The Contribution of Endogenous and Exogenous Factors to Male Alopecia: A Study of Identical Twins

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Background: The purpose of this study was to investigate the potential contribution of environmental factors and testosterone on male alopecia.
Methods: Ninety-two identical male twins were recruited from 2009 to 2011. A comprehensive questionnaire was completed followed by the acquisition of sputum samples for testosterone analysis and standardized digital photography. Frontal, temporal, and vertex hair loss was assessed from these photographs. Hair loss was then correlated with survey responses and testosterone levels between twin pairs. Two independent, blinded observers also rated the photographs for hair thinning.
Results: Increased smoking duration ($p < 0.001$) and the presence of dandruff ($p = 0.028$) were significantly associated with increased frontal hair loss. Increased exercise duration ($p = 0.002$), consumption of more than four alcoholic drinks per week ($p = 0.042$), and increased money spent on hair loss products ($p = 0.050$) were all associated with increased temporal hair loss. Daily hat use ($p = 0.050$), higher body mass index ($p = 0.012$), and higher testosterone levels ($p = 0.040$) were associated with decreased temporal hair loss. Factors that were significantly associated with increased vertex hair loss included abstinence from alcohol consumption ($p = 0.030$), consumption of more than four alcoholic drinks per week ($p = 0.004$), increased smoking duration ($p = 0.047$), increased exercise duration ($p = 0.050$), and increased stress duration ($p = 0.010$). Lower body mass index, more children, increased caffeine consumption, history of skin disease, and abstinence from alcohol were significantly associated with increased hair thinning scores ($p < 0.05$).
Conclusion: This study offers substantial evidence that exogenous factors may have a clinically significant impact on hair loss. (*Plast. Reconstr. Surg.* 131: 794e, 2013.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, III.

Hair and its beauty have long been associated with traits such as youth, virility, strength, and attractiveness. The converse is also true, with both historical and current cultural opinions associating the elderly or unattractive with a lack of hair.[1–3] Studies have demonstrated that the prevalence of significant androgenic alopecia in men is 11 to 16 percent in the 18- to 29-year-old age group, 53 percent in the 40- to 49-year-old age group, and 65 percent in men older than 60 years.[4–6]

Androgenic alopecia can be a psychologically difficult problem for men, provoking both anxiety and insecurity.[7,8] These negative psychological effects have led those suffering from androgenic alopecia to seek a wide variety of treatments ranging from shampoos and creams to more costly interventions such as medications and surgery. IBISWorld, a market research organization, estimated that the hair loss market generated $310 million in revenue in 2010.[9] However, the efficacy of U.S. Food and Drug Administration–approved therapies for androgenic alopecia,

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such as minoxidil (Rogaine; McNEIL-PPC, Inc., Fort Washington, Pa.) and finasteride (Propecia; Merck & Co., Inc., Whitehouse Station, N.J.), have been controversial and their results inconsistent. Follicular unit transplantation offers a viable long-term alternative but is expensive and invasive, and requires multiple operations to achieve desirable results.[10] Follicular unit transplantation is also not without its own morbidity. Follicular unit transplantation requires an adequate hair-bearing donor site and carries a 5 percent complication rate, including donor-site necrosis, hypertrophic scarring, keloids, and folliculitis.[11–14]

Several studies have shown higher dihydrotestosterone and androgen receptor concentrations in the scalp of androgenic alopecia patients.[15,16] Although these molecular associations have been well defined, the specific causes leading to increased dihydrotestosterone or androgen receptor concentrations have not been well elucidated. It is suspected that genetics is a primary contributor to androgenic alopecia, but even among family members, there is significant variation in both the expression and penetrance of androgenic alopecia. A study of elderly male siblings estimated that androgenic alopecia had 79 percent heritability, but did not address the remaining 21 percent attributed to exogenous effects.[3] Although there are many theories regarding the cause and treatment of androgenic alopecia, truly empiric studies are lacking and relatively limited to laboratory analysis or subjective clinical results.

The study of genetically identical male twins provides a unique opportunity to examine the putative contributions of genetics and environment. Through this study, we hope to examine these potential contributions to androgenic alopecia and assign a relative strength to genetics and certain behaviors.

PATIENTS AND METHODS

Institutional review board approval was obtained and identical male twins were recruited at the Twins Days Festival in Twinsburg, Ohio, from 2009 to 2011. These participants were asked to complete a comprehensive questionnaire followed by the acquisition of standardized digital photographs. Digital images were taken by professional photographers at preset distances and settings to obtain the highest level of standardization. Photographs included four views: a frontal (anteroposterior) view, bilateral temporal views (left and right), and a vertex/coronal view. The photographs were analyzed by a single individual on the research team using Adobe Photoshop (Adobe Systems, Inc., San Jose, Calif.) software to obtain hair loss measurements in pixels. This individual was blinded to all questionnaire responses. Participants were also asked to provide sputum samples for testosterone analysis. Specific methods for each hair loss measure and for the analysis of saliva samples can be found below.

Frontal Hair Loss

Frontal hair loss was measured using the intercanthal distance as a standard point of reference. A horizontal line was drawn in all patients from medial canthus to medial canthus to obtain the intercanthal distance. Frontal hair loss was then measured by drawing a perpendicular line from the bisection of the aforementioned intercanthal distance line to the level of hair recession. This measurement was then divided by the intercanthal distance as a correction measure to adjust for photographic variation.

Temporal Hair Loss

Temporal hair loss was measured using the distance from the tragus to the lateral canthus as a standard point of reference. A line was then drawn from the lateral canthus to the point of maximal temporal hair loss. This value was then divided by the standardized tragus-to–lateral canthus distance. These steps were then repeated for the contralateral side. A composite measurement was then obtained by using the average of these two temporal hair loss measurements and used in the final analysis.

Vertex Hair Loss

Vertex hair loss was assessed as a ratio of the measured hair loss divided by the total scalp area. The amount of hair loss was measured by using the Adobe Photoshop selection tool. Total scalp area was measured by using the glabella-to-occiput distance and the bitemporal distance.

Testosterone

Saliva samples were collected and measured in accordance with the protocol provided by Salimetrics, LLC (State College, Pa.) for their Salivary Testosterone Enzyme Immunoassay Kit. Testosterone levels were represented in picograms per milliliter.

Hair Thinning

Hair thinning was assessed subjectively from the patient photographs by two independent,

blinded observers using a Likert scale, where 0 = no thinning, 1 = minimal thinning, 2 = mild thinning, 3 = moderate thinning, and 4 = severe thinning. The observers' responses were averaged for all three views and analyzed according to questionnaire responses.

Statistical Analysis

Linear regression modeling was used to identify independent predictors of hair loss measures based on survey data and testosterone levels. Twins with incomplete survey results were eliminated using a pairwise step for each analysis. The effects of age and genetics on testosterone were also individually investigated. Differences between twins were analyzed using the *t* test with concomitant Levene test. Sample sizes represented by the total number of twins are provided for all factors that were found to be significant (e.g., value, *p* value, total number of twins). Thickness assessments for all three views were assessed for interrater reliability and were found to have a highly significant degree of agreement between evaluators (all kappa values >0.7).

RESULTS

Demographics

Ninety-two male twins with a mean age of 51.05 ± 16.30 years (range, 23 to 84 years) had available survey data and photographs for analysis. From this group, testosterone samples were available for 32 men with a mean age of 55.19 ± 4.05 years and a mean testosterone value of 116.82 ± 91.17 pg/ml (range, 47.59 to 572.20 pg/ml).

Testosterone Analysis

Age (F = 2.366; $p = 0.137$) and genetics (F = 1.879; $p = 0.183$) were not found to have a significant predictive value. However, increased body mass index was found to have a significant association with increased testosterone levels (F = 6.025; $p = 0.022$). Table 1 is a summary of the following results.

Frontal Hair Loss

Regression Modeling

Genetics was the strongest predictor of frontal hair loss (F = 12.657; $p = 0.001$). Increasing age was also found to be a significant predictor of increased frontal hair loss (F = 3.493; $p = 0.025$).

Table 1. Summary of Factors that Contribute to Hair Loss

	Hair Loss		
	Frontal	**Temporal**	**Vertex**
Genetics	+		+
Older age	Increased	Increased	Increased
Smoker	Increased		Increased
Dandruff	Increased	Increased	
More children	Increased		
Increased caffeine	Increased		Increased
Decreased BMI		Increased	Increased
Increased exercise duration			Increased
Wear hats		Decreased	
>4 drinks per week		Increased	Increased
Refrain from alcohol		Increased	Increased
Increased money spent on alopecia prevention products		Increased	
Increased testosterone		Decreased	Increased
Increased stress duration		Decreased	Increased
Skin disease history		Increased	Increased

BMI, body mass index.

Intertwin Analysis

A positive smoking history was found to have statistically significant effects on frontal hair loss. Although quantity of smoking was not found to be statistically significant, the twins who started smoking earlier ($r = -0.798$; $p < 0.001$; $n = 20$) and stopped smoking later ($r = -0.544$; $p = 0.097$; $n = 12$) had associated increases in frontal hair loss. The presence of dandruff was also correlated with significantly greater frontal hair loss (−0.320; $p = 0.039$; $n = 20$).

Several factors demonstrated trends toward greater frontal hair loss but were not statistically significant: regular exercise (0.075; $p = 0.116$; $n = 18$), increased dandruff severity (0.129; $p = 0.104$; $n = 18$), and increased money spent on hair loss prevention products (0.201; $p = 0.068$; $n = 14$).

Testosterone Analysis

Testosterone level was not found to be a significant factor in frontal hair loss (F = 0.055; $p = 0.817$).

Frontal Hair Thinning

Male twins with more children (0.696; $p = 0.014$; $n = 44$) and those with increased caffeine consumption (0.5; $p = 0.003$; $n = 46$) had significantly higher hair thinning scores.

Temporal Hair Loss

Regression Modeling

The most significant factor in greater temporal hair loss was increasing age (F = 10.132; $p = 0.002$). Lower body mass index (F = 0.0291; $p = 0.040$) was also significantly associated with greater temporal

hair loss. Genetics did not play a factor in temporal hair loss (F = 0.070; $p = 0.792$).

Intertwin Analysis

Lower body mass index was associated with significantly greater temporal hair loss (–0.0291; $p = 0.012$; $n = 64$). Increased duration of exercise (in hours) was also significantly associated with increased temporal hair loss (0.053; $p = 0.002$; $n = 40$). Similar to frontal hair loss, dandruff was correlated with increased temporal hair loss (0.327; $p = 0.016$; $n = 18$). Twins who spent more money on hair loss prevention products had significantly increased temporal hair loss (0.076; $p = 0.008$; $n = 8$). Twins with less temporal hair loss were also significantly more likely to wear hats on a regular basis (0.0225; $p = 0.050$; $n = 8$). Furthermore, twins who drank more than four alcoholic drinks per week had a significant increase in temporal hair loss compared with their twin who drank four or fewer drinks per week (0.041; $p = 0.042$; $n = 28$).

Testosterone Analysis

Testosterone levels were not a significant independent factor based on linear regression analysis (F = 0.322; $p = 0.576$). However, when performing comparison between twin pairs, higher salivary testosterone was significantly associated with less temporal hair loss (0.076; $p = 0.04$; $n = 32$).

Temporal Hair Thinning

Male twins with a history of skin disease (1.083; $p < 0.001$; $n = 6$) or those who abstained from alcohol (0.875; $p = 0.027$; $n = 8$) had significantly higher hair thinning scores when compared with their twin.

Vertex Hair Loss

Regression Modeling

Genetics (F = 12.107; $p = 0.001$) and increasing age (F = 11.854; $p = 0.001$) were associated with increased vertex hair loss. Notably, when age and genetics were both entered into the regression model, the combination was more significant than either factor alone (F = 12.676; $p < 0.001$).

Intertwin Analysis

Twins who reported a longer duration of stress (0.019; $p = 0.010$; $n = 26$) had significantly greater vertex hair loss than their counterparts (Fig. 1). Twins who reported relatively increased durations of exercise had more vertex hair loss (0.014; $p = 0.050$; $n = 40$). Twins who refrained from drinking had significantly more vertex hair loss (0.036; $p = 0.030$; $n = 6$), but those who drank more than four drinks per week also had more vertex hair loss (0.033; $p = 0.004$; $n = 28$). Lastly, twins who smoked had significantly more vertex hair loss than their nonsmoking siblings (0.833, $p = 0.047$, $n = 20$) (Fig. 2).

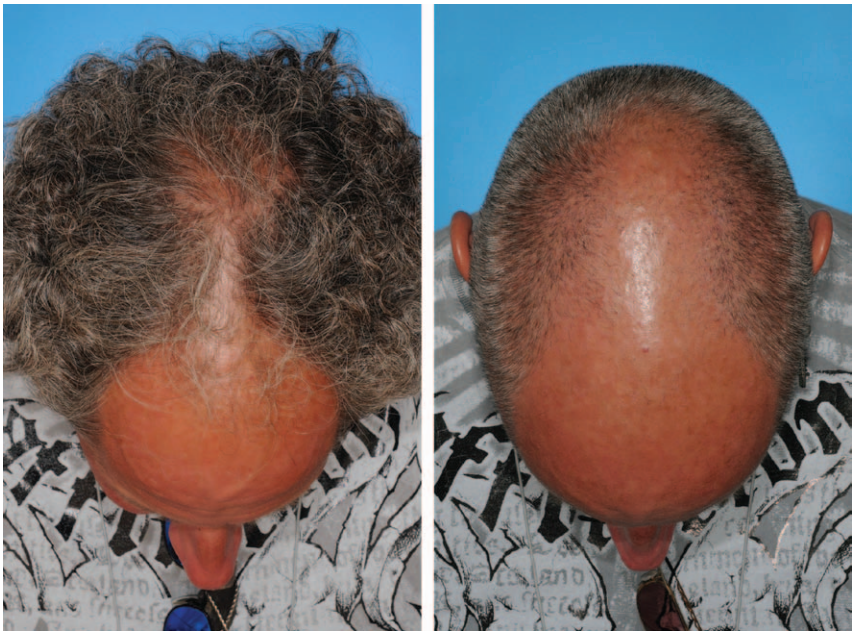

Fig. 1. Stress and vertex hair loss in twins A and B, both 43 years of age. Twin B reported an increased duration of stress and had a lower body mass index compared with twin A. Twin B had an associated 0.17 increase in vertex hair loss.

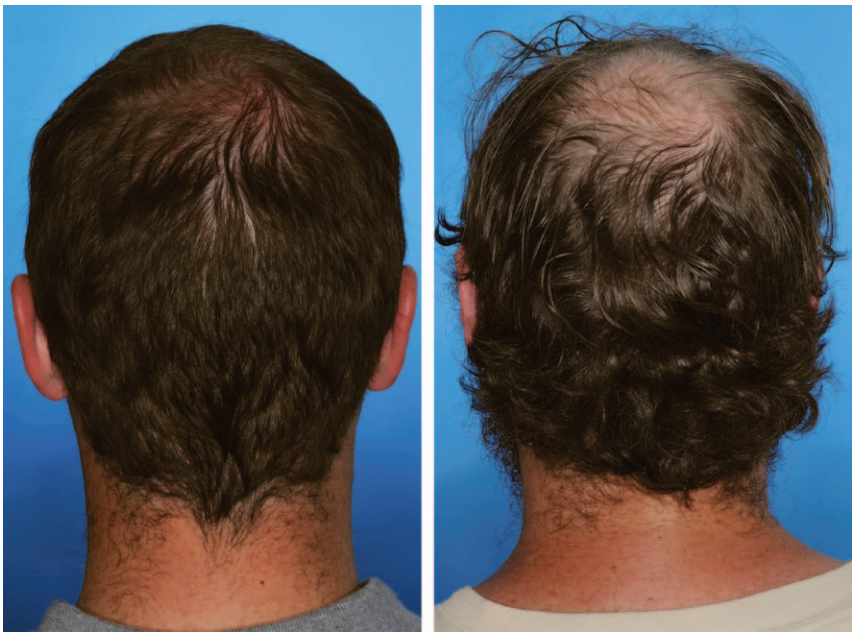

Fig. 2. Alcohol, tobacco, and vertex hair loss in twins A and B, both 41 years of age. Twin B drank more than four drinks per week and was an active smoker, whereas twin A drank fewer than four drinks per week and was a nonsmoker. Twin B had an associated 0.12 increase in vertex hair loss.

Testosterone Analysis

In contrast to higher testosterone levels beings associated with decreased temporal hair loss, increased testosterone levels were associated with increased vertex hair loss ($F = 4.133$; $p = 0.050$). However, difference in testosterone levels between twins was not a significant predictor of vertex hair loss (0.076; $p = 0.841$; $n = 32$).

Vertex Hair Thinning

Men with lower body mass indexes (0.4359; $p = 0.030$; $n = 78$), increased caffeine consumption (0.3636; $p = 0.004$; $n = 44$), a history of skin disease (0.833; $p = 0.002$; $n = 6$), or those men who abstained from drinking (0.6250; $p = 0.010$; $n = 8$) had significantly higher hair thinning scores.

DISCUSSION

Male androgenic alopecia is attributed to a mix of endogenous and environmental factors. Although genetics and age were the most significant predictors of androgenic alopecia, exogenous factors such as smoking, increased exercise duration, and excessive alcohol consumption also had significant effects on frontal, temporal, and vertex hair loss. We have also found that these exogenous factors affect hair loss in a distinct spatiotemporal fashion. Furthermore, our study supports the role of testosterone in hair loss, which itself is influenced by both endogenous and exogenous factors.

Androgenic alopecia is thought to be directly related to testosterone and its metabolites. Free testosterone is converted to dihydrotestosterone, its more potent form, by the enzyme 5α-reductase. Conversion of free testosterone to dihydrotestosterone within the dermal papilla is thought to be one of the central players affecting hair growth and is the basis for using competitive inhibitors of 5α-reductase such as oral finasteride.[15,16] The total testosterone level measured in saliva is primarily free from sex hormone–binding globulin and thus serves as an indirect measurement of serum free testosterone. We believe that the protective effect of higher free testosterone on temporal hair loss denotes a decrease in the conversion of testosterone to dihydrotestosterone by 5α-reductase. Furthermore, the association between lower body mass index and increased temporal hair loss and vertex hair thinning supports the dihydrotestosterone-induced androgenic alopecia model. Measurement of steroid hormones in 750 healthy men showed that men with a lower body mass index had significantly lower sex hormone–binding globulin levels than nonobese men with a higher body mass index.[17] This suggests that men with a lower body mass index may have greater free testosterone levels because of lower sex hormone–binding globulin

and thus have a greater conversion to dihydrotestosterone, resulting in increased temporal hair loss. However, obese men also have significantly decreased sex hormone–binding globulin but normal 5α-reductase activity, leading to significantly elevated dihydrotestosterone and subsequent androgenic alopecia.[18]

The association of serum free testosterone and androgenic alopecia has been inconclusive in the literature thus far. Newman and Socransky showed that men with androgenic alopecia had lower free testosterone than men without androgenic alopecia,[19] whereas Demark-Wahnefried et al. demonstrated that men with vertex and frontal hair loss had higher free testosterone.[20] Our results help clarify the role of testosterone in different patterns of hair loss. Our significant correlation of higher free testosterone and lower temporal hair loss is consistent with the findings of Newman and Socransky while not contradicting those of Demark-Wahnefried et al. Furthermore, although not statistically significant, our trend of higher testosterone and greater vertex hair loss is directly supported by the findings of Demark-Wahnefried et al. It may be that frontotemporal hair loss and vertex hair loss are affected differently by differences in testosterone levels.

The significant association between smoking and increased frontal and vertex hair loss is consistent with previously published results. The survey by Su and Chen of 740 men demonstrated a strong association between smoking status and intensity with moderate to severe androgenic alopecia.[21] However, despite the strong sample size, Su and Chen used subjective Norwood classifications to assess the degree of hair loss. Our study is the first to demonstrate the association of smoking using objective hair loss measurements. The effects of cigarette smoking on increased arterial stiffness, arterial vasoconstriction, and the production of reactive oxygen species may explain the pathogenesis of smoking-induced alopecia.[22–24] Oxidative stress can facilitate the entry of dihydrotestosterone into dermal papillary cells, whereas reactive oxygen species causes sebaceous gland hyperplasia and a subsequent increase in 5α-reductase activity.[16,25] Furthermore, compromised blood flow to the dermal papilla will lead to miniaturization and eventual loss of hair follicles.[26] These mechanisms may help explain the contribution of smoking to androgenic alopecia at the molecular level.

Duration of workouts was an environmental factor that may have had a direct effect on serum testosterone levels. Extended aerobic exercise has been shown to significantly decrease serum testosterone, whereas intense anaerobic exercise has been associated with increased testosterone levels.[27–30] Decreased testosterone from prolonged aerobic exercise can contribute to increased temporal hair loss, whereas increased testosterone from prolonged anaerobic exercise can show temporal hair preservation.

The association of prolonged duration of stress and increased vertex hair loss may be explained by the immune-mediated reaction to stress. Studies have shown that stress induces corticotropin-releasing hormone release, which in turn causes degranulation of mast cells near hair follicles, releasing histamine and inducing the catagen phase of the hair-follicle cycle.[31] Conversely, the association of stress and androgenic alopecia may be explained by reverse causality, where increased hair loss induces prolonged stress in the androgenic alopecia patient.[7,8] It is interesting to note that men with more children had greater frontal hair thinning. It is unclear whether increased stress contributed to this association.

The association of decreased temporal hair loss with daily hat use may be explained by the protection against sun exposure to the scalp. Our results support previously published associations between sun exposure and increased risk of androgenic alopecia.[32] Moreover, because hair plays a pivotal role in protecting the scalp from ultraviolet radiation, androgenic alopecia patients are more at risk of ultraviolet light–induced diseases such as scalp leukoderma.[33] Furthermore, our results indicate an association between skin disease and increased frontal and vertex hair thinning. Unfortunately, the direct effect of ultraviolet radiation on the hair follicle is not completely understood.

Alcohol can be both beneficial and detrimental to hair preservation, depending on the amount consumed. Twins who consumed mild to moderate (less than or equal to four drinks per week) amounts of alcohol had decreased vertex hair loss, but twins who had excessive (more than four drinks per week) alcohol consumption showed significantly greater temporal hair loss and vertex hair loss, and twins who abstained from alcohol had greater temporal and vertex hair thinning. The benefits of moderate consumption of alcohol, especially red wine, have been widely documented.[34] Previously reported data have shown that alcohol consumption of 3.5 drinks per week was significantly associated with decreased mortality.[35,36] Our putative hypothesis is that moderate alcohol consumption decreases plasma viscosity,

likely improving blood flow to the dermal papilla, thereby improving hair health and longevity.[37] However, the molecular mechanism of alcohol consumption on androgenic alopecia has not been addressed in the literature, and other mechanisms could simultaneously contribute to the preservation of hair. Alternatively, the detrimental effects of excessive alcohol consumption, such as coronary heart disease, type 2 diabetes mellitus, stroke, hypertension, and peripheral arterial disease, have also been widely published.[34] However, to our knowledge, there had been no published studies demonstrating a genetically independent association between heavy alcohol consumption and increased androgenic alopecia until now.

We believe that the same environmental factors that could potentially increase androgenic alopecia may also negatively affect the long-term outcome of hair transplantation because the molecular mechanisms of these factors can damage both native hair follicles and transplanted follicles alike. Exogenous factors affecting hair loss may pose an increased risk to transplanted follicles, as they are very susceptible to metabolic and vascular insults. Patients with a family history of androgenic alopecia and patients who are undergoing hair transplantation should be educated on the environmental factors that exacerbate androgenic alopecia because behavior modification can potentially decrease the extent of their androgenic alopecia and improve surgical outcomes.

Outside of this study, there have been only a few studies that have attempted to objectively identify the cause of androgenic alopecia. One study found that intertwin correlation of hair loss was significantly stronger for monozygotic twins compared with dizygotic individuals, revealing a heritability of 79 percent.[3] This group attributed the remaining variation to nonshared environmental effects but felt that there was only a weak and statistically nonsignificant association. However, this study used subjective assessments of hair loss and, more importantly, did not attempt to identify these environmental factors. Our study is the first of its kind that has been able to demonstrate a significant effect of specific external factors on hair loss.

Our study is not without methodologic limitations. The most salient weakness is our limited sample size, which predisposes us to potentially missing significant factors and exaggerating effects because of outliers. Despite our limited sample size, each twin offered an effective genetic control, which strengthened the validity of our findings. Our behavioral data are recorded by means of a self-reported survey and are therefore subject to misrepresentation and recall bias. In our cohort, we also found a high degree of behavioral similarity between twins, making it difficult to examine all aspects that may contribute to hair loss. Finally, we have introduced a novel but unverified approach to measuring hair loss. Although this may provide a new noninvasive and objective method for examining hair loss, it is subject to error because of differences in hair styles, position, color, and texture. Furthermore, our hair density assessment was based on subjective reviewer ratings instead of the criterion standard objective analysis of hair follicle specimens.

We have also introduced the use of sputum assays, as they have been demonstrated to have a high correlation with serum levels. Although physiologic variability in hormonal levels because of extraneous factors (e.g., diurnal hormonal effects) may complicate the interpretation of such results,[38,39] we collected samples from twins at the same time. Thus, we believe our analysis was not affected by this variation.

In general, more invasive measurements of serum testosterone and hair follicle densities would be desirable. However, it would not be logistically feasible in the setting in which the subjects were asked to participate.

CONCLUSIONS

Several nongenetic factors may significantly contribute to hair loss in men. Our study provides evidence that smoking, excessive alcohol consumption, increased exercise duration, increased duration of stress, and lower body mass index all contribute to increased hair loss. Also, although a higher testosterone level protects against temporal hair loss, it exacerbates vertex hair loss.

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PATIENT CONSENT

Patients provided written consent for the use of their images.

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