun exposure may have a protective effect against the development of naevi, as observed in people who have higher average weekend sun exposure [38]. A second hypothesis postulates that intermittent UV

exposure has strong 'naevogenic' effect on melanocytes [32], as observed in people with higher holiday exposure and increased naevus counts in intermittently exposed body sites compared with chronically exposed body sites [30, 38]. However, the correlation between total body and body site-specific naevus counts was high (range: 0.83–0.88), regardless of whether intermittent or chronically exposed body sites were considered.

When the size of naevi was considered, some studies found that small naevi (< 5 mm, [37] or < 2 mm [47, 55] which are often considered as lentigines) are more common on chronically exposed sites of the body than on intermittently exposed sites. Autier et al. proposed that small and large naevi are both independent risk factors for melanoma, reflecting two different biological pathways under genetic and environmental influence involved in melanoma development [49]. In summary, this review shows that the relationship between sun exposure and naevus development and growth is very complex and requires further investigation.

This review focused on adult general population-based samples only, and the results do not reflect the more often used high-risk cohorts. Further, there was a lack of naevus studies reporting site distribution in the recent past, and the majority of the studies included in the review were more than 20 years old. The results may therefore not reflect contemporary cohorts and sun exposure patterns, or changes in practices and definitions among dermatologists regarding what constitutes a naevus. One of the other main limitations of the review is due to our narrow inclusion criteria and lack of naevus studies in non-white and people of colour; our review mainly consists of information of Caucasian adults. Even though we applied stringent eligibility criterion to select studies for the review, summarising the results was difficult due to the varied methods of aggregating anatomical sites and reporting naevus prevalence. For example, while English (1988) [33] considered both legs together as 'lower limbs' to report the number of naevi, Augustsson (1992) [32] reported details for the anterior and posterior aspect of the thigh.

Future studies could benefit from using a standardised method of aggregating body sites. To best address the differences in sun exposure and sun damage due to clothing [56], naevus counts ≥ 2 mm and ≥ 5 mm should be reported separately for head and neck, upper anterior trunk, lower anterior trunk, upper posterior trunk, lower posterior trunk, upper arms, lower arms, upper legs and lower legs. It is also recommended that all summary measures of naevus distribution are reported stratified by sex due to the evidence for genetic and environmental differences in naevus development.

Novel technologies such as 3D total-body imaging could improve the precision in naevus counts and tracking in the future [57, 58]. Figure 2 shows an example of how such information could be presented as a skin cancer education and awareness tool. An interactive dashboard would visualise the number and density of naevi people have on different body sites; could allow filtering by a person's characteristics as shown in Fig. 2, or by naevus size, colour and other naevus features; and provide comparisons with the wider population.

Before new technologies such as 3D imaging are widely rolled out to achieve automated naevus counts, a number of scientific hurdles still need to be overcome. Firstly, IARC protocol [21], which was developed more than 30 years ago, needs to be updated and should provide guidance for how state-of-the-art skin imaging technologies and emerging artificial intelligence algorithms should be integrated. Automated naevus counts are likely a better alternative for naevus counting [59], as they could overcome issues of intra- and inter-observer reliability, as well as observer training and experience [60], but this needs to be confirmed in future studies. Secondly, currently available automated naevus identification algorithms still have limitations such as low accuracy for people with severely photodamaged skin and those with many seborrheic keratoses [59], and datasets used for training the algorithms are mainly comprised of images from Caucasian adults. Hence these algorithms need to be trained with larger and unbiased datasets [61], but are promising to improve the

accuracy of this complex naevus identification and counting task.

CONCLUSION

In conclusion, environmental and behavioural aspects related to UV radiation exposure, as well as genetic factors impact the number, site distribution and size of melanocytic naevi. Given the important role that naevi play in the development and understanding of melanoma, reproducible studies using large unbiased population-based samples need be undertaken to further assess these relationships.

ACKNOWLEDGEMENTS

Funding. This research was supported by the Centre of Research Excellence for the Study of Naevi funded by the National Health and Medical Research Council, Australia (NHMRC; Grant ID: APP1099021) and Princess Alexandra Hospital foundation. H. Peter Soyer holds an NHMRC MRFF Next Generation Clinical Researchers Program Practitioner Fellowship (APP1137127). Dilki Jayasinghe is funded by a research training program (RTP) PhD scholarship.

Author Contributions. Conceptualization: Dilki Jayasinghe, Monika Janda and Kaitlin L. Nufer; Methodology: Dilki Jayasinghe and Monika Janda; Literature search, screening and synthesis: Dilki Jayasinghe; Interpretation of results: All authors; Writing—Original draft preparation: Dilki Jayasinghe; Writing—Review and editing: All authors; Funding acquisition: Monika Janda and H. Peter Soyer; Supervision: Monika Janda, Brigid Betz-Stablein and H. Peter Soyer; Project Administration: Dilki Jayasinghe. All authors have read and approved the final manuscript.

Disclosures. The presented work is original research that has not been published and is not under consideration for publication elsewhere. H. Peter Soyer is a shareholder of MoleMap NZ Limited and e-derm-consult GmbH, and undertakes regular tele-dermatological reporting for both companies. H. Peter Soyer is also a Medical Consultant for Canfield Scientific Inc., MoleMap Australia Pty Ltd, Blaze Bioscience Inc, Revenio Research Oy and a Medical Advisor for First Derm. Dilki Jayasinghe, Monika Janda, Brigid Betz-Stablein and Kaitlin L. Nufer declare that they have no competing interests.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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