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# Reference Values for Skin Microanatomy: A Systematic Review and Meta-Analysis of *ex-vivo* studies

**Haoming Xu, BS**[1,¥], **Maira Fonseca, MD**[1,¥], **Zachary Wolner, BA**[1,¥], **Esther Chung, BA**[1], **Xinyuan Wu, MD**[1], **Shamir Geller, MD**[1], **Stephen W. Dusza, DrPH**[1], **Antonio P. DeRosa, MDS, MLIS, AHIP**[2], **Ashfaq A. Marghoob, MD**[1], **Klaus J. Busam, MD**[3], **Allan C. Halpern, MD**[1], and **Michael A. Marchetti, MD**[1]

[1]Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10022, USA

[2]Medical Library, Information Systems, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

[3]Dermatopathology Service, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY 10022, USA

## Abstract

**Background—**Few studies have characterized reference values of normal human skin microanatomy parameters.

**Objective—**To quantify histologic measurements of epidermal thickness (ET), melanocyte density (MD), hair follicle density (HFD), and eccrine gland density (EGD), as a function of age and anatomic site.

**Methods—**We searched PubMed, Embase, Web of Science and Cochrane databases for articles published through May 25, 2017. Two reviewers independently screened 2,016 articles; 327 relevant articles and 151 additional articles found via forward or reference citations underwent full-text review by one of four reviewers for relevance, data extraction, and critical appraisal. Weighted averages, meta-analysis, and meta-regression were used in statistical analysis.

**Results—**Fifty-six articles were included; using all anatomic locations, overall estimates for ET, MD, HFD, and EGD were 99.75 microns (95% CI 83.25–116.25), 955.05 cells/mm$^2$ (95% CI 880.89–1029.21), 1.40 hairs/mm$^2$ (95% CI 0.91–1.89), and 1.28 glands/mm$^2$ (95% CI 0.91–1.64), respectively.

**Limitations—**There was significant data heterogeneity across studies, possibly due to differences in histological techniques and absence of standardized microanatomy definitions.

Corresponding Author: Michael A. Marchetti, MD; Dermatology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 16 E. 60th Street, New York, NY 10022; Telephone: (646) 888-6016; Fax: (646) 227-7274. marchetm@mskcc.org.
¥Contributed equally

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**Conclusion—**We established summary estimates for normal human skin microanatomy parameters.

### Keywords

Normal skin; epidermal thickness; melanocyte density; eccrine gland density; hair follicle density; systematic review

## Introduction

The microanatomy of human skin is structurally complex and potentially influenced by a multitude of factors, such as age, sex, genetics, skin type, medical comorbidities, and environmental exposures.[1–5] Previous studies have reported significant anatomic variation in the morphologic characteristics of the skin;[3,6] however, considerable diversity in study design and methodology makes comparison and synthesis of morphologic characteristics difficult. A compilation of the existing evaluations of healthy skin across varied anatomical sites can inform knowledge and the study of site-dependent morphology of cutaneous inflammatory and neoplastic processes and guide interpretation of non-invasive imaging modalities.

The objective of this study was to use meta-analysis techniques to: (1) combine histological measurements of epidermal thickness, stratum corneum thickness, melanocyte density, hair follicle density, and eccrine gland density across anatomic sites, and (2) compare histological characteristics of certain skin microanatomy parameters with respect to age.

## Methods

### Literature Search

Systematic literature searches were conducted on November 22, 2013 and May 25, 2017 in four databases [MEDLINE (via PubMed), Embase, the Cochrane Library, and Web of Science] for references written in all languages without sex, age, or publication type restrictions. For PubMed, Embase, and Cochrane Library searches, both controlled vocabulary and text words were used in search strategy development. The Web of Science database does not employ a controlled vocabulary, so it was searched using only text words. All search results were combined in a bibliographic management tool (EndNote) and duplicates were eliminated electronically and manually.

The search strategy had two components and both concepts were linked together with the AND operator: (1) anatomic site including head/neck, chest, abdomen, torso, posterior and back, buttocks, genitalia, upper extremities, and lower extremities; (2) microanatomy parameters including epidermal and stratum corneum thickness, melanocyte density, hair follicle density, and sweat/eccrine gland density. For a complete list of MeSH and keyword terms used, please refer to the accompanying PubMed search strategy (Supplemental Information).

## Data Abstraction

Two reviewers (M.M. and X.W. or H.X. and Z.W.) independently screened all article titles and abstracts. All identified articles subsequently underwent full-text review by one of four independent reviewers (M.F., X.W., E.C., or Z.W.). Articles were excluded if they lacked relevant microanatomy parameters, were not written in English, measured skin microanatomy in non-healthy participants, or failed to report data numerically. All potentially relevant forward or reference citations underwent full-text review. Data on microanatomy parameter, methodology, technique, subject age, sex, skin type, race and ethnicity, anatomic site, sample size, mean, and standard deviation were systematically extracted from all included articles. Two additional independent reviewers (Z.W. and H.X.) re-examined all articles to exclude studies and extract additional data relevant to analyses.

## Skin Microanatomy Parameters and Eligibility Criteria

Multiple different modalities investigating skin microanatomy were found, including *ex vivo* techniques such as histological sampling as well as *in vivo* imaging techniques such as reflectance-mode confocal laser microscopy (RCM) and optical coherence topography (OCT). Our original intent was to also include all modalities in our analyses, but given the lack of robust data in our literature search, we restricted analyses to studies with histopathology only.

Epidermal thickness (ET) was defined as distance between top of the stratum corneum to top of the dermis. A wide range of measurement definitions for ET were found in the literature. Many studies used distance between top of the stratum granulosum to top of the dermis. To categorize this measurement, we created an additional parameter called granulosa-epidermal thickness (GET). Stratum corneum thickness (SCT) was defined as the distance between top of the stratum corneum to bottom of the stratum corneum. All thickness parameters were reported in micrometers. Studies with measurements not in metric units (e.g. number of layers) were excluded.

Melanocyte density (MD) was defined as number of melanocytes per $mm^2$. Hair follicle density (HFD) was defined as number of hair follicles per $mm^2$. Eccrine gland density (EGD) was defined as number of eccrine glands per $mm^2$. Studies with measurements not convertible to these units (e.g. number per high power field) were excluded.

All studies with aggregated data from multiple patients that did not include a measure of variance (e.g. standard deviation or standard error) were excluded from analysis. For studies providing individual patient data, the mean and standard deviation of the various parameters were calculated.

Anatomic locations from which skin microanatomy parameters were taken were categorized into six groups: head/neck, upper extremities (including dorsal hand), trunk (including chest, back, abdomen, and axilla), lower extremities (including buttocks and dorsal foot), palms/soles, and genitalia. Since reported age range varied between and within studies, mean patient age for each study was calculated. Mean age was categorized as two categories (0–60 and >60 years) or three categories (0–18, 19–60, and >60 years) according to available data.

### Statistical Analysis

Weighted averages for each parameter of interest (ET, GET, SCT, MD, HFD, and EGD) were calculated for all relevant studies and stratified by anatomic location. Weighted averages for ET and melanocyte density were calculated for all relevant studies and stratified by mean age. Meta-analysis was performed using a random-effects model, with each skin microanatomy parameter as an effect size (ES, 95% CI). The $I^2$ statistic was calculated to measure heterogeneity among studies. Forest plots were constructed for each microanatomy parameter. Meta-regression was used to compare skin microanatomy parameters among different anatomic locations as well as age groups. All statistical analyses were carried out using Stata v.14.1 software (Stata Corp., College Station, TX, USA).

## Results

### Literature Search

The initial systematic literature search yielded 2,016 unique articles, of which 896 were found in MEDLINE (via Pubmed), 715 in Embase, 348 in Web of Science, and 57 in the Cochrane Library (Figure 1). Of these, a total of 327 articles passed the initial screening based on article title and abstract. Full-text reviews of these 327 articles for relevant forward or reference citations yielded an additional 151 potential articles. Full-text reviews were conducted on a total of 478 articles, of which 422 were excluded, and 56 were included in the final analysis (Supplemental Information).

### Epidermal thickness (ET)

Fifteen studies were included with 29 observations of ET by anatomic location.[3,6–19] A forest plot of ET at each anatomic location is presented in Figure 2. The overall ET across all anatomic locations was 99.75 microns (95% CI 83.25–116.25); excluding palms and soles, the overall ET was 76.50 microns (95% CI 62.76–90.04). The palms and soles had the thickest epidermis, followed by the lower extremities, upper extremities, trunk, head/neck, and genitalia. On meta-regression, the palms and soles were significantly thicker compared to the head/neck ($\beta = 669.17$, $p<0.001$). No other significant differences in thickness were observed between anatomic locations.

Twelve of 15 studies included age data, yielding 16 observations of ET by mean age (Figure 3).[3,5–7,9,10,12–15,17,18] Overall ET was found to be 75.03 microns (95% CI 53.90–96.16) for ages 0–60 compared to 45.56 microns (95% CI 34.99–56.13) for ages 60 and older. While not reaching significance, meta-regression found the ET of the ages > 60 group to be thinner compared to the ages < 60 group ($\beta = -18.75$, $p=0.089$).

Results of analyses for GET[3,20–36] and SCT[3,8,10,35,37–41] by anatomic location are in Supplemental Information.

### Melanocyte Density

Nine studies were included with 25 observations of MD by anatomic location (Figure 4).[4,42–49] The overall estimate of MD was 955.05 cells/$mm^2$ (95% CI 880.89–1029.21). The genitalia had the highest MD, followed by the head/neck, upper extremities, lower

extremities, and trunk. There was only one observation of MD for the palms/soles (ES 1400.00, 95% CI 574.82–2223.18). On meta-regression, no anatomic locations exhibited significantly different melanocyte densities compared to the head/neck. In addition, 7 studies included age data yielding 15 observations of MD (Figure 5). Overall MD was found to be 1578.00 cells/mm$^2$ (95% CI 805.33–2350.67) for ages 0–18, 1311.90 cells/mm$^2$ (95% CI 1043.70–1580.10) for ages 19–60, and 849.02 cells/mm$^2$ (95% CI 715.22–982.82) for ages 60 and older. On meta-regression, a trend of decreasing MD was observed with increasing age, but there were no significant differences in MD between the 19–60 age group and >60 age group compared to the 0–18 age group ($\beta = -327.79$, p=0.40 and $\beta = -650.56$, p=0.11, respectively).

### Hair Follicle Density (HFD)

Eight studies were included in the meta-analyses for HFD with 16 observations of HFD by anatomic location (Figure 6).[18,48,50–55] The overall estimate of HFD was 1.40 hairs/mm$^2$ (95% CI 0.91–1.89). The head/neck had the highest HFD, followed by the trunk, upper extremities, and lower extremities. There was only one observation of HFD for the genitalia and palms/soles. On meta-regression, the upper extremities, trunk, and lower extremities exhibited a lower HFD compared to the head/neck ($\beta = -2.94$, p =0.07; $\beta = -2.86$, p=0.08; and $\beta = -3.02$, p=0.067, respectively). However, no statistically significant differences in HFD were observed.

### Eccrine Gland Density (EGD)

Six studies were included in the meta-analyses for EGD with 19 observations of EGD by anatomic location (Figure 7).[48,50,56–59] The overall estimate of EGD was 1.28 glands/mm$^2$ (95% CI 0.91–1.64). The palms/soles had the highest EGD, followed by the head/neck, lower extremities, upper extremities, genitalia and trunk. On meta-regression, no anatomic locations exhibited significantly different EGD compared to the head/neck.

## Discussion

Current knowledge of cutaneous function and skin microanatomy stems largely from investigations into its disease processes.[60] Yet, there are few standardized metrics to characterize often-described microanatomy parameters such as ET in healthy skin. Our study aimed to examine and synthesize previous literature and compare histological measurements of various skin microanatomy parameters by age and anatomic site. Establishing such parameters would offer insight for future histopathological correlation studies and could serve to inform the interpretation of *in vivo* imaging technologies such as RCM and OCT. Moreover, there seems to be limited consensus as to how these parameters should be defined, illustrated by the multitude of definitions of ET in the literature.[10,17,61] For example, our review found ET to be reported as: top of the stratum corneum to top of the dermal papillae, top of the stratum corneum to middle of the dermal papillae, and top of the stratum corneum to bottom of the dermal papillae. This lack of standardization led us to define epidermal thickness as top of the stratum corneum to the top of the dermis, therefore including studies using any of the above definitions. The variable definitions highlight a

significant challenge in parameter standardization and contribute to the limitations to our study.

The trends and values reported in our study are congruent with our current understanding of skin physiology. For example, the palms/soles were found to have the thickest epidermis and highest EGD, while the head/neck had the highest density of hair follicles. Additionally, studies have consistently shown that the MD of the human skin decreases with advancing age.[4,43,49] There was also a degree of consistency with regard to our findings on the various thickness parameters ET, GET and SCT. The overall ET across all anatomic locations (99.75 microns) was found to be comparable to the sum (97.13 microns) of the overall GET (76.60 microns) and SCT (20.53 microns).

There are significant limitations to our study. First, the lack of observations across various anatomic locations (such as the genitalia and palms/soles) for some parameters made it difficult to identify trends with respect to anatomic location and evaluate differences between anatomic locations using meta-regression. The paucity of sample size for meta-analyses can be attributed to many studies not reporting measures of variance and the lack of standardization with regards to units of measurement. As a result, the trends observed for some parameters in our study were not statistically significant. For example, the difference in HFD of the head/neck was an order of magnitude greater than other anatomic locations. However, there were only two studies that investigated the HFD of anatomic locations other than the head/neck, which limited the statistical power of our analyses. Second, our study did not account for the various techniques used to create histological samples. The studies included in our meta-analysis featured a wide range of techniques involving every step of tissue specimen preparation, including: type of histology (surgical vs autopsy), fixation (formalin vs osmium tetroxide), processing (frozen vs paraffin), staining (H&E vs methylene blue), and sectioning (vertical vs horizontal). Additionally, some studies adjusted for specimen shrinkage while others did not, which could result in significant discrepancies in measurements.[62,63] We acknowledge the importance of adequately controlling for histological technique, but also recognize the futility of conducting further subgroup analyses owing to the sample size of the current meta-analysis. Third, our analysis included literature from 1934 to 2017, which may have resulted in increased variation between studies attributed to the changes to the preparation and analysis of tissue specimens over the years. This was especially relevant to the determination of MD. DOPA staining, which was more commonly employed in older studies, relies on an enzymatic reaction within melanocytes to produce melanin. However, cross-reactivity with other cells may occur, leading to overestimations in the data. Immunohistochemistry, which stains for specific cell markers on the surface of melanocytes, may therefore be a more accurate enumeration method. Finally, due to variability in the reporting of age ranges between and within studies, we only compared skin microanatomy parameters by mean patient age for each study, which may not be completely representative of how age affects these measurements. All of these factors likely contributed to the substantial heterogeneity of study outcomes in our analyses.

Our study identified and aggregated the findings from previous literature in an attempt to unify the observations of various skin microanatomy parameters. From these results, it is clear that substantial variability exists among the existing studies quantifying these

parameters, which is largely attributable to differences in histological methodology, advancement in histological techniques with time, and definition of parameters. The heterogeneity of data found in our study also highlights the need for the creation of metrics to measure healthy skin microanatomy parameters. To better characterize skin pathologies, a consensus on the characteristics of "normal" skin is required. In order to achieve this, we must first define each individual parameter, and then decide on an optimal method for measuring and reporting the parameter. Finally, we should consider the creation of baseline values and ranges of skin microanatomy parameters to which future findings may be compared.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

| | |
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| **ET** | epidermal thickness |
| **GET** | granulosa-epidermal thickness |
| **SCT** | stratum corneum thickness |
| **MD** | melanocyte density |
| **HFD** | hair follicle density |
| **EGD** | eccrine gland density |

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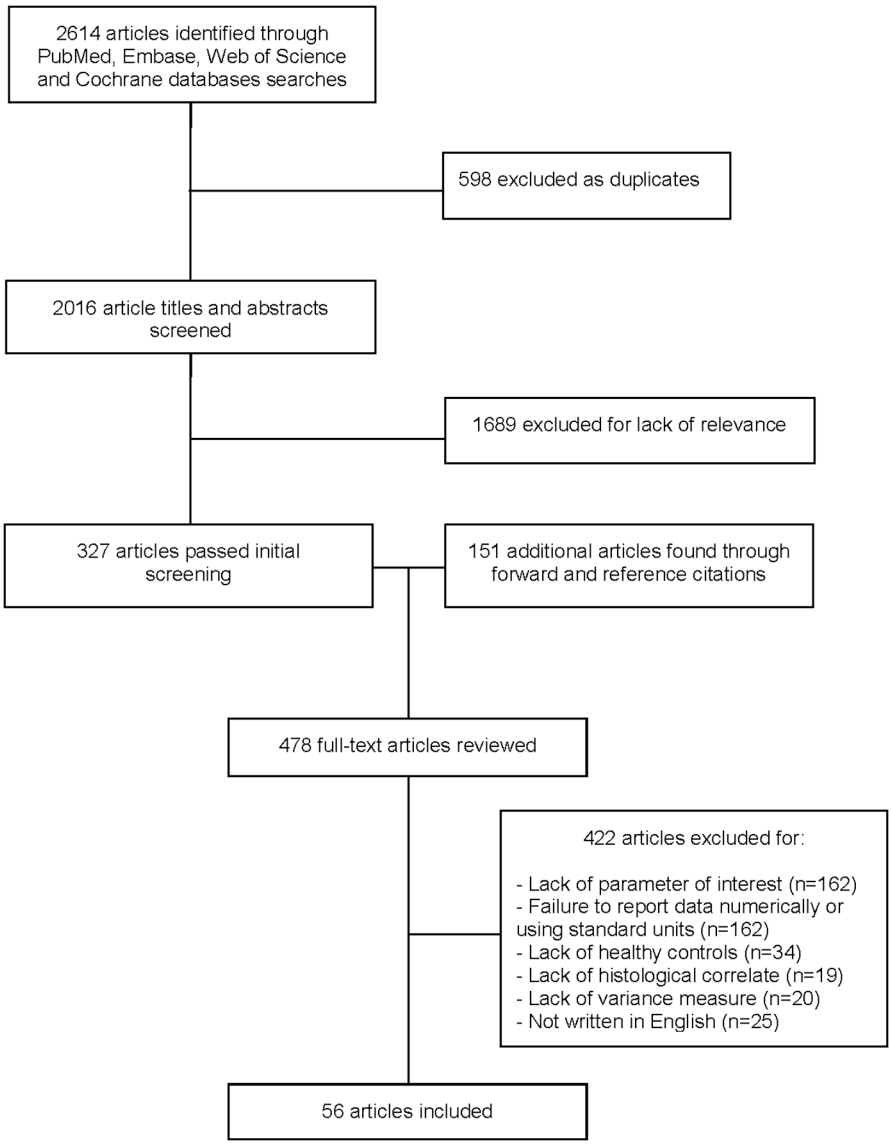


**Figure 1.**
Flowchart of studies of skin microanatomy parameters

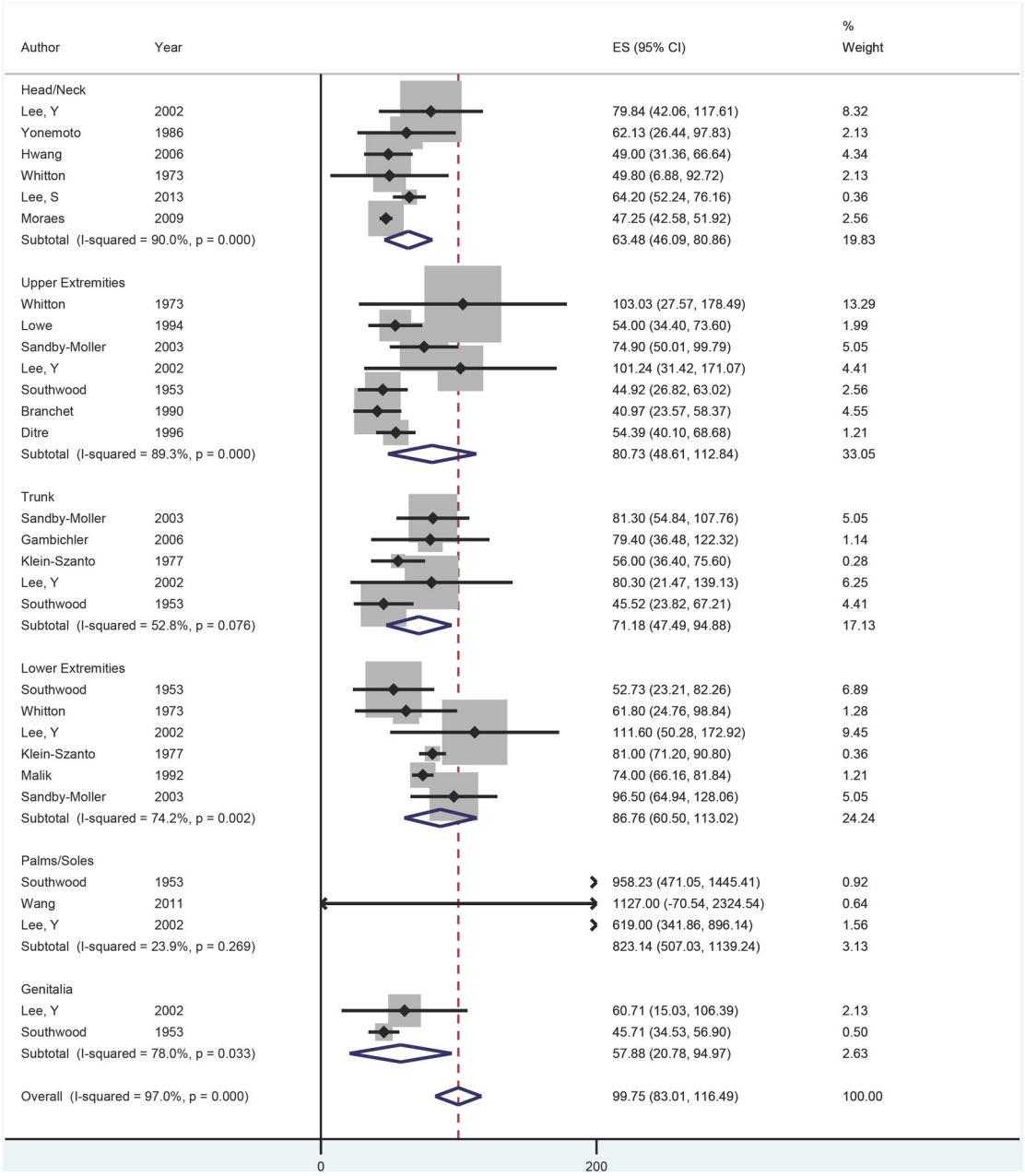


**Figure 2.**
Forest plot of epidermal thickness by anatomic location

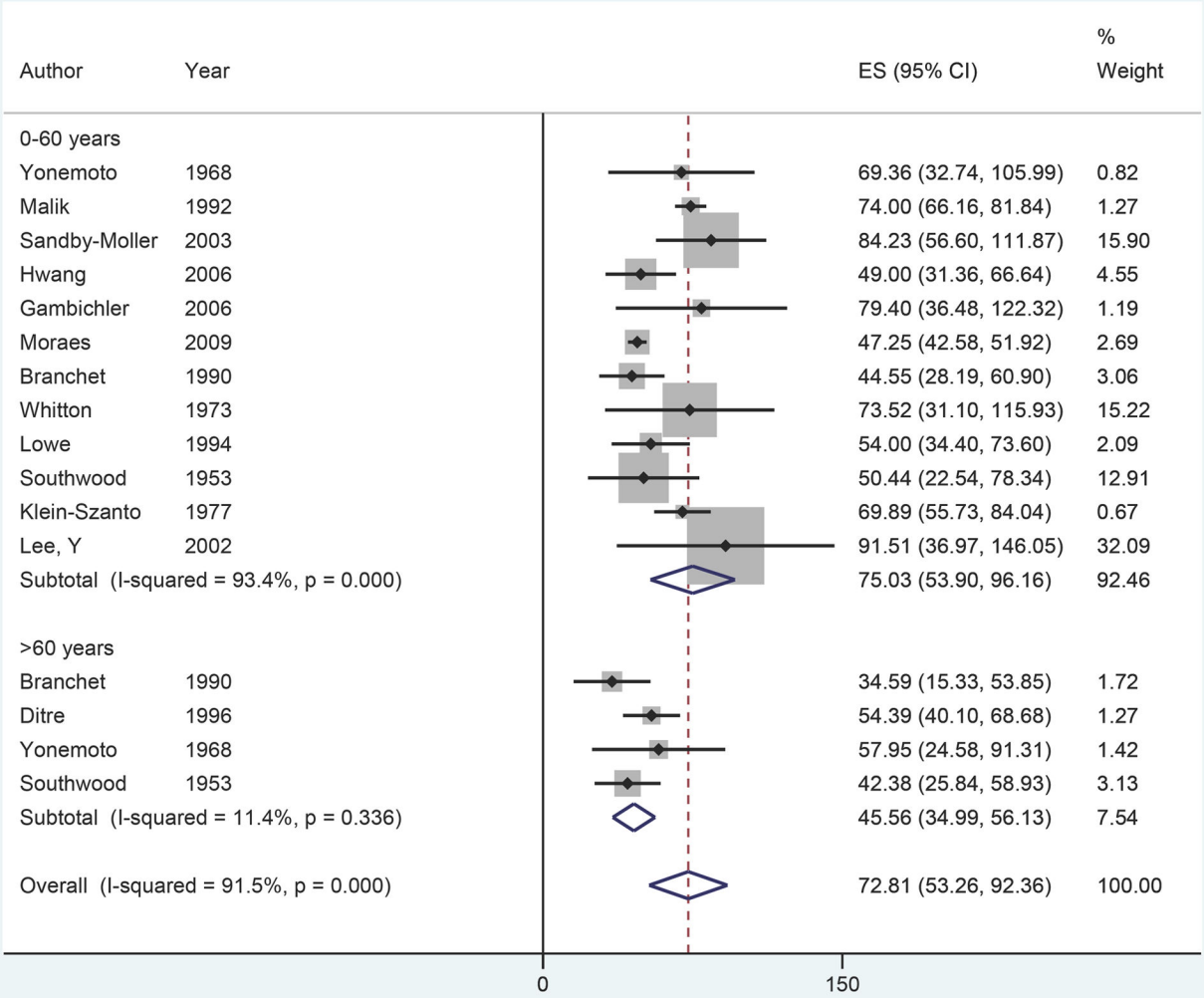


**Figure 3.**
Forest plot of epidermal thickness by age

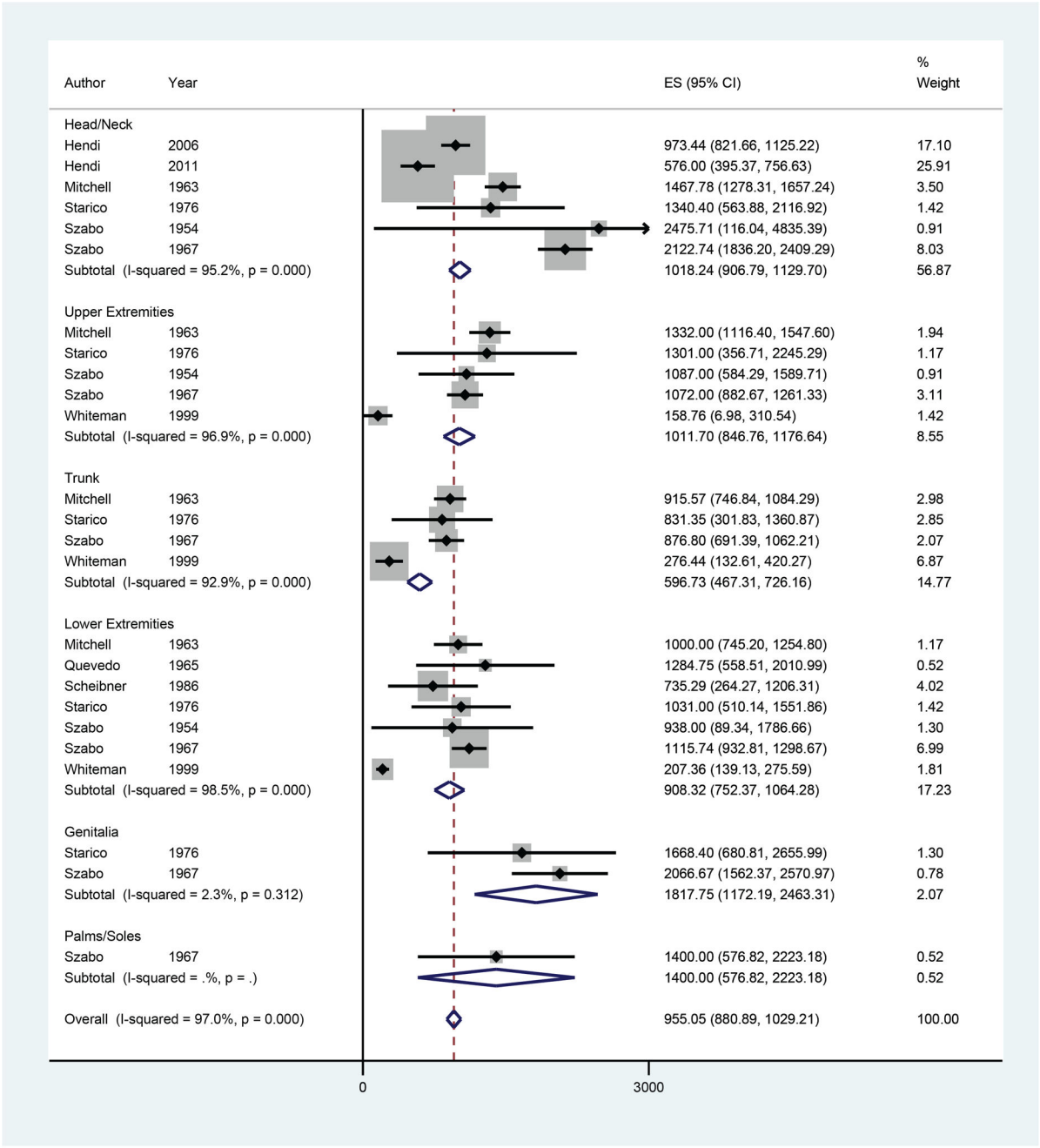


**Figure 4.**
Forest plot of melanocyte density by anatomic location

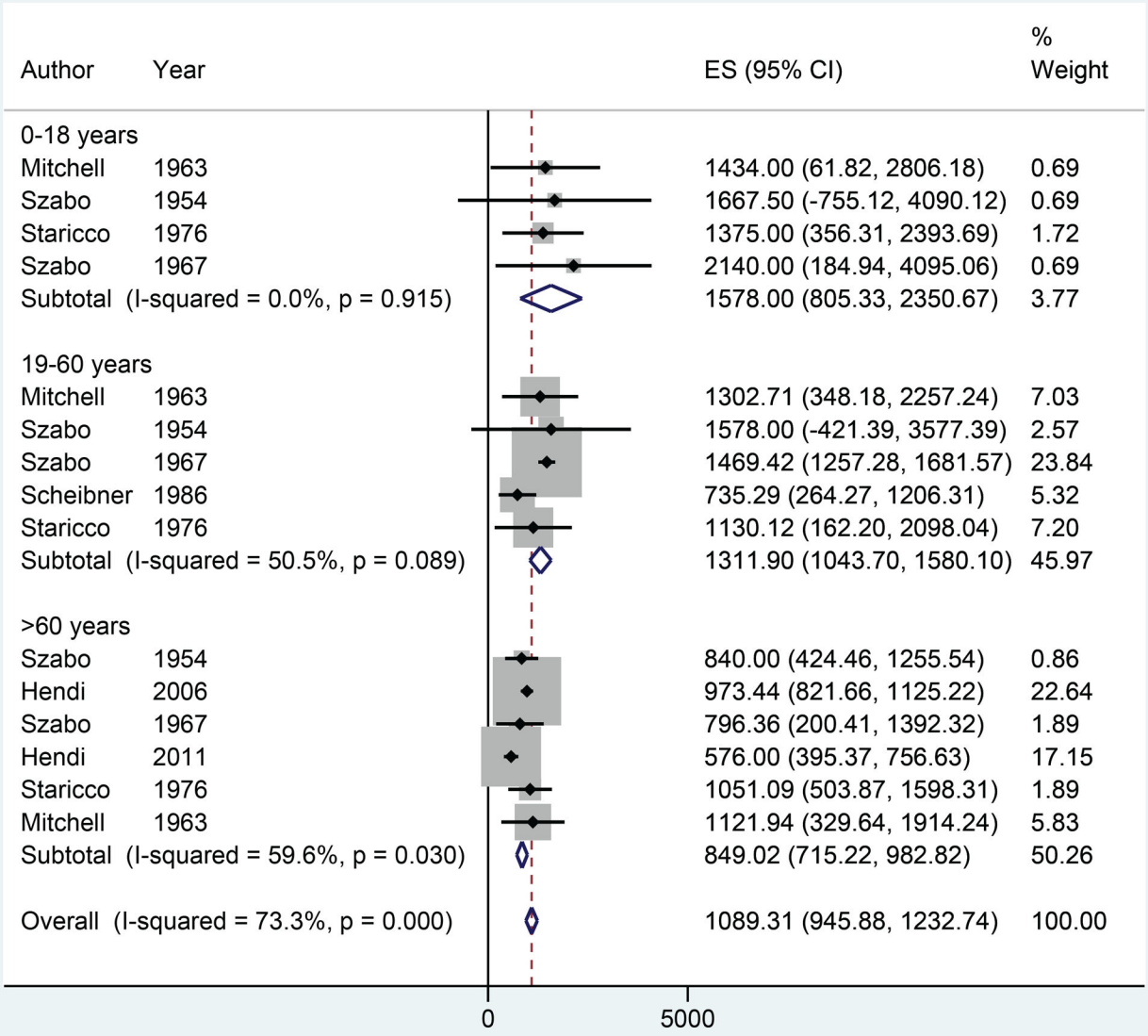


**Figure 5.**
Forest plot of melanocyte density by age

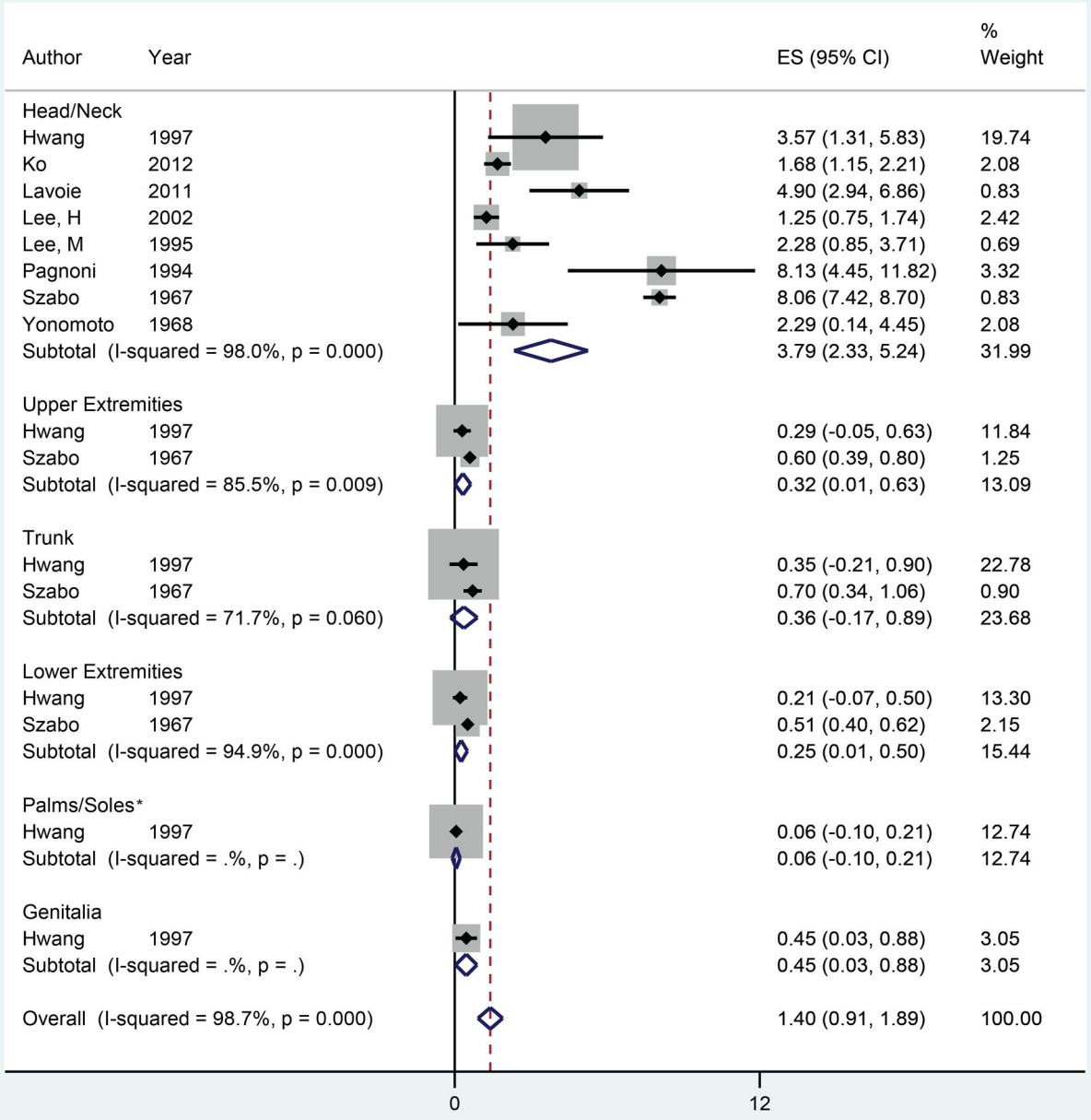


**Figure 6.**

Forest plot of hair follicle density by anatomic location

*Analyses of Palms/Soles include data on dorsal hand, dorsal feet, and fingers.

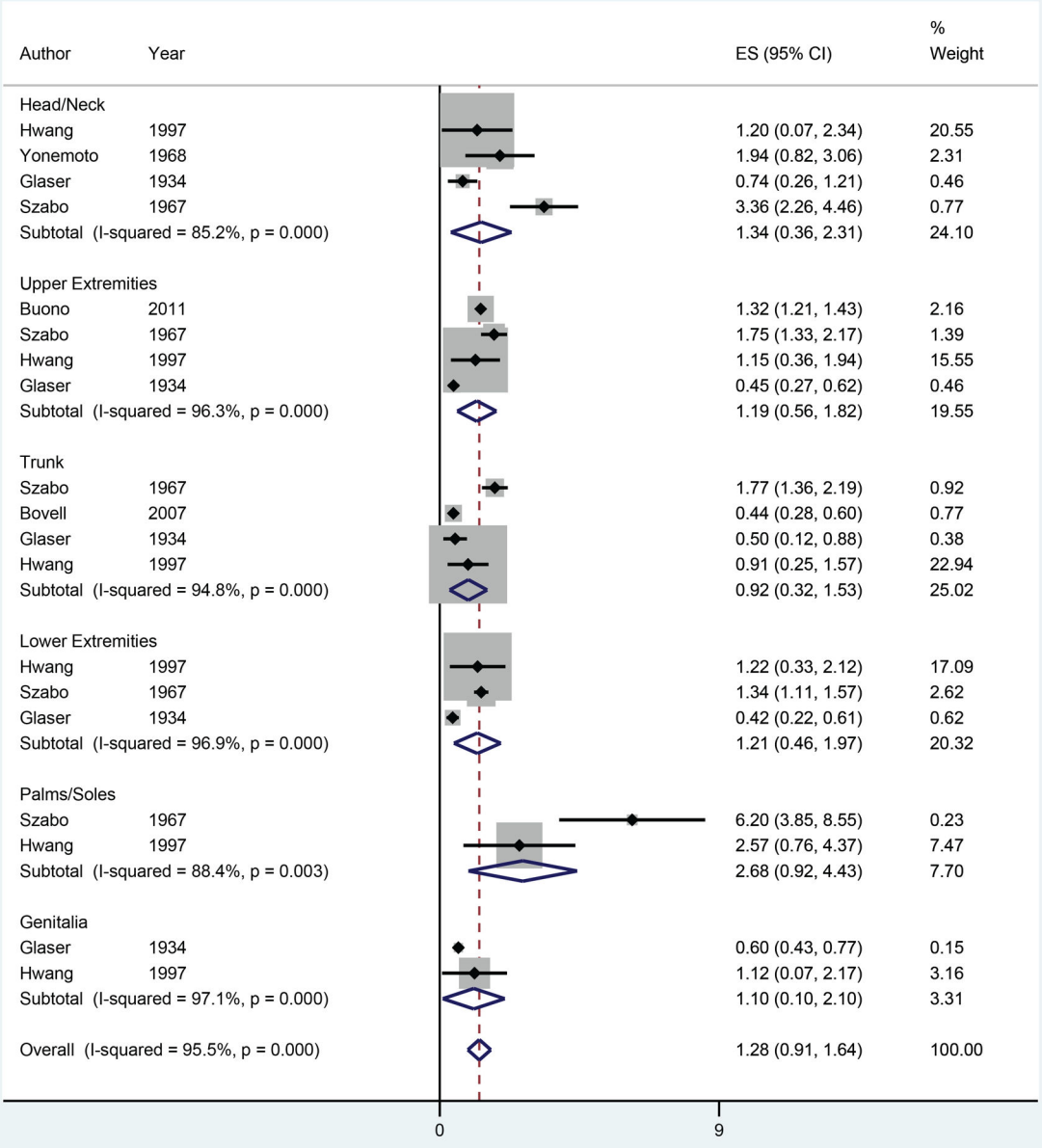


**Figure 7.**
Forest plot of eccrine gland density by anatomic location