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REVIEW

Unbearable transepidermal water loss (TEWL) experimental variability: why?

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Abstract
Despite the wide breadth of research, much disparity exists in transepidermal water loss (TEWL) research data—possibly due to uncontrolled experimental variables. We determined whether such experimental variables significantly impact TEWL studies and cause this disparity. An initial literature search regarding TEWL was performed to determine potential confounding variables. A subsequent search procured relevant and representative studies investigating the impact of these variables on TEWL. Variables, such as age, anatomic site, and temperature, impact TEWL and should be controlled for in TEWL studies. Other variables, such as smoking and menstrual cycle, have inconclusive results or do not provide sufficient data breadth to make a conclusion regarding its effect, if such an effect exists, on TEWL metrics. Therefore, these variables require further research to determine their potential impact on TEWL. Matching for as many experimental variables as possible may reduce the disparity in TEWL data/conclusions.

Keywords Transepidermal water loss · Experimental variables · Stratum corneum · Skin · Evaporimeter

Introduction

Stratum corneum plays critical roles in human survival; one such role is as a barrier against excessive water loss [17]. Transepidermal water loss (TEWL), a widely used and accepted means of quantifying the stratum corneum's effectiveness as a barrier against water loss, quantifies water lost from the body by non-eccrine sweating [19]. TEWL's importance is highlighted by the fact that TEWL in humans has been investigated since the 60s and remains a major field of research, related to topics ranging from its effect on human aging and skin of color on TEWL [21, 25, 44].

Although a wide breadth of TEWL research exists, there is much disparity in their conclusions. For example, we reviewed 26 major studies investigating the impact of the skin of color on TEWL; results conflicted. Many studies contradicted each other on whether skin of color significantly impacts TEWL or not and, even if a significant effect was found, studies disagreed on what the significant impact was [53].

In a major review on TEWL and aging by Kottner et al. conducted a metanalysis comparing TEWL results from 152 studies and found that TEWL is generally lower in older adults; however, this was only for 11 of 21 comparisons and, therefore, were unable to make clear conclusion regarding age and TEWL [33]. The conflicting results in both large data sets indicate a need to evaluate possible confounding variables.

We suggest that one reason there is variation in TEWL data rests with confounding variables that significantly impact TEWL. Many TEWL studies attempt to control for such variables, including room temperature and the consumption of certain foods; however, TEWL research lacks uniformity regarding which variables to control for and often only a select few variables are matched for [1, 47].

Here, we identify multiple important confounding variables that can significantly impact TEWL. By matching study subjects for as many of these variables as possible, we can potentially reduce disparity in TEWL metrics.

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Materials and methods

We searched EMBASE, PubMed, Google, Google Scholar, the Miner Library Online Database of the University of Rochester in Rochester, NY, USA, standard dermatology textbooks, and the Dermatology library at the University of California, San Francisco, CA, USA. An initial search was conducted using keywords related to TEWL (i.e. TEWL, standardization, evaporimeter, water loss) to generate a list of potential confounding variables. A subsequent search included words pertaining to these variables (i.e. aging, gender, seasons, ambient temperature, obesity, smoking) and words pertaining to TEWL (i.e. TEWL, stratum corneum, skin, skin barrier function, water loss). These references were reviewed, and relevant and representative publications were procured. For every article, only results regarding basal TEWL were analyzed and presented. Both articles independently reviewed cited articles.

Results

Experimental variables

Sample size and power

Sample size is an important aspect of any experimental design. Large sample sizes may identify differences that are not biologically important, while small sample sizes are poorer representatives of a population and may not discern biological differences—even if they are important, i.e. small sample sizes have low power [29]. Power is the probability that the experiment would be able to reject the null hypothesis when it is rightly false. A higher power limits the chance of committing a type II error and is often set at least 0.8. Power is related to inter-individual variance, sample size, and the acceptable risk level, α [28]. Therefore, an adequate sample size ensures a study has power and, therefore, has strong evidence to support its conclusion. One can calculate the necessary sample size needed for a study to have accurate power for an acceptable risk level. However, of the articles reviewed here, only one explicitly stated that they used power analysis to determine the minimum sample size required for adequate power [68]. Two other articles did some sample-related calculations as well but did not explicitly state whether they conducted power analysis. Mehta et al. stated they calculated sample size using software and Young et al. calculated effect sizes [44, 79]. Without power analysis, one cannot determine if the study included enough subjects to be considered strong evidence. For example, Hillebrand et al. reanalyzed Wilson et al. Wilson et al. investigated the relationship between race and TEWL by measuring TEWL in skin from 12 white subjects and 10 African American individuals [72]. Hillebrand et al. used their own data on forearm TEWL in 452 Chinese women of various age groups to calculate the coefficient of TEWL variance forearm. As these data were specific to Chinese women, they also compared their coefficient with studies that investigated other populations and ethnic groups to confirm its accuracy [28]. Wilson et al. observed a significant difference ($p < 0.01$) with African American skin having 10% higher in vitro TEWL versus their white skin counterparts [72]. However, after conducting power analysis, Hillebrand et al. found that to observe a 10% difference between white and African American individuals in vivo with 80% power and statistical significance ($p < 0.05$), one would require at least 172 white and 172 African American individuals. This highlights the importance of taking sample size and power into consideration when planning/conducting and analyzing studies [28].

Evaporimeter standardization

Evaporimeter standardization is another potential variable. Three major techniques for determining TEWL have been described. The first is a closed chamber method, where a hygroscopic substance inside a glass tube is placed on the skin and the change in the weight of this substance is used to measure TEWL. However, there are drawbacks to this method; this substance is saturable and, therefore, at high relative humidity this method is ineffective, this method cannot continuously measure TEWL, and one must control for the relative humidity and vapor in the chamber prior to introducing the substance. Another method is via a ventilated chamber that passes gas of a known humidity and velocity through a chamber placed on the skin and then comparing the effluent and affluent air to determine TEWL. Its disadvantage is that it introduces a forced convection factor that increases TEWL by physically removing a layer of more humid air from the skin surface. Finally, the open chamber method, commonly used in many evaporimeters, measures the water gradient at two points in the water gradient boundary of the skin and, therefore, is not impacted by this convection factor. Note that it is impacted by local air currents and relative humidity fluctuations [73].

Pinnagoda et al. determined intra-instrumental variability in TEWL in vitro and in vivo recorded with four evaporimeters and determined small standard deviations and therefore a low intra-instrumental variability. There was greater variability between individual instruments. This was hypothesized to be the result of the age of the instrument as older instruments tended to stabilize slower and measured lower

TEWL [55]. Pinnagoda et al. subsequently suggested that aging of instruments may be due to the aging of the probe sensors [54]. This underscores the importance of regularly checking and calibrating the instrument.

In addition, there appears to be variation between instruments made by different manufacturers. De Paepe et al. compared two commonly used evaporimeters made by two manufacturers when measuring forearm skin TEWL. One machine measured significantly higher TEWL values than the other. This illustrates that using more than one brand of machine can cause potential result variation [16]. Another aspect of evaporimeter standardization was the use of probe protection covers. Pinnagoda et al. describe how the use of a cover can elevate the probe above the necessary boundary where TEWL measurements must occur. TEWL measurements will thus be lower with a probe cover. Furthermore, the higher the TEWL rate the greater the difference between the TEWL values when using and when not using the cover [54]. A goal still to be met will be an international standardization method.

Technician training

Another confounding variable investigated was technician training, how the instrument is handled and how the measurement process is conducted impacts the resultant TEWL value. Training errors can be minimized by a complete understanding of the equipment and training in the use of the instrument based on the instrument handbook. For example, the ServoMed Evaporimeters handbook discusses zero drift, wherein changes in relative humidity and the temperature of the probe can affect measurements. When conducting a measurement, the probe is exposed to skin's high humidity and temperature. Hence, condensation will remain in the probe and the instrument will have a non-zero water evaporation value (WE) zero level [61]. Pinnagoda et al. describe that having the technician wave the probe vertically up and down speeds up the time for the probe to return to normal, within 2–4 min [55]. Temperature zero drift can occur since contact with human skin can raise probe temperature. This can be due to the subject's skin or the technician's hand. The handbook states that a change in water evaporation zero level $\pm$ 1–2 g/m^{2}h can occur due to a 5 min measurement with the technician holding the probe [61]. Pinnagoda discussed accessories for holding the probe, such as insulating gloves, that the technician can use to avoid skin contact [54]. Finally, Nilsson et al. investigated the impact of contact pressure on TEWL. They measured TEWL on the thigh with increased mechanical load on the probe and observed an increase of about 10% in the evaporation rate for every additional 100 g applied to the probe [48]. These findings highlight the importance of adequate technician training and instrument operation on TEWL measurements.

Room temperature

The room temperature room for TEWL measurement also potentially impacts TEWL. Cravello et al. measured TEWL in 6 women at three ambient temperatures (20 °C, 25 °C, and 30 °C) and found significant correlation between ambient temperature and TEWL; TEWL increased with increasing temperature [12]. Lamke et al. measured water evaporation from the skin in 9 men and 10 women who spent 30 min in a climate chamber at 3 temperatures, 15 °C, 28 °C, and 41 °C and observed a significant increase in mean evaporation between 15 °C and 28 °C, between 15 °C and 41 °C and between 28 °C and 41 °C [35]. Chen et al. investigated the effect of experiencing changes in temperature on TEWL from outside to a temperature-controlled building. A subject may experience the same effect when coming into a temperature-controlled environment for TEWL measurements. Chen et al. measured TEWL in 8 male and 8 female subjects during three temperature changes (32–24 °C, 28–24 °C and 20–24 °C). The immediate difference in the TEWL value was significant for all temperature change sets, with TEWL decreasing with the down-steps in temperature [7]. Pinnagoda et al. recommend a room temperature of 20–22 °C to minimize such fluctuations [54].

Environmental variables

Season

Seasonal changes correspond to climatic changes including changes in temperature, wind, humidity, etc. Therefore, such climatic changes can impact the skin and barrier function and hence TEWL (Table 1). Most studies investigating the relationship between TEWL and seasonal fluctuations compared TEWL during winter and summer seasons. Kikuchi et al. examined 39 Japanese females and measured their TEWL on the cheek and forearm during summer and winter. TEWL increased significantly at both sites in winter compared with summer [32]. Similar results were found in other studies. Li et al. measured TEWL in 40 Chinese adults and 40 Chinese children on the elbow, face, décolletage, dorsal hand, outer forearm, lower outer leg, and heel during winter and summer. TEWL was higher during winter at all sites except the heel, which had a lower TEWL in the winter compared to summer [39]. Wei et al. found the same results in 25 females from Ohio on the lower legs; as did Muizzuddin et al. on the cheeks of 40 females from Arizona and New York, and Yang et al. in 72 females from China on cheek, but not forearm [46, 69, 76].

However, Song et al. measured TEWL in 100 Korean men during summer and winter on the forehead, cheek, and forearm, and TEWL was significantly higher for the forehead and forearm during the summer. Cheek had a similar

Table 1 TEWL (transepidermal water loss): impact of season—all studies found an impact of season on TEWL

Study	Subjects (age range or mean ± SD, sample size, sex)	Season (months)	Site	Season and TEWL result
Black et al. [4]	18–35 y, $n=24$ females	February, April, July, December	Calf, inner forearm, crow's foot wrinkle area on face	Forearm and calf: July > February, April and December ($p<0.05$) crow's feet: same trend but not significant
Kikuchi et al. [32]	20 s, $n=9$, 30 s, $n=$", 40 s, $n=$", 50 s, $n=5$, 60 s, n = 4, 70 s, $n=3$ Japanese females	Summer (August–October); winter (December–April)	Cheek, mid flexor forearm	Cheek ($p<0.0001$) and forearm ($p<0.01$): winter > summer
De Paepe et al. [15]	21–31 y, $n=16$, females	Autumn (October); winter (February to March)	Nasolabial area, forehead	Winter > autumn for both sites ($p<0.01$ for both)
Muizzuddin et al. [46]	18–45 y, $n=18$ (Tucson, Arizona), $n=22$ (Long Island, NY) Caucasian females	Summer (June–August); winter (December–February)	Cheek	Baseline TEWL winter > summer ($p<0.001$)
Li et al. [39]	"Parents"40–50 y, $n=40$ 'Children' 18–25 y, $n=40$ Chinese males and females	Winter (January); summer (August–September)	Elbow, face, décolletage, dorsal hand, outer forearm, lower outer leg, heel	Winter > summer at all sites except at heel summer < winter. No statistical significance stated in baseline TEWL
Song et al. [62]	20–59 y, $n=100$. Korean males	Summer (July); winter (January)	Forehead, cheek, forearm	Forehead and forearm: summer > winter ($p<0.05$). Cheek: summer > winter but did not reach significance
Wei et al. [69]	23–64 y, $n=25$ females	Summer and winter, *No months stated, season in Cincinnati, OH	Lower legs	Winter > summer ($p<0.0001$)
Yang et al. [76]	19–28 y, $n=72$ females in China	Spring, summer, autumn, and winter	Cheek, forearm	Cheek: spring > summer ($p<0.05$), winter > summer ($p<0.05$). Forearm: no significant differences
Ye et al. [77]	19–53y, $n=24$ Chinese females. *All with a 5% lactic acid stinging test result ≥ 3 and > 3 sensitivity factors	Spring (April); summer (July); autumn (October); January (winter)	Forehead, cheek, submaxilla	Forehead: spring and autumn < summer and winter ($p<0.001$ and $p<0.05$). submaxilla: spring and autumn < summer and winter ($p<0.01$). Cheeks: autumn < spring and summer and winter ($p<0.001$)

Most studies found that TEWL was increased in winter compared to summer; however, two found opposite results and some no significant differences. Conflicting results were also found when investigating four seasons

SD standard deviation

trend but did not achieve significance [62]. Black et al. also had contradicting results to the above; they collected TEWL values in 24 women during February, April, July, and December of the same year on their calf, inner forearm, and crow's feet area. For the forearm and calf, there was a significant increase in TEWL in July compared to all other months. Crow's feet area had a similar trend but did not reach significance. Black et al. only described December as winter and July as summer, but did not describe the seasons of the other 2 months [4].

Others compared TEWL values during autumn and spring as well. De Paepe et al. measured TEWL on the nasolabial area and the forehead of 16 females during autumn and winter. TEWL increased significantly in winter compared to autumn [15]. Ye et al. investigated TEWL in 24 individuals from China with 5% lactic acid stinging scores greater or equal to 3 and had 3 sensitivity factors during all four seasons on the forehead, cheeks, and submaxilla. Forehead and submaxilla TEWL was significantly greater during summer and winter compared to spring and autumn. On cheeks, TEWL was significantly greater in spring, summer and winter seasons compared to autumn. Both studies determined TEWL to be higher in winter compared to autumn [77]. Lastly, Yang et al. had a cohort of 72 women from China and measured TEWL during all four seasons on the cheek and forearm and found no significant difference in TEWL on the forearm between seasons. However, on the cheek TEWL during spring was significantly higher than in summer; and consistent with the previously discussed findings that TEWL in winter was significantly higher than in summer [76].

Altitude

Transepidermal water loss's potential relationship with altitude has only been recently investigated: Lee et al. measured TEWL in 136 Sudanese females with 49 from Jakarta, with an altitude of 7 m, and the remaining 87 from Bandung, with an altitude of 768 m, on the forehead and cheek and observed no significant effect of altitude on TEWL at both sites [38].

Individual variables

Age

Physical and biological properties of skin change with age. The effect of age on TEWL has been widely studied (Table 2). Several found no significant TEWL effect of age. For example, Rougier et al. studied 23 males in age groups 20–30 y, 45–55 y, and 65–80 y and observed no significant difference in TEWL between the groups [59]. Fluhr et al. compared TEWL in two age populations, comprising of 44 children 1–6 y and one of their adult parents 21–44 y, and found no significant differences between the groups [20]. Marrakchi et al. saw no significant difference in TEWL between 10 individuals 24–34 y and 10 individuals 66–83 y at 9 anatomic sites [43]. Firooz et al. compared a more expansive group with 10 people from each decade of life within the 10–60 y range and observed no significant differences in TEWL, as did Sato et al. comparing an elderly population with a middle-aged population in Tokyo at all anatomic sites measured [18, 60].

However, much of the literature reviewed found a decrease in TEWL in older individuals. Cua et al. investigated differences in TEWL between 7 young adult females with a mean age of 25.9 y and 8 elderly females with a mean age of 74.6 y and observed that the elderly population had a significantly lower basal TEWL. However, they measured TEWL on the forehead, upper arm, volar and dorsal forearm, postauricular area, palm, abdomen, upper back, thigh, and ankle and only saw a significant difference in the upper arm and abdomen. Nonetheless, mean TEWL was lower in the elderly at all sites, except the postauricular region [13]. Cua et al. conducted another study comparing 14 young adults with 15 elderly individuals at the same anatomic site as their first study and in this study, also included the lower back. Again, the elderly population had significantly lower baseline TEWL at all the sites, except at the palm and the postauricular area the younger population had lower baseline TEWL [14]. This difference in the relationship between age and TEWL based on anatomic site measured by the two Cua et al. studies may be attributed to the low sample size and potentially low power of their initial study. Also, their initial study only contained females, whereas the second study included women and men which may have impacted results [13, 14]. Wilhelm et al. found remarkably similar results in which they also measured at TEWL in 14 male and female young adults with mean age of 26.7 y and another group of 15 male and female elderly individuals with a mean age of 70.5 y at the same anatomic sites as the second Cua et al. study. TEWL was significantly lower in the elderly population at all regions except the postauricular area and palm, consistent with Cua et al.'s second study [14, 71].

Conti et al. investigated a different age range by comparing subjects aged 12–60 y and 61–92 y and found the older population had significantly lower TEWL values but only at certain sites measured including the epigastrium, buttocks, and calves [11]. Several other studies showed a similar decrease in TEWL with age [6, 44, 70]. Finally, Baumrin et al., took a slightly different approach and compared TEWL in infants of 3 different age groups (6 weeks–3 months, 3 months–6 months, and 6 months–12 months) with female adults in the 18–35 y age range. Infants had higher TEWL than adults with a linear decrease in TEWL with age at all sites [2].

Table 2 TEWL (transepidermal water loss): impact of age—while not all the studies agree, most found that older than 60 had significantly lower baseline TEWL compared to younger individuals

Study	Subjects (age, sample size, sex) by age strata	Site	Age and TEWL result
Rougier et al. [59]	20–30 y, $n=8$, males, 45–55 y, $n=8$, males, 65–80 y, $n=7$ males	Upper–outer arm	No significant differences
Cua et al. [13]	"Young adult" (25.9 ± 1.4 y), $n=7$, females. "Elderly" (74.6 ± 1.9y), $n=8$, females Caucasians	Forehead, upper arm, volar and dorsal forearm, postauricular, palm, abdomen, upper back, thigh, ankle	Elderly had significantly lower basal TEWL at the upper arm ($p \le 0.05$) and abdomen ($p \le 0.01$). Lower in elderly at all other sites except postauricular but not significant
Cua et al. [14]	"Young" (24.9 ± 1.1 y), $n=7$, females. "Old" (75.3 ± 2.4 y), $n=7$, females. "Young" (28.7 ± 0.5 y), $n=7$, males "Old" (73.8 ± 1.9 y), $n=8$ males Caucasians	Forehead, postauricular, upper arm, volar and dorsal forearm, palm, abdomen, thigh, ankle, upper back, lower back	Significantly lower baseline TEWL in the older population compared to young at all body regions ($p \le 0.05$) except postauricular, palm
Wilhelm et al. [71]	"Young adult" (26.7 ± 2.8 y), $n=14$, males and females. "Aged" (70.5 ± 13.8), $n=15$, males and females	Forehead, dorsal aspect upper arm, dorsal and volar aspect forearm, postauricular, palm, abdomen, upper and lower back, extensor surface of thigh, ankle	TEWL was significantly lower in the aged group compared to young adults in all regions ($p \le 0.05$) except postauricular and palm
Conti et al. [11]	12–60 y, $n=63$, males and females. 61–92 y, $n=24$, males and females	Forehead, cheek, forearm extensor and flexor, antecubital fossa, abdomen, upper back, lumbar region, buttocks, pretibial, calf, palm, dorsal hand, sole	TEWL significantly higher in younger compared to older group on epigastrium, buttocks, and calf ($p < 0.05$)
Fluhr et al. [20]	"Children" 1–6 y, $n=44$, males and females. "Parent" 21–44 y, $n=44$, males and females	Volar forearm	No significant differences
Marrakchi et al. [43]	24–34 y, $n=10$, not stated 66–83 y, $n=10$, not stated	Forehead, upper eyelid, nose, cheek, nasolabial and perioral areas, chin, neck, volar forearm	No significant differences
Wen et al. [Abstract] [70]	$n=62$	Neck, inner side of flexible forearm	TEWL significantly lower in subjects older than 60 than younger ($p < 0.05$)
Firooz et al. [18]	10–20 y, $n=10$, 20–30 y, $n=$", 30–40 y, $n=$", 40–50y, $n=$", 50–60 y, $n=$" all groups with males and females	Forehead, cheek, nasolabial fold, neck, forearm, dorsal side of the hand, palm, leg	No significant differences
Boireau-Adamezyk et al. [6]	18–30 y, $n=10$, 30–40 y, $n=$", 40–55y, $n=$", 55–70, $n=$" french females	Face, dorsal forearm, upper inner arm	Linear regression: significant decrease in TEWL with age at face and upper inner arm ($p < 0.05$); no significant correlation for dorsal forearm
Sato et al. [60]	"Elderly" 70–89 y, $n=41$, "middle-aged" 35–45 y, $n=20$ males and females in Tokyo	Buttocks, back*, outer side of lower leg**, inner forearm. *1 "middle-aged" subject did not measure TEWL at this site. **1 "elderly" subject did not measure TEWL at this site	No significant differences
Baumrin et al. [2]	Infants (6 weeks–12 months). G1: 6 weeks–3 months, $n=12$. G2: 3 months–6 months, $n=11$. G3: 6 months–12 months, $n=20$. Adults 18–35 y, $n=60$ all females, all South African	Dorsal forearm, ventral upper arm	Higher TEWL in infants than adults. Linear decrease with age at both sites: dorsal forearm $R=0.37$, $p=0.01$. Ventral arm $R=0.18$, $p=0.23$

Table 2 (continued)

Study	Subjects (age, sample size, sex) by age strata	Site	Age and TEWL result
Mehta et al. [44]	G1: 5–20 y, $n=110$, G2: 21–35 y, $n=169$, G3:36–50 y, $n=126$, G4: 51–70 y, $n=95$. Indian males and females	Scalp, forehead, forearm, leg	TEWL significantly higher in G1 and G2 compared to G3 and G4 at all sites ($p<0.05$) but not significant on forearm
Xie et al. [74]	G1: 16–20 y, $n=45$, G2: 21–25 y, $n=$”, G3: 26–30 y, $n=$”, G4: 31–35 y, $n=$”, G5: 36–40 y, $n=$”, G6: 41–45 y, $n=$”, G7: 46–50 y, $n=$”, G8: 51–55 y, $n=$”, G9: 56–60 y, $n=$”, G10: 61–66 y, $n=$” Chinese females	Midpoint of the connection line between lower edge of ear and suprasternal fossa	G4 and older had significantly higher TEWL than G1 ($p<0.05$)

SD standard deviation

An outlier to the analysis above is Xie et al. in that the TEWL positively correlated with age. They measured TEWL in 10 age groups (16–20 y, 21–25 y, 26–30 y, 31–35 y, 36–40 y, 41–45y, 46–50 y, 51–55 y, 56–60 y, and 61–66 y) of Chinese females and individuals 31 y and older had significantly higher TEWL than the individuals in the youngest group and suggested this difference may be due to geographic and ethnic variations since many of the other studies that concluded TEWL decreases with age were performed in America [74].

Anatomic site

Effect of anatomic site on TEWL is also an extensively studied (Table 3); many compared facial TEWL values with values on the extremities. Boireau-Adamezyk et al. investigated TEWL levels in 40 French women and elucidated the following relationship in TEWL: face > dorsal forearm = upper inner arm [6]. Mehta et al. measured TEWL in 500 Indians at the scalp, forehead, forearm, and leg. Scalp and forehead had significantly higher TEWL than the extremities, consistent with Boireau-Adamezyk et al.'s findings that the face has weaker barrier function than the extremities [6, 44].

Many studies conducted an even more expanded comparison by examining at a variety of anatomic sites. Rougier et al. found the following relationship after measuring TEWL in various anatomic sites of 7–8 males: forearm (ventral elbow) < forearm (ventral mid) < arm (upper outer) ≤ abdomen < forearm (ventral-wrist) < postauricular < forehead [59]. Machado et al. measured TEWL in 6 sites in a group of male and female Asians, and Caucasians and determined the following relationship in TEWL: forehead > wrist > ventral mid-forearm close to the ventral wrist = ventral mid-forearm close to the ventral elbow = elbow = abdomen [42]. Mohammed et al. measured TEWL in 22 Caucasian and Black males and females and observed the following: cheek > wrist > abdomen = mid-ventral forearm [45]. Note that the face has the highest TEWL followed by the wrist, but the extremities and abdomen show conflicting results.

Several studies accomplished a more detailed approach and investigated whether TEWL differences exist between different areas within a general anatomic site. For example, many studies compared TEWL in different forearm areas. This is an area of significant interest since many investigations measure TEWL at the forearm. Panisset et al. compared TEWL in 14 males and females on the ventral forearm at 3.5, 6.5, 9.5, 12.5, 15.5, 18.5 and 20.5 cm up from fold of wrist. The wrist had a significantly higher TEWL than all the other sites with no significant differences between the other sites [52]. Van der Valk et al. measured TEWL in 4 males and 6 females at a site next to the wrist fold, next to the cubital fossa, and 3 equidistant sites between and found the highest TEWL at the wrist and a gradual decrease

Table 3 TEWL (transepidermal water loss): impact of anatomic site—most studies found a significant relationship between site and TEWL

Study	Subjects (age range or mean ± SD, sample size, sex)	Site	Anatomic site and TEWL result
Rougier et al. [59]	20–30 y, 7–8 subjects per anatomic site, males	Forehead, postauricular, arm (upper-outer), forearm (ventral-elbow), forearm (ventral-mid), forearm (ventral-wrist), abdomen	Forearm (ventral elbow) < forearm (ventral mid) < arm (upper outer) ≤ abdomen < forearm (ventral-wrist) < postauricular < forehead (no statistical significance noted)
Van Der Valk et al. [67]	22–64 y, $n = 10$, males and females	Volar forearm: cubital fossa, wrist fold, and 3 equidistant sites between	Significant variation in mean baseline TEWL from wrist to elbow ($p < 0.05$); Gradual decrease wrist to elbow and increase at cubital fossa
Panisset et al. [52]	20–42 y, $n = 14$ males and females	Ventral forearm: 3.5, 6.5, 9.5, 12.5, 15.5, 18.5 and 20.5 cm from fold of wrist at 1.5 cm on sides of a median line	Mean TEWL at wrist significantly higher than all other sites ($p < 0.002$); no significant differences in TEWL between all other sites
Chilcott et al. [8]	18–28 y, $n = 17$ males and female Caucasians	Volar forearms: five 2.5 cm diameter circular areas (1 cm apart and uppermost 4 cm from antecubital fossa)	Most proximal site > midpoint ($p < 0.001$); most distal site > midpoint ($p < 0.01$)
Bock et al. [5]	25–54 y, $n = 25$ males and females	Volar forearm: 'distal' site 5 cm from wrist, 'mid volar' site, 'proximal' site 5 cm from cubital fossa	No significant difference in baseline TEWL between all sites
Machado et al. [42]	20–60 y, $n = 90$ males and female Asian and Caucasian	Ventral wrist, ventral mid forearm close to ventral wrist (FA1), ventral mid forearm close to ventral elbow (FA2), ventral elbow, forehead*, abdomen**. *$n = 84$, **$n = 59$	Forehead > wrist > FA1 = FA2 = elbow = abdomen ($p < 0.05$)
Mohammed et al. [45]	20–58 y, $n = 22$ males and females Caucasian and Black	Cheek, abdomen, wrist, mid-ventral forearm	Cheek > wrist > abdomen = mid-ventral forearm ($p < 0.05$)
Boireau-Adamezyk et al. [6]	18–30 y, $n = 10$, 30–40 y, $n =$ ", 40–55 y, $n =$ ", 55–70 y, $n =$ ' French females	Face, dorsal forearm, upper inner arm	Face > dorsal forearm = upper inner arm
Baumrin et al. [2]	Infants (6 weeks–12 months), G1: 6 weeks-3 months, n = 12, G2: 3 months–6 months, $n = 11$, G3: 6 months–12 months, n-20. Adults 18–35 y ($n = 60$). All adults females	Dorsal forearm, ventral upper arm	Infants: ventral upper arm > dorsal forearm ($p = 0.008$). Adults: no significant difference
Mehta et al. [44]	G1: 5–20 y, $n = 110$, G2: 21–35 y, $n = 169$, G3:36–50 y, $n = 126$, G4: 51–70 y, $n = 95$ Indian males and females	Scalp, forehead, forearm, leg	Scalp and forehead > extremities ($p < 0.05$)

In general, face has the highest TEWL, followed by wrist, and then abdomen and extremities. No conclusive relationship found regarding abdomen and extremities

SD standard deviation

towards the elbow. However, there was a slight increase at the site near the cubital fossa compared to the more distal site [67]. Conversely, Chilcott et al. determined TEWL in 17 male and female Caucasians at five 2.5 cm diameter circular areas 1 cm apart on the volar forearm; the most distal site and most proximal site had significantly higher TEWL than the midpoint [8]. Finally, Bock et al. measured TEWL in 25 males and females on the volar forearm at a distal, a mid-volar, and a proximal site—with no significant differences between any of the three sites [5]. With all studies yielding different results, a true correlation between TEWL and the placement on the forearm region cannot be derived.

Sex

Studies have found no significant impact of sex on TEWL at multiple sites (Table 4). These include Lammintausta et al. comparing 7 white females and 7 white males, Rougier et al. comparing groups of 7–8 males and females, Cua et al. comparing 14 Caucasian females and 15 Caucasian males, and Wilhelm et al. comparing 14 males and 15 females [14, 36, 59, 71].

However, others found a difference in TEWL based on sex. Conti et al. compared TEWL between 35 males and 58 females at 14 sites. Males had a greater TEWL than females at most sites; however, it was only significant at the cheek, upper back, and calf [11]. Chilcott et al. measured TEWL in 8 Caucasian males and 9 Caucasian females on the forearm and males had a significantly higher TEWL than females, about 5% higher [8]. This contradicts Conti et al. who did not find a significant difference between males and females at the forearm. Firooz et al. measured TEWL in 25 males and 25 females and overall males had significantly higher results than females when comparing the mean TEWL from multiple sites [18].

Two studies found age-related sex differences, but with conflicting results. Luebberding et al. studied six groups with the following age ranges: 20–29 y, 30–39 y, 40–49 y, 50–59 y, and 60–74 y. Each had 30 females and 30 males. Until the age of 50, men had significantly lower TEWL than women, regardless of site. However, this difference in TEWL diminished with age at most anatomic sites [41]. Mehta et al. studied 4 age groups (5–20 y, 21–35 y, 36–50 y, and 51–70 y) comprised of Indian females and males. Males had a significantly greater TEWL than females at all ages, except for the 51–70 y group where there was no significant difference [44].

Skin of color

Much literature investigating impact of skin of color on TEWL, compared black skin and white skin. However, in another manuscript we reviewed 26 articles and found conflicting results; several determined no significant difference in TEWL between black and white skin, some finding black skin to have a greater TEWL, and some finding white skin to have a greater TEWL [53].

Skin of color research has expanded beyond white and black skin and includes other groups, such as Hispanic and East Asian groups. However, we found a similar spread of results with varying significance and TEWL relationships between skin of color groups [53]. For example, Berardesca et al. determined baseline TEWL values in 15 Black volunteers with parents and grandparents that were described as Black, 12 white volunteers of Anglo-Saxon ancestry, and 12 Hispanic volunteers who were Mexican immigrants in Northern California and found no significant difference between baseline TEWL between the three groups [3]. On the other hand, Sugino et al. (abstract only) examined a wider expanse of various skin of color groups, with Black, Caucasian, Hispanic and Asian participants and found TEWL values of the groups to be in the following order: Black > Caucasian ≥ Hispanic ≥ Asian [64].

Finally, we found that even within skin of color groups, for example, Asians, there were inconclusive results regarding whether TEWL differences exist between subgroups of these overarching skin of color categories, such as between Indonesians and Vietnamese individuals [53].

Circadian rhythm

Spruit was the earliest to investigate whether time influences TEWL. He measured a subject's TEWL on their forearm at 8:00 and 16:00 every day from March 21st to April 13th, 1970 (Table 5). TEWL was higher at 16:00 compared to 8:00 [63]. Reinberg et al. investigated this topic in detail measuring TEWL on the forearm for 48 h at 4:00, 9:00, 14:00, 19:00, 23:00 in female Caucasians. There were troughs in TEWL at 14:00 and peaks during the night. This somewhat coincides with Spruit who found higher TEWL during the latter part of the day [57, 63]. Yosipovitch et al. took frequent measurements every 2 hrs in 2 sessions over a cumulative 24-h span in 9 men and 7 women, measuring TEWL at the forehead, upper back, forearm, and shins. TEWL had a significant time dependence at all sites, with a maximum TEWL around 20:00 and a minimum from 8:00 to 10:00 at most sites. However, shin had 2 peaks at 12:00 and 4:00. Yosipovitch et al. generated a curve of the circadian rhythm of TEWL on forearm and forehead, which coincides with Spruits' findings that at 16:00 the TEWL is higher than at 8:00 [63, 78]. However, it did not have a trough at 14:00 that Reinberg et al. had found [57]. Ostermeier et al. (abstract only) measured cheek and forehead 4 times in a 12 hr span in 24 individuals and evening TEWL was higher than at all other time points [50].

Table 4 TEWL (transepidermal water loss): impact of sex—most found that males had higher baseline TEWL compared to females and only one study found the opposite

Study	Subjects (age range or mean ± SD, sample size, sex)	Site	Sex and TEWL result
Lammintausta et al. [36]	19–65 y, $n=7$, females, 16–64 y, $n=7$, males Caucasians	Right upper back above the scapula (3 areas)	No significant baseline differences
Rougier et al. [59]	20–30 y, $n=7$ or 8 per group, males and females	Upper-outer arm (8 males and 7 females), forehead (7 males and 8 females)	No significant differences
Cua et al. [14]	"Young" (24.9 ± 1.1 y), $n=7$, females, "Old" (75.3 ± 2.4 y), $n=7$, females, "Young" (28.7 ± 0.5 y), $n=7$, males, "Old" (73.8 ± 1.9 y), $n=8$, males Caucasians	Forehead, postauricular, upper arm, volar and dorsal forearm, palm, abdomen, thigh, ankle, upper back, lower back	No significant differences
Wilhelm et al. [71]	"Young adult" (26.7 ± 2.8 y), $n=7$, males, "Young adult" (26.7 ± 2.8 y), $n=7$, females, "Aged" (70.5 ± 13.8), $n=8$, males, "Aged" (70.5 ± 13.8), $n=7$, females	Forehead, dorsal aspect upper arm, dorsal and volar aspect forearm, postauricular region, palm, abdomen, upper and lower part of the back, extensor surface of the thigh, ankle	No significant differences
Conti et al. [11]	2–92 y, $n=93$, 35 males and 58 females	Forehead, cheek, extensor and flexor side of the forearm, antecubital fossa, abdomen, upper back, lumbar region, buttocks, pretibial area, calf, palm, dorsal hand, sole	Males > females significant at cheek, upper back, and calf ($p<0.05$)
Chilcott et al. [8]	18–28 y, $n=17$, 8 males and 9 females Caucasians	Volar forearm (five 2.5 cm diameter circular areas (1 cm apart and uppermost area 4 cm from antecubital fossa)	Males > females ($p<0.05$)
Firooz et al. [18]	10–60 y, $n=50$, 25 males and 25 females	Forehead, cheek, nasolabial fold, neck, forearm, dorsal side of the hand, palm, leg	Males > females ($p<0.05$)
Luebberding et al. [41]	G1: 20–29 y, $n=60$, G2: 30–39 y, $n=60$, G3:40–49 y, $n=60$, G4: 50–59 y, $n=60$, G5 60–74 y, $n=60$, 30 males and 30 females in each group	Forehead, cheek, neck, volar forearm, dorsal hand	Independent of age: female > male ($p<0.05$). Age-dependent differences: G1–G3: females > men of same age at face, neck, and forearm ($p<0.05$). Older than 50y: difference diminishes with age at face and neck but not forearm
Mehta et al. [44]	G1: 5–20 y, $n=61$, males. G1: 5-20y, $n=49$, females. G2: 21–35 y, $n=79$, males. G2: 21–35 y, $n=90$, females. G3:36–50 y, $n=64$, males. G3:36–50 y, $n=62$, females. G4: 51–70 y, $n=63$, males. G4: 51–70 y, $n=32$, females Indians	Scalp, forehead, forearm, leg	Median TEWL males > females at all ages except G4 ($p<0.05$)

Studies that found no significant difference in TEWL based on sex were the oldest

SD standard deviation

Table 5 TEWL (transepidermal water loss): impact of circadian rhythm—all studies found a relationship between time and baseline TEWL; however, findings were inconclusive due to the disparity in results

Study	Subjects (age range or mean ± SD, sample size, sex)	Measurement times	Site	Circadian rhythm and TEWL result
Spruit [63]	$N = 1$ *age and sex unknown	8:00 and 16:00 from March 21 to April 13, 1970	Volar aspect of forearm at 3 sites	Baseline water vapor loss: 16:00 > 8:00
Reinberg et al. [59]	27.9 ± 2.7 y, $n = 7$ females All Caucasian	48 h time span day 1 18:00-Day 3 15:00 h. Measurement times each day: 4:00, 9:00, 14:00, 19:00, 23:00	Flexor forearm	Troughs at 14:00 and peaks during night
Yosipovitch et al. [78]	23–53 y, $n = 16$, males and females	Measured every 2 h in 2 sessions (daytime and nightime) over a cumulative 24 h*. *6 subjects not examined during the daytime session	Forehead, upper back, Forearm, Shins	TEWL time dependent at all sites ($p \leq 0.05$). Most subjects: max at the evening (~ 20:00); minimum in the morning (8:00–10:00) except shins. Shin: 2 peaks (12:00 and 4:00). All sites peak to trough difference significant ($p < 0.05$)
Chilcott et al. [8]	18–28 y, $n = 17$ males and females Caucasians	Measured every 2 h from 9:00 to 17:00	Volar forearm (five 2.5 cm diameter circular areas 1 cm apart and uppermost 4 cm from antecubital fossa)	Baseline TEWL: 9:00 > 17:00 ($p < 0.05$); 9% decrease
Le Fur et al. [37]	21–32 y, $n = 8$ females Caucasians	Measured every 4 h for 48 h	Face, volar forearm	Circadian rhythm: circadian face ($p < 0.0005$) forearm ($p < 0.03$) 12 h rhythm for face ($p < 0.05$) and forearm ($p < 0.0001$), 8 h rhythm face ($p < 0.0005$) forearm ($p < 0.0006$), face: 2 peaks at 8:00 and 16:00; trough at 20:00–0:00, forearm: 2 peaks at 8:00 and 16:00; 2 troughs at 12:00 and 0:00
Ostermeier et al. [Abstract] (2018) [50]	21–39 y; $n = 24$ sex not mentioned	Measured 4 times in 12hrs	Cheek, forehead	Evening higher than at all other times

SD standard deviation

Conversely, two studies observed a peak in TEWL in the morning, unlike the previously mentioned studies. Chilcott et al. measured TEWL every 2hrs from 9:00 to 17:00 in 8 male and 9 female Caucasians on forearms; TEWL at 9:00 was significantly higher than at 17:00 [8]. Le Fur et al. measured TEWL every 4hrs for 48hrs in 8 female Caucasians on the face and volar forearm. There were 24 hr, 12 hr, and even 8 hr significant rhythms on both sites. However, face had 2 peaks at 8:00 and 16:00 and a trough at night from 20:00 to 0:00 and the forearm 2 peaks at 8:00 and 16:00 and 2 troughs at 12:00 and 0:00 [37].

Sleep

Impact of sleep on TEWL is a recently explored variable (Table 6). Altemus et al. investigated a 42 hr sleep deprivation in 11 females compared to baseline and there were no significant differences in TEWL on the forearm or face [1]. Choi et al. (abstract) investigated lack of sleep and alcohol on 20 Korean males, who frequently drink and did not get enough sleep. They compared TEWL after a good night of sleep to the morning after not having slept and drinking alcohol for 1 h the night before and found no significant TEWL differences [10].

Conversely, Oyetakin-White et al. analyzed TEWL in poor and good Caucasian female sleepers. Poor sleepers were defined as having a Pittsburg Sleep Quality Index (PSQI) greater than 5 and sleep duration of less than or equal to 5 h and good sleepers as having a PSQI of less than or equal to 5 and a sleep duration of 7–9 h. Poor sleepers had significantly higher baseline TEWL than good sleepers [51]. Jang et al. (abstract) found similar results in a group of 32 Korean women. They measured TEWL before sleeping and after washing to after 7 h of sleep the next morning. TEWL decreased post sleeping [31].

Food

Studies suggest that certain foods impact TEWL (Table 7). Hong et al. investigated TEWL impact of galacto-oligosaccharides (GOS) as found in infant formula as a supplement, milk products, certain beverages, and products [66]. Hong et al. compared TEWL levels in individuals receiving 1 g of GOS twice daily to those consuming 100% dextrin placebo and measured TEWL at the crow's feet area in 79 Koreans with crow's feet, observing a significantly greater decrease in TEWL in those who consumed GOS compared to the placebo by week 4. There was no significant TEWL difference in placebo group at week 12 compared to baseline. There, however, was a significant difference in the GOS group compared to their baseline at week 12 [30].

Fukunaga et al. compared TEWL in 17 individuals on forearm and cheek after the subjects had consumed either 1.8 mg of glucosylceramide (GlcCer) daily or a placebo. GlcCer occurs in foods like barely, rice, and corn. Individuals had significantly lower TEWL after consuming GlcCer compared to before consumption and the difference in TEWL before consuming GlcCer to after consuming GlcCer

Table 6 TEWL (transepidermal water loss): impact of sleep—two of four studies found that sleep decreases baseline TEWL; however, the others found no significant differences in TEWL due to sleep

Study	Subjects (age range or mean ± SD, sample size, sex)	Sleep	Site	Sleep and TEWL result
Altemus et al. [1]	18–29 y, $n=11$ females	42 h of sleep deprivation (compared to baseline)	Cheek, flexor forearm	No significant differences
Oyetakin-White et al. [51]	30–50 y, $n=60$ females Caucasians	Poor sleepers ($n=30$) PSQI > 5, sleep duration ≤ 5 h. Good sleepers ($n=30$) PSQI ≤ 5, sleep duration 7–9 h	Upper inner arm	Baseline TEWL: poor sleepers > good sleepers ($p=0.04$)
Choi et al. [Abstract] [10]	30–36y, $n=20$ males Koreans who often drink and lack sleep	Measurement 1: day 1- morning after good night sleep. Measurement 2: day 2 drank 360 mL 17.5% alcohol for 1 h at night and measured the next morning after not sleeping	Facial areas	No significant differences
Jang et al. [Abstract] [31]	'Old group' (mean age 47.9 ± 5.1 y): $n=21$ females, 'Young Group' (mean age 27.5 ± 2.8 y): $n=11$ females Koreans	Measurement 1: before sleep (after wash). Measurement 2: after 7 h sleep in morning. Measurement 3: after wash	Not stated	Baseline TEWL: before sleeping > after sleeping

SD standard deviation

Table 7 TEWL (transepidermal water loss): impact of food—all studies found an impact of a specific food or food supplement on TEWL

Study	Subjects (age range or mean ± SD, sample size, sex)	Food	Site	Food and TEWL result
Hong et al. [34]	32–68 y, $n = 79$ males and females Koreans with fine wrinkles at outer corner eyes	12 weeks food: 1 g of galacto-oligosaccarides (GOS) 2x/day, control: 100% dextrin	Crow's feet area	Week 4: GOS reduction from baseline > control reduction from baseline ($p < 0.05$). Week 12: no significant difference between control W12 and control baseline GOS W12 < GOS baseline ($p < 0.05$)
Fukunaga et al. [23]	> 20 y (mean age 43.6 ± 10.3 y): $n = 17$ males and females	Measurement 1: baseline, Measurement 2: 4 weeks after food: 1.8 mg of glucosylceramide (GlcCer) 1 × daily or Placebo: same pill without GlcCer 1 × daily, Measurement 3: after 4 weeks washout, Measurement 4: after 4 weeks GlcCer or Placebo ingestion 1 × daily (given the opposite treatment to what was given for Measurement 2)	Forearm, cheek	Forearm: after ingestion GlcCer < before ingestion GlcCer ($p = 0.02$); difference between before digestion and after digestion of control vs. GlcCer: GlcCer significantly lower than Control ($p = 0.01$). Cheek: no significant differences
Kuwano et al. [34]	25–52 y, $n = 36$ males Japanese	6 months food: glucono-δ-lactone (GDL) 2000 mg/day. Placebo: same pill without GDL	Face	GDL and placebo group: 6 months > baseline rate of Change TEWL compared to placebo > GDL ($p < 0.05$)
Vaughn et al. [68]	25–59 y, $n = 30$ males and females	4 weeks, 4 tablets 2 × daily, G1: Placebo, G2: 500 mg/tablet turmeric, G3: 500 mg/tablet organic herbs	Forehead, cheek	Placebo and turmeric: no significant differences. Herbal: baseline > 4 weeks ($p = 0.003$)

SD standard deviation

was significantly lower than just taking the placebo. However, these differences were only at forearm but not cheek [23].

Kuwano et al. investigating TEWL impact of glucono-δ-lactone (GDL), a food supplement and found naturally in wine and honey, had 36 Japanese males consume 2000 mg/day of GDL or placebo for 6 months. Both groups had higher TEWL levels compared to baseline. However, they attributed this to seasonal changes, as the weather changed to winter at the 6-month benchmark. Rate of TEWL change in the placebo group was significantly greater than the GDL group, suggesting GDL helped preserve barrier function in winter [34].

Vaughn et al. examined TEWL effect of turmeric and herbal combination tablet consumption. Turmeric, a widely used spice in certain ethnic groups, and herbal supplements are often taken. Thirty participants were given either a placebo or a tablet containing 500 mg of turmeric or tablet containing 500 mg of an herbal combination—4 tablets twice daily for 4 weeks. No significant differences were observed between the placebo and turmeric groups, but the herbal combination group had a significantly decreased TEWL after 4 weeks of consumption compared to baseline [68].

Body mass index (BMI)

Several studies investigated BMI and obesity's potential impact on TEWL (Table 8). Guida et al. compared forearm TEWL in an obese group defined by a BMI of ≥ 30 kg/m^2 to a control group with BMI ranging from 18.5 to 24.9 kg/m^2. Control had significantly greater BMI compared to the obese group, but there were no significant differences based on BMI level within the obese group. In addition, within the obese group, those with abdominal obesity had significantly lower TEWL compared to those without [26]. However, Nino et al. found contrasting results; they measured forearm TEWL in an overweight group with BMI between the 85th–95th percentile and an obese group greater than the 95th percentile and compared it to the TEWL of a normal weight group. Those with abdominal obesity had significantly higher TEWL than those without. Also, obese, and overweight individuals had a significantly greater TEWL compared to normal weight individuals. They did not find significant correlation between TEWL and BMI value [49]. Löffler et al. found results similar to Nino et al.'s findings; they compared an underweight/normal group with a BMI under 25 kg/m^2, an overweight group of 25–30 kg/m^2, and an obese group with a BMI greater than 30 kg/m^2. The obese group had significantly greater TEWL than the normal/underweight group, but no significant difference between the overweight and normal/underweight group. They also, unlike the other two groups, found a significant positive correlation between BMI value and TEWL [40]. Finally,

Table 8 TEWL (transepidermal water loss): impact of BMI—in three of four studies either an increase in BMI or obesity lead to an increase in TEWL

Study	Subjects (age range or mean ± SD, sample size, sex)	BMI/obesity	Site	BMI/obesity and TEWL result
Löffler et al. [40]	18–60 y, $n = 63$ Males and females	G1: BMI < 25 kg/m^2 (underweight and normal). G2: BMI 25–30 kg/m^2 (overweight). G3: BMI > 30 kg/m^2 (obese)	Flexor forearm	G3 > G1 ($p < 0.05$); trend of increase from G1 to G3; significant correlation between BMI and baseline TEWL ($p < 0.01$)
Guida et al. [26]	Obese (mean age 37.1 ± 13.1 y): $n = 60$. Control (mean age 41.0 ± 12.3 y): $n = 20$ males and females	Obese: BMI ≥ 30 kg/m^2 control: BMI 18.5–24.9 kg/m^2	Volar forearm	Control > Obese ($p < 0.05$) no significant TEWL differences based on BMI level in obese group. Obese group: without abdominal obesity > with abdominal obesity ($p < 0.05$)
Nino et al. [49]	Overweight and Obese (age 8-15 y): $n = 65$. Normal weight (age 7–15 y): $n = 30$ males and females	Overweight: BMI 85–95 percentile. Obese: BMI > 95 percentile. Normal weight percentile based on age and sex	Volar forearm	Obese > normal weight ($p < 0.05$). No significant differences according to BMI level, with abdominal obesity > without abdominal obesity ($p < 0.05$)
Tavares et al. [Abstract] [65]	20–46y, n = 51 females	All subjects obese or overweight	Face, breast, abdomen	Positive correlation between BMI and TEWL at all sites (between 0.282 and 0.601)

Opposing results were found regarding the impact of abdominal obesity on TEWL

SD standard deviation

Tavares et al. (abstract only) investigated the correlation between BMI value and TEWL in obese and overweight subjects at the face, breast, and abdomen. There was a positive correlation between BMI and TEWL at all sites [65].

Smoking status

Impact of smoking status on TEWL appears to be uncertain (Table 9). Muizzuddin et al. compared TEWL in active smokers, passive smokers, and non-smokers. They defined active smoker as someone smoking 1 pack of cigarettes or more daily for more than 5 years. Passive smoker was defined as someone who never smoked but had lived or worked with a heavy smoker for 20 years. Non-smoker was defined as those never smoking and was only exposed to smoke causally such as in public places.

Non-smokers had significantly lower levels of TEWL compared to both active and passive smokers. No significant difference was observed between active and passive smokers [47]. Xin et al. found contradicting results where they analyzed TEWL in non-smokers, light to moderate smokers who smoked less than 20 cigarettes a day, and heavy smokers who smoked 20 or more cigarettes per day. There was no significant difference in TEWL between the groups and no correlation between basal TEWL and years the individual had smoked [75].

Eccrine sweating

Sweating can be the result of high temperature, physical activity, and emotion. Since the temperature has been researched as a separate variable and subjects are usually not doing intensive physical activity during TEWL studies, we examined the impact of emotional sweating on TEWL. Being a part of an experiment and having one's TEWL measured can be potentially anxiety or emotion-inducing, therefore it is a relevant variable of interest. Pinnagoda et al. showed how emotional sweat impacted TEWL and used physical activity to induce sweating. However, prior to exercising, they measured baseline TEWL in the 44 men and women on forearm with and without a topical agent used to inhibit sweating. In most cases, this difference pre-exercise in treated and untreated was not significantly different. Nonetheless, they found 6 'emotional sweaters', whose pre-exercise TEWL without a sweat inhibitor was significantly higher than the treated side [56].

Menstrual cycle

Effect of the menstrual cycle and menopause on TEWL remains uncertain (Table 10). Harvell et al. measured TEWL in females on day of maximal estrogen secretion, the day of maximal progesterone secretion, and day of minimal estrogen/progesterone secretion. On the day of minimal estrogen/progesterone secretion subjects had significantly higher TEWL than on the day of maximal estrogen secretion on the back and forearm. However, note that Harvell et al. determined these measurement days based on menstrual cycle start date and admitted there was inherent uncertainty when doing so. As a result, 67% of the data was obtained within a day of the expected event (i.e. day of maximal progesterone secretion) and 92% of the data was within two days [27]. Fujimura et al., on the other hand, investigated menopause effects by comparing TEWL in young and middle-aged females to post-menopausal females at multiple sites; there were no significant differences in TEWL based on menopause [22].

Table 9 TEWL (transepidermal water loss): impact of smoking status—the two studies have differing results and therefore no conclusion can be made on whether smoking status impacts TEWL and if it does how

Study	Subjects (age range or mean ± SD, sample size, sex)	Smoking status	Site	Smoking status and TEWL result
Muizzuddin et al. [47]	≥ 35 y, $n = 100$ People from New York, New Jersey, and Pennsylvania. *Sex not mentioned	Active smoker: ≥ 1 pack of cigarettes/day for > 5 y. Passive smoker: never smoked and lived/worked with heavy smoker for 20 y. Non-smokers: never smoked and not exposed to smoke except casually	Cheek	Baseline TEWL: non-smokers < active and passive ($p < 0.001$)
Xin et al. [75]	41–65 y, $n = 99$ males	Non-smokers. Light to moderate smokers: < 20 cigarettes/day. Heavy smokers: ≥ 20 cigarettes/day	Forearm	No significant TEWL differences between groups and no correlation between basal TEWL and years smoked

SD standard deviation

Table 10 TEWL (transepidermal water loss): impact of menstruation—based on the findings of the two studies menstrual cycle may impact TEWL while menopause may not

Study	Subjects (age range or mean ± SD, sample size, sex)	Menstrual cycle	Site	Menstrual cycle and TEWL result
Harvell et al. [27]	19–46 y, $n=9$ females	Measurement days: day of maximal estrogen secretion. Day of maximal progesterone secretion, day of minimal estrogen/progesterone secretion	Volar forearm, interscapular area of upper back	Baseline TEWL: day of minimal estrogen/progesterone secretion > day of maximal estrogen secretion at forearm ($p=0.021$) and back ($p=0.037$). Trend of higher TEWL from day maximal estrogen secretion to day of minimal estrogen/progesterone secretion
Fujimura et al. [22]	Younger group 21–39 y, $n=31$. Middle-aged group 40–49 y, $n=28$. Older post-menopausal group 47-60y, $n=40$ females from Bangkok	Pre-menopause: younger and middle-aged group. post menopause: older group	Labia majora, groin, mons pubis, inner forearm, inner thigh	No significant differences between pre- and post-menopausal groups

SD standard deviation

Discussion

Based on the summarized studies, several variables impact TEWL or may potentially impact TEWL measurements and therefore should be controlled for when conducting such experiments. Sample size and power should be a primary consideration where realistic, when conducting a TEWL experiment (and any experiment in general). Many TEWL experiments observed no significant correlation between their variable of interest and TEWL, but, without a power calculation, conclusions offered cannot be considered strong evidence or provide statistically acceptable significance due to the possibility of a type II error. Vaughn et al. was the only paper assessed here that explicitly stated that they conducted power calculation to determine the minimum necessary sample size [68]. Most sample sizes in other studies do not appear to include a significantly large sample size and no statistical analysis or margins of error have been established by them. Absence of power calculation is an aspect that is lacking in much TEWL research. In addition, having a small sample size does not readily and accurately reveal real and important biological findings to the researchers.

Next, evaporimeter standardization and technician training have a clear impact on the measurements and are important variables that should be controlled for. Room temperature has a positive correlation with TEWL. Pinnagoda et al. recommends a room temperature of 20–22 °C to avoid potential fluctuations in measurements and avoid sweating [54]. Rogiers et al. suggest a room temperature below 22 °C; however, at 18 °C it may be impossible to test due to persons complaining of cold and not wanting to continue the study [58]. Many TEWL studies follow this temperature guideline and conduct TEWL measurement in temperature-controlled environments or with sweat inhibitors to eliminate potential adverse impact of a high-temperature environment [30, 37, 56].

Climatic factors are critical in the measurement of TEWL. As discussed previously, evidence exists that temperature has an impact on TEWL. Relative humidity has also been described as being a complex but important variable in determining TEWL and advised to be kept close to but lower than 50% [58]. Therefore, we decided to determine how many of the inspected papers controlled for climatic conditions during TEWL measurement and if so, were the conditions described. Abstracts were not included as it could not be determined from the limited information provided whether climatic factors were controlled. Words such as "standardized", "maintained", and "use of air conditioning" were considered to indicate a controlled environment. Of the 57 papers inspected, 33 controlled for and identified the temperature and relative humidity of the test environment and 1 paper controlled for and identified only temperature. 2 papers stated that they controlled for climatic conditions but did not describe them; 16 papers did not control for climatic conditions but measured and reported temperature and relative humidity in the test area; and 5 papers did not control for or report climatic conditions. Overall, around 60% of the papers reviewed controlled for these variables. Such conditions are critical variables that must be controlled for in all studies. Furthermore, the methods of control varied from air conditioning to climatic chambers to undescribed methods [1, 5, 8]. Standardization of how climatic factors are controlled is also important in validating results as some methods may be more effective than others. Finally, it is important to note that even within the controlled studies variation existed in how much "control" was placed on the climatic conditions. For example, Mehta et al. stated that they maintained the temperature and relative humidity, but the reported limits were 20–27 °C and 10–60%, respectively [44]. On the other hand, Xie et al. also controlled for these conditions but maintained the testing conditions at 20 ± 1 °C and 55 ± 3% relative humidity [74]. While most of the papers with identified controls had tighter limits like Xie et al. it is important to standardize the acceptable amount of variation in temperature and relative humidity when controlling for climatic conditions.

Environment that the subjects experience impacts TEWL, but no consistent relationship has been determined. Studies compared TEWL during winter and summer; most determined that during winter humans have higher TEWL values. Wei et al. suggest this reduction in skin barrier function may be the result of changes in levels and ratios of stratum corneum lipids and keratin levels that occur during the winter [69].

Some had conflicting results with skin having higher TEWL in summer compared to winter. Song et al. suggests this may be due to an increase in skin hydration that helps persevere the skin barrier because of the often increase in humidity during summer [62]. Additionally, when evaluating TEWL over all seasons, it appears that in general summer and winter cause significantly higher TEWL than autumn and spring. This further validates the notion that season impacts TEWL and should be controlled for. Next, only one study was conducted on altitude impact with no significant effect [38]. However, power analysis was not conducted and more studies investigating the relationship between altitude and TEWL are needed.

Physiological factors considered age; most concluded that TEWL decreases with age, especially as one reaches their 60–70s. This has been illustrated in a review by Rogiers et al. that suggested that significant differences in TEWL may occur during certain periods of life; however, they found no significant difference overall [58]. Several studies observed no significant difference with age, but such studies were far less in number. Some like those by Rougier et al. and Marrakchi et al. had small sample sizes [43, 59]. Fluhr et al. had the eldest participants at 44y, while many studies found significant differences in TEWL at much older ages [20]. Baumrin et al. did find a significant difference in adults of a younger age, but they compared adults to infants, while Fluhr et al. compared adults to children [2, 20]. One possible explanation for this is that elderly stratum corneum has more skin barrier function as well as decreased permeability. In contrast, premature infant skin has increased permeability due to a lack of fully developed skin barrier function, affecting TEWL. Furthermore, the amount of photodamage increases with age, which can affect skin barrier function as well [24].

Xie et al. was the only contrasting result, that older subjects having higher TEWL values. They suggest this discrepancy may be due to geographic or ethnic differences since most studies, other than theirs, that concluded that the elderly had lower TEWL were conducted in America. This was also the only study where the anatomic site studied was the neck [74]. Several studies saw site-specific differences in age effects on TEWL, so it is possible that the effect of age on TEWL changes based on anatomic site. Boireau-Adamezyk et al. suggested that this change in TEWL with increasing age may be partly due to a thickening of the stratum corneum with age, as observed in their study [6].

A definite relationship between TEWL and anatomic site exists; however, the exact relationship between every anatomic site's TEWL value remains unclear since the data varies. In general, face had highest TEWL values followed by the wrist and then abdomen and extremities. Data regarding the extremities and torso is inconclusive. This conclusion, however, differs from the order identified in previous older literature such as in the Rogiers et al. review of literature from 1977 to 1988, supplementing the need for an update [58]. Furthermore, some even suggest significant differences in TEWL in different regions on a singular anatomic site, such as the forearm. Although data regarding the TEWL on different sites of the forearm are inconclusive and often contradict each other, it is important to explore and substantiate any potential relationship. Forearm is a widely used site for TEWL measurement and, therefore, such variation in site on the forearm in TEWL could lead to a discrepancy in the data. Rogiers et al. even suggest avoiding some sites like the palm and the wrist due to high interindividual variability at such locations [58].

Most studies analyzing the relationship between sex and TEWL determined that males had higher TEWL values than females. A possible explanation by Firooz et al. is that males tend to engage in more outdoor activities and have more damaged skin [18]. Only one study had opposing results. However, note that this study collected data for females in autumn of 2009 and males in autumn of 2011 [41]. Potential climate differences, timing differences, or instrument differences could have impacted their results. Several found no significant relationship between sex and TEWL. Interestingly, these were the oldest studies conducted on sex and TEWL reviewed and all had small sample sizes [14, 36, 59, 71].

Based on the data regarding race or ethnicity and TEWL, no clear conclusion can be drawn, as there is much variation in the data with no majority findings. Controlling for other related variables, such as the ones listed here could help reveal a more defined relationship between race/ethnicity and TEWL.

All studies investigating the impact of time and circadian rhythm on TEWL determined differences in TEWL based on time. However, there is disparity in the data regarding the actual rhythm itself, with some studies seeing forearm TEWL peaks at night and others finding peaks in the morning. Yospovitch et al. for example propose that peaks at night could be a result of some unknown circadian cellular or metabolic activity in the epidermis during night [78]. In addition, some studies suggest that different TEWL circadian rhythm curves exist based on anatomic site measured [37, 78]. Differing levels of cortisol offer a possible explanation for the peaks in TEWL in the morning. A previous study examined the effect of psychological stress and how it deteriorates skin barrier function. Psychological stress was associated with increased levels of salivary cortisol 30 min after awakening, which is generally considered the time cortisol peaks. In addition, this psychological stress was connected to increases in basal TEWL and stratum corneum hydration, while stratum corneum integrity was decreased [9].

Based on studies analyzed, it appears that more sleep does result in lower TEWL values. However, data are limited, and two of the four studies investigated found no significant TEWL sleep impact. Therefore, more data are needed for a definite conclusion.

The literature suggests that certain foods may impact TEWL. However, each study analyzed one specific food product and there was no commonality of food products across the studies, making it difficult to make well-defined conclusions regarding the impact of individual foods on TEWL. Further research is needed on specific foods to provide clearer guidelines for TEWL studies.

There was limited variation in data regarding the impact of BMI and obesity on TEWL. In three of four studies, an increase in BMI or obesity leads to a TEWL increase. Löeffler et al. suggest this could be due to increased sweat gland activity in obese individuals at rest [40]. Conversely, Nino et al., who found increased TEWL in those with abdominal obesity compared to those without, suggested the roles of adipokines causing replacement of the stratum corneum and leptin promoting fibroblast proliferation and collagen synthesis could explain the increased TEWL in obese patients [49]. Interestingly, Guida et al. had the opposite results to Nino et al., but referenced the exact same mechanisms of adipokines and leptin activity as a potential cause for lower TEWL values in obese individuals [26, 49]. Further data regarding the impact of obesity and abdominal obesity on TEWL is warranted.

Smoking impact on TEWL is also not conclusive given the scarcity of data and discrepancy in results, with one study suggesting that not only smoking, but even being exposed to excessive smoking increases TEWL and another finding no TEWL impact of smoking [47, 75]. Thus, this is another area for further data.

Emotional eccrine sweating impacts TEWL results and significantly increases measured values. Adequate rest time for the patient, multiple 'dummy' measurements, or application of a sweat inhibitor are all potential methods to control this variable.

Finally, menstrual cycle may impact TEWL, while menopause has no effect. However, once again there is insufficient evidence for a well-defined conclusion. It is, therefore, imperative that additional research should be conducted on the impact of menstruation and menopause on TEWL.

Conclusion

Transepidermal water loss research is a widely studied field that despite more than 60 years of evidence, continues to show variation in results and, in some instances, conflicting results. We outline variables impacting, or may be potentially impacting, TEWL and stress matching and controlling for these, which should reduce the conflicting results, as noted here. Doing so will determine real and biologically important relationships regarding stratum corneum barrier function and variables, such as sex and age.

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Compliance with ethical standards

Conflict of interest Not applicable.

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