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Lower birthweight and left-/mixed-handedness are associated with intensified age-related sex steroid decline in men. Findings from the Men's Health 40+ Study

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SUMMARY

In males, age-related decline in free testosterone (T) and dehydroepiandrosterone (DHEA) by 2–3% per year has been reported. Estradiol (E2) and progesterone (P) seem to decrease as well, but to a lesser extent. Lower sex steroid levels in men have been related to physical and mental symptoms. Low birthweight and left-/mixed-handedness (L/MH) are indicators of an adverse fetal environment during pregnancy, and both have been linked to morbidity in later life. The aim of this study is to examine the relationship between lower birthweight as well as L/MH and age-related sex steroid decline. In a cross-sectional study design, saliva samples were collected under standardized conditions from healthy men for subsequent steroid hormone analysis using standard luminescence immunoassays. T (M = 67.57 pg/mL), DHEA (M = 247.91 pg/mL), E2 (M = 1.29 pg/mL), and P (M = 28.20 pg/mL) have been quantified leading to a final sample of 256 men providing complete data on sex hormones (M_{Age}=57.8; SD_{Age} = 10.8). Information on participants' birthweight was obtained from birth reports (N = 134), and participants were asked about their handedness (right-handed, left-handed, mixed-handed) (N = 256). Multivariate-adjusted linear regression models relating each sex hormone individually and the principal component of declining steroid hormones (DSH)—an integrated hormonal parameter—with handedness and birthweight did not identify significant associations except for handedness and E2. Moderation analysis using robust regression accounting for bias due to influential data points detected a significant association between age and DSH for handedness ($\beta = -0.0314$, $p = 0.040$) but only a trend for birthweight ($\beta = 0.0309$, $p = 0.073$). For lower birthweight, a trend toward intensified age-related sex steroid decline in men was observed, while for L/MH, a significant association with intensified age-related sex steroid decline was identified. These results indicate that L/MH and potentially also lower birthweight might be considered as early risk factors for endocrine health in later life.

INTRODUCTION

Birthweight can be seen as a marker of fetal growth and is therefore an indicator of the quality of the fetal environment (Schlotz & Phillips, 2009). In pregnancy, numerous factors affect fetal growth. Maternal smoking, alcohol intake, exposure to toxins/drugs, malnutrition, or prenatal stress have been shown to reduce birthweight (Khashan *et al.*, 2008; Schlotz & Phillips, 2009; Harris & Seckl, 2011). Low birthweight defined as birthweight below 2500 g has been linked to a higher risk of disease and mortality throughout life (McCormick, 1985; Harris & Seckl, 2011; Risnes *et al.*, 2011). In childhood, low birthweight has been associated with attention deficit/hyperactivity disorder (ADHD) (Mick *et al.*, 2002). In adulthood, low birthweight has been related to hypertension, allergies, and depression or anxiety symptoms (Nomura *et al.*, 2007). However, low birthweight (<2500 g) is a relatively rare condition in industrialized countries, and thus, lower levels of birthweight, for example, below a median of male boys after 40 weeks of gestation (<3400 g) have also been related to worse health (8). In addition, left-/mixed-handedness (L/MH) has been linked to prenatal stress and is considered to be an indicator for atypical anatomical variation in brain region development during pregnancy, which itself represents a risk factor for various symptoms (Weinstock, 2001; Glover *et al.*, 2004). Witelson & Goldsmith (1991) postulate that lower levels of testosterone lead to less regressive events in certain brain regions, including the temporo-parietal region, and subsequently result in a larger isthmus of the corpus callosum and less functional asymmetry in the male brain. Associations with symptoms have been found between L/MH and high blood pressure and epilepsy (Bryden *et al.*, 2005). Left-handedness seems to increase the risk of

schizophrenia (Webb *et al.*, 2013) or anxiety (Lyle *et al.*, 2012). Therefore, lower birthweight and L/MH may be regarded as general risk factors for health threat throughout life.

In males, higher sex steroid levels have been associated with better general health (Walther & Ehlert, 2015). Low levels of sex steroids have been related to depression (Schmidt *et al.*, 2005), dementia (Barron & Pike, 2012), or mortality (Hsu *et al.*, 2016). With age, testosterone (T) (Feldman *et al.*, 2002; Singh, 2013), dehydroepiandrosterone (DHEA) (Parker, 1999; Feldman *et al.*, 2002; Singh, 2013), and estradiol (E2) (Vermeulen *et al.*, 2002; Frost *et al.*, 2013) decline due to physical degeneration processes. A slower age-related decline has been linked to better general health (Samaras *et al.*, 2014). In particular, a decelerated decline of a combined hormonal parameter including T, DHEA, E2, and P has been related to healthy aging (Walther *et al.*, 2016).

In literature, lower birthweight and L/MH are generally negatively related to health parameters and it is not yet clear whether increasing age might further potentiate these associations. The current study therefore aimed at investigating the association between lower birthweight, L/MH, and age-related alterations of T, DHEA, E2, and P, as well as a more collective marker that integrated all hormonal parameters by unifying the shared variance of the hormones. This marker was named principal component of declining steroid hormones (DSH) as previously described (Walther *et al.*, 2016).

MATERIALS AND METHODS

Participants

Data stem from the Men's health 40 + study, which is part of a larger research project on the 'Dynamics of Healthy Aging' at the University of Zurich aiming to investigate factors that contribute to healthy physical and mental aging and quality of life from the middle to the old age (Walther *et al.*, 2016). The sample for the study on Men's health 40+ included two hundred and seventy-one men between the ages 40 and 75 years living in Switzerland (N = 271; M_{Age} = 57.06; SD_{Age} = 10.68). All participants provided psychometric and biological data. However, due to extreme values in hormone concentrations or levels below the detection range attributable to sample contamination or measurement error in specific samples, the sample size for our analysis shrunk by 15 observations to 256 individuals providing data on all hormonal variables and handedness. Participants were recruited via online platforms and by the use of flyers, which were distributed at public places, such as different railway stations or shopping malls. Further criteria for study participation were sufficient knowledge of the German language and the absence of any current and acute medical or psychiatric disorder. All men provided information about their current health status and medication intake via standardized questionnaires. The sample characteristics including age, current health condition, body mass index (BMI), education according to the International Standard Classification of Education (Schneider & Kogan, 2008), smoking status, medication intake, birthweight, and handedness are shown in Table 1.

The study Men's Health 40+ was conducted with the approval of the local ethics committee of the University of Zurich. All men provided written informed consent prior to participating and were given a comprehensive individual feedback of their psychometric and biological parameters for the participation. Recorded data have been rendered anonymous.

Table 1 Sample characteristics

Total (N = 256)		
Age (mean/SD)	57.8	10.8
Current health condition (N/%)		
Very good	121	47.3
Good	132	51.6
Fair	3	1.2
Bad	0	0.0
Very bad	0	0.0
Body mass index (kg/m^2) (Mean/SD)	25.5	3.1
Education (N/%)		
Tertiary education	100	39.1
Post-secondary non-tertiary education	54	21.0
Higher secondary school	72	28.0
Lower secondary education	28	11.1
Did not finish regular school	2	0.8
Current smoking status (N/%)		
Non-smoker	211	82.4
Occasional smoker	23	9.0
Smoker	22	8.6
Medication intake (N/%)		
No	167	65.2
Yes	89	34.8
Birthweight (g) (mean/SD)	3422	552.4
Handedness		
Right-handed	220	85.9
Left-handed	22	8.6
Mixed-handed	14	5.5
Left-/mixed-handed (L/MH)	36	14.1
Testosterone, pg/mL (T) (mean/SD)	67.57	27.05
Dehydroepiandrosterone, pg/mL (DHEA) (mean/SD)	247.91	212.96
Estradiol, pg/mL (E2) (mean/SD)	1.29	0.99
Progesterone, pg/mL (P) (mean/SD)	28.20	18.76
Principal component (DSH)	−0.12	0.94

The principal component of declining steroid hormones (DSH) was computed by a principal component analysis with testosterone (T), dehydroepiandrosterone (DHEA), estradiol (E2), and progesterone (P). Only non-contaminated saliva samples, values above the detection limit, and those not identified as outliers were included for the computation of DSH (N = 256). Data on birthweight were available for 134 participants.

Procedure

Data collection for the study Men's Health 40+ is fully described elsewhere (Walther *et al.*, 2016). In the year 2014, the 271 men completed three online psychometric test batteries and subsequently attended to one biological examination at the laboratory of the Department of Clinical Psychology and Psychotherapy. Participants were asked to bring their birth reports along to this biological examination.

Handedness

Using a standardized item in the initial online questionnaire, participants were asked to indicate their handedness using the response options 'right-handed', 'left-handed', and 'mixed-handed'. Left- and mixed-handed subjects were included in one group termed 'left-/mixed-handed'.

Birthweight

Information on participants' birthweight was obtained from birth reports. Of the 256 men included for the analysis on endocrine data and handedness, only 134 provided information on birthweight from birth records. Low birthweight is defined by the WHO as a weight of <2499 g at birth. The present data set contained only four cases that fall into this category. Therefore, a median split was chosen to categorize individuals into two

groups—a lower birthweight group (<3400 g) and a higher birthweight group (≥3400 g). The mean (SD) birthweight for the lower birthweight group was 3020.8 g (389.2), while for the higher birthweight group, it was 3851.3 g (363.4). The validity of this median split separation in this sample is supported by large epidemiological reports showing for males at birth with 40 weeks of gestation a 50th percentile of 3400 g (8).

Salivary analytes

Saliva samples were obtained in a standardized procedure. To control for diurnal variation in hormone secretion, all saliva samples were taken between 8:00am and 8:15am. Each participant provided saliva on a weekday using three successive salicaps of 2 mL capacity each (SaliCaps; IBL International GmbH, Hamburg, Germany). Participants were instructed not to consume caffeinated or alcoholic beverages 48 h prior to the collection of saliva, to additionally refrain from sports 24 h beforehand and not to smoke, eat, brush their teeth, or chew bubble gum 2 h beforehand. No salivation aids were used.

All saliva samples were kept frozen at −20 °C (until assay; until being transferred to the laboratory). Biochemical analysis of the four sex steroids was performed using standard luminescence immunoassays: testosterone (T), dehydroepiandrosterone (DHEA), estradiol (E2), and progesterone (P). Intra- and interassay coefficients for sex steroids were below 10%. Sensitivity was in the expected range according to IBL International GmbH (Hamburg, Germany) guidelines (T: 1.9 pg/mL, DHEA: 1.3 pg/mL, E2: 0.15 pg/mL, P: 0.045 pg/mL).

Potential covariates and confounders

Covariates included body mass index, water balance, smoking status, alcohol consumption, drug consumption, medication intake, current health condition, present disease, and the amount of hours of physical activity per week and in the last 12 h, having children, academic and professional education, and income, as well as condition of employment. In particular, with regard to the salivary analytes, controlled confounders included gum bleeding or injuries in the mouth during the last two weeks, and starting time of saliva sampling. Self-reported stress level (measured with the short form of the Trier Inventory of Chronic Stress (TICS) Schulz & Schlotz, 1999) and whether the average intake of fatty or sweet food increased over the period of the last three months were further included as covariates.

Statistical analyses

For the statistical analyses, birthweight was used as continuous variable. For visualization of moderation effects, we used a median split to separate the sample into two groups 'lower birthweight' (≤3400 g) and 'higher birthweight' (>3400 g). Left- and mixed-handed participants were merged to one group. Thus, for the statistical analyses, the two groups 'right-handed' and 'left-/mixed-handed' were used.

Statistical analyses were calculated using R version 3.2.2. (Team RC, 2012) and SPSS (IBM Statistics, Version 23, Armonk, NY: IBM Corp.). For robust regression, the R-Package 'ROBUSTBASE' was used following the recommendation of Koller & Stahel (2011). For the salivary parameters, outliers were identified and excluded. Values were regarded as outliers, if they were greater or less than three standard deviations around the mean. Outliers were removed in a data cleaning step before further analyses were conducted (see Appendix S1 for outlier description). From the initial sample of 271 observations, for T 1.1% (n = 3), for DHEA 1.1% (n = 3), for E2 0.4% (n = 1), and for P 2.2% (n = 6), observations trespassed concentration levels of three or more standard deviations and were removed. Two quantifications for P (0.8%) did not reach detection range and those observations could not further be included in the analysis. Therefore, of the initial sample of 271 observations, 15 (5.5%) observations were removed, leaving a sample 256 observations providing data on all endocrine parameters.

In some cases, it seems to be insufficient to interpret adequately an individual's hormonal state by only examining one single hormone. For example, high levels of T not always imply a healthy hormonal state in aging men, namely whether simultaneously levels of DHEA and P are below a critical range (Miller & Auchus, 2011; Turcu & Auchus, 2015). To accommodate this problem and to unify the shared variance of the four hormones T, DHEA, E2, and P, one principal component was extracted using principal component analysis (Everitt, 2005). This principal component of declining steroid hormones (DSH) represents an integrated hormone parameter explaining 54% of the variance (Table 2), which seems to be a more appropriate parameter to interpret the hormonal state of an individual than the examination of single hormones (Walther *et al.*, 2016). For 256 participants, complete data on hormone concentrations was present to compute the DSH, which was further used for statistical analyses.

In a first step, multivariable-adjusted regression models relating both potential moderators, birthweight and handedness, with each sex hormone individually and the principal component DSH were computed to analyze their adjusted effects. Adjustment was made on the basis of the above-mentioned covariates and confounders. In addition, zero-order correlations were calculated to better assess and compare the effect of birthweight and handedness on each hormone as well as DSH (Table 3).

To test for nonlinearity of the relationship between age and DSH, a LOWESS smoothing (33) was applied revealing a linear association as shown in Fig. 1. Subsequently, two moderation analyses' approaches were used to examine the moderation effects of birthweight and handedness on the association between age and DSH. The previously mentioned potential covariates and confounders were included in the analyses. Therefore, analyses with regard to handedness were based on the total sample including 256 participants, while analyses with regard to birthweight were based on the 134 of the 256 participants, which were providing data on birthweight. This resulted for the analysis of age-related alterations of DSH (N = 256) moderated by birthweight in a sample size of 134 individuals providing both, DSH and birthweight. For the analysis of age-related alterations of DSH moderated by handedness, an N of 256 was

Table 2 Results of the principal component analysis

	PC1 loadings (DSH)	h^2
T	0.78	0.60
DHEA	0.70	0.50
E2	0.69	0.47
P	0.76	0.58
Eigenvalue	2.15	

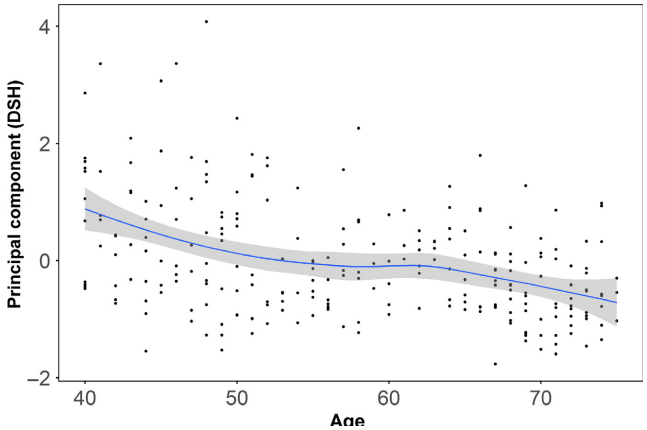
PC1 was then used as an integrated hormone parameter for T, DHEA, E2, and P explaining 54% of the shared variance.

Table 3 Multivariable-adjusted regression models relating birthweight and handedness to the four steroid hormones individually and the cluster variable DSH

	Zero-order *r*	*b*	95% CI	R^2
Birthweight				
T	−0.11	−0.01	−0.20, 0.18	0.18
DHEA	0.04	0.09	−0.10, 0.28	0.24
E2	0.02	0.03	−0.15, 0.21	0.29
P	−0.06	0.02	−0.17, 0.21	0.19
DSH	−0.04	0.04	−0.15, 0.24	0.25
Handedness				
T	0.02	−0.03	−0.15, 0.09	0.18
DHEA	0.05	0.02	−0.09, 0.14	0.23
E2	−0.11	−0.15*	−0.27, −0.03	0.16
P	0.10	0.05	−0.07, 0.18	0.17
DSH	−0.03	−0.03	−0.14, 0.09	0.26

The above-mentioned confounders and covariates were included in the regression models. Regression coefficients are given as standardized values. *$p < 0.05$.

Figure 1 Inspection of linearity using a locally weighted scatterplot smoother (LOWESS) with 95% CI. [Colour figure can be viewed at wileyonlinelibrary.com]



analyzed. For each model, a comprehensive residual analysis was performed. Because of potential influential data points, two solutions were computed. One solution was calculated through ordinary least squares (OLS) regressions. The second solution puts lower weights on extreme data points to lessen their influence on the dependent variable and their standard error estimates (robust regression) (Farcomeni & Ventura, 2012). Cross-sectional calculated slopes for the relationship between age and DSH moderated by birthweight for a lower (<3400 g) and a higher birthweight group (≥3400 g) will be reported as well as cross-sectional calculated slopes for the relationship between age and DSH moderated by either right- or left-/mixed-handedness. Level of significance was fixed at $\alpha = 0.05$.

RESULTS

Characteristics of the sample, descriptive statistics of sex steroids, DSH, birthweight and handedness are described in Table 1. Note that only 134 participants were able to provide data on birthweight, while of 256 participants information on handedness was available. The 134 participants reporting birthweight differed significantly from the 122 participants not reporting birthweight in age and income. The participants not reporting birthweight were significantly older (61.13 vs. 54.22 years) and had significantly lower incomes. This was expected because more than 60 years ago, birthweight was not systematically recorded in Switzerland and therefore rarely obtainable from older participants. In addition, after retirement age, which is around 65 years in Switzerland, participants receive less income than during active work. No other variables were significantly different.

Correlation analysis revealed no significant associations between birthweight and handedness with the sex steroids and DSH (Table 3). Furthermore, with exception of handedness with E2 ($\beta = -0.15$, $t = -2.41$, $p = 0.02$), the multivariable-adjusted linear regression models showed no significant associations between birthweight and handedness with the sex hormones and DSH (Table 3). For handedness, sex steroids were not significantly different between groups. Two different regression techniques were used to conduct moderation analysis for the relation between age and DSH either moderated by birthweight or handedness. Moderation analysis by OLS detected a significant association between age and DSH for handedness ($\beta = -0.0353$, $p = 0.028$) as well as for birthweight ($\beta = 0.0384$, $p = 0.026$). Moderation analysis using robust regression showed significant associations between age and DSH for handedness ($\beta = -0.0314$, $p = 0.040$; Fig. 2) and a trend for birthweight ($\beta = 0.0309$, $p = 0.073$; Fig. 2).

The mean rate of change in DSH is −0.042 units. One standard deviation below the mean in birthweight is associated with a decline in the rate of change in DSH of 0.0424, while one standard deviation above the mean nearly no alteration is demonstrated (0.0007). L/MH is associated with an increased rate of change in DSH of −0.0683, while right-handedness is associated with a rate of change in DSH of −0.0329 (Fig. 2).

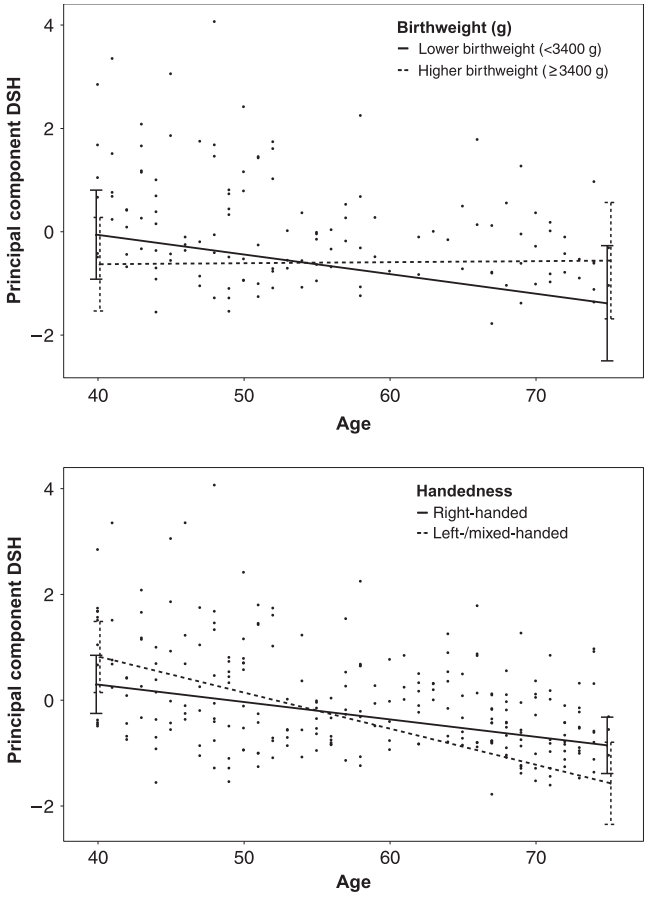
DISCUSSION

The annual decline of DSH reflecting the rate of change in declining steroid hormones in aging men was previously suggested as parameter for healthy aging in men (Walther *et al.*, 2016). Our findings show that lower birthweight and L/MH are associated with an intensified age-related sex steroid decline in healthy men between 40 and 75 years. For T, DHEA, E2 (Walther & Ehlert, 2015), and P (Nankin *et al.*, 1981) negative associations with age have previously been reported. In a prior study, we were able to show for DSH an annual decrease of 0.042 units and DSH to be moderated by depressive symptoms, chronic stress, and general health perception (Walther *et al.*, 2016). This study further contributes to these findings by adding two well-studied risk factors for general morbidity and mortality. Both lower birthweight and L/MH imply to go along with a steeper age-related sex steroid decline and to intensify the rate of change in DSH. On the other hand, higher birthweight and right-handedness seem to buffer the age-related sex steroid decline and are associated with a lower rate of change in DSH and could be regarded as protective factors.

The use of an additional moderation analysis approach—namely robust regression—further emphasizes the robustness of the results with regard to single influential observations. However, for the OLS approach, both lower birthweight and L/MH became significant moderators of the association between age and DSH. For the robust regression approach, only L/MH emerged as a significant moderator, while lower birthweight demonstrated only a statistical trend ($p = 0.073$). This might be due to power problems because of the significantly smaller sample size (134 vs. 271) available for the calculations including birthweight.

Moderation analyses show that both lower birthweight and L/MH moderate the negative association between age and DSH. Several authors have drawn attention to the relationship of low

Figure 2 Moderation plots of the associations between age and the principal component of declining steroid hormones (DSH) by birthweight (upper) and handedness (lower).



birthweight and sex steroids. In young men, low birthweight has been linked to low levels of T. Cicognani *et al.* (2002) found in adolescent men born with low birthweight low levels of T tending toward hypogonadism. Also, Vanbillemont *et al.* (2010) reported in a sample of men between 20 to 45 years of age that the T concentrations were positively associated with birthweight. However, conflicting findings exist as well, which report no relationship between low birthweight and T (Szathmári *et al.*, 2001). Harris & Seckl (2011) argue that exposure to an adverse environment in utero can have long-lasting effects on the development of the fetal tissue structure and organ functioning. In the literature, lower birthweight is indicated as a marker of fetal exposure to environmental adversities in utero (Harris & Seckl, 2011). Lower birthweight might therefore be a risk factor for the T-producing Leydig cells resulting in overall lower T levels and as T declines with age an intensified age-related T decline. The results of the present investigation support these findings and add insight into the moderating role of birthweight on the age-related T decline. In our study, lower birthweight moderates the age-related decline of DSH comprising of the shared variance of T, DHEA, E2, and P. The indirect effect of lower birthweight on DSH levels was mainly due to its moderating effects on the association between age and DHEA and to a lesser extent T (data not shown). These results need to be reflected with regard to other studies indicating that birthweight and levels of DHEA (Szathmári *et al.*, 2001; Papadatou-Pastou *et al.*, 2006) as well as E2 (Vanbillemont *et al.*, 2010) are unrelated in men. In the present study, no direct association of lower birthweight with T, DHEA, E2, or P was revealed confirming previous results.

For L/MH, an intensifying effect on the age-related decline of sex steroids in men was demonstrated. Research extensively investigated the relationship between handedness and T reporting conflicting results (for an overview, see Papadatou-Pastou *et al.* 2006). Some authors report left-handedness to go along with lower levels of T (Hampson & Sankar, 2012), while others found left-handedness to be associated with higher levels of T (Faurie *et al.*, 2011) or did not observe any relation between handedness and levels of T (Papadatou-Pastou *et al.*, 2006). The results of the present investigation contribute to the ongoing discussion by reporting no difference between right-handed and left-/mixed-handed with regard to T concentrations. However, literature on the relationship between L/MH and DHEA, E2, and P is lacking which needs to be addressed by future research.

In addition, E2 was associated significantly with right-handedness in the multivariable-adjusted linear regression models. One potential explanation for this finding might be related to the androgen receptor-CAG repeat length—a genetic marker of the capacity of the androgen receptor to respond to T. Several study results show in males with mixed-handedness a longer CAG repeat sequence than in males with right- or left-handedness (Hampson & Sankar, 2012; Arning *et al.*, 2015). Further, longer CAG repeats have been linked to increased E2 and T (Huhtaniemi *et al.*, 2009; Brokken *et al.*, 2013). However, the underlying mechanism for these associations is poorly understood, although some suggest a relation of longer CAG repeats to reduced T sensitivity with longer CAG repeats (>23 repeats) causing higher circulating sex hormone levels in general in males (Von Eckardstein *et al.*, 2001; Rodríguez-González *et al.*, 2009).

Across lifespan, physical age-related changes are well known. Alterations can be seen in declining concentrations of sex steroids emerging from physical degeneration processes (Singh, 2013). Age-related attrition of the Leydig cells in the testes (Kaler & Neaves, 1978) and the attrition of the cells in the Zona reticularis in the adrenal glands (Parker *et al.*, 1997) lead to declining concentrations of sex steroids in men. For males after the age of 40, fT (Feldman *et al.*, 2002; Singh, 2013) and fDHEA (Parker, 1999; Feldman *et al.*, 2002; Singh, 2013) gradually decline by 2–3% per year. fE2 also decreases, but to a lesser extent (Vermeulen *et al.*, 2002; Frost *et al.*, 2013). Further, changes with age might be a result of age-related changes of the metabolic function as it is the case with increased aromatization of T to E2 or an increased binding capacity of the sex hormone binding globulin (SHBG) for E2 (Vermeulen *et al.*, 2002). Mixed results are reported for the association between age and free progesterone (fP) (Kozloski *et al.*, 2014; Walther *et al.*, 2016). Not only physical aging processes influence the declining concentrations of sex steroids, but also factors that influence development during the prenatal period, such as maternal smoking or prenatal stress. Exposure to adverse fetal environment in pregnancy can have long-lasting impacts on an individual's tissue structure and function (Barker, 1998; Harris & Seckl, 2011). These effects of so-called developmental programming seem to underlie pathophysiology in childhood and later life (Seckl, 1998; Harris & Seckl, 2011). In research, lower birthweight and L/MH either reflect fetal exposure to an adverse intrauterine environment or indicate an atypical anatomical variation in brain region development, and both are associated with prenatal stress (Glover *et al.*,

2004; Khashan *et al.*, 2008; Harris & Seckl, 2011). In addition, lower birthweight and L/MH were unrelated in our study (data not shown), although there is previous research reporting higher birthweight to be associated with right-handedness in 726 boys, but with left-handedness in 661 girls (Petridou *et al.*, 1994). The lack of association in our study might be due to the relatively small sample size not detecting such small effects or the relatively high birthweight in the sample. In the present investigation, the age-related decline of DSH is reinforced by lower birthweight or L/MH. For one standard deviation below the mean in birthweight, an annual decline in the rate of change in DSH of 0.0424 was calculated, while for one standard deviation above the mean, nearly no alteration in the rate of change in DSH (0.0007) was demonstrated. In the current study with regard to L/MH, an annual decline of 0.0683 in the rate of change in DSH has been reported yet with regard to right-handedness an annual decline in the rate of change in DSH of 0.0329 was found. This suggests that the quality of the fetal environment during pregnancy, among other factors, incorporated by lower birthweight and L/MH, might represent a risk factor for endocrine health and may therefore potentially deteriorates successful aging in men.

Several study limitations should be noticed. First, the present study was conducted using a cross-sectional design. From these between-subject effects, no causality can be assumed between age and sex steroid decline. To confirm the present results, longitudinal data as part of a within-subject design are required. Second, the generalizability is restricted to men between the ages of 40 and 75 years, who report a good health state. To investigate men with stress-related symptoms or a defined clinical syndrome may lead to further insights in the relation between age, hormonal alterations, and lower birthweight or L/MH. Third, salivary parameters were measured at one time point only. However, concentrations of steroid hormones can vary from day to day. Thus, it would be more accurate and reliable to assess salivary parameters on several days and subsequently to calculate a mean of each hormonal parameter. Fourth, concerning low birthweight, participants were not asked whether the birth was premature or on the predicted due date. This could have been important, because prematurity is also associated with developmental problems itself and could have confounded the results (Harris & Seckl, 2011). With regard to these limitations, it is important to note that the associations found in the present study were robust. Lower birthweight and L/MH were evaluated by two different moderation analysis techniques, and both of them distinguished lower birthweight and L/MH to be moderators.

CONCLUSION

In conclusion, lower birthweight and L/MH seem to represent early risk factors related to worse aging in men. An intensified age-related decline in sex steroids was observed in both lower birth weight and L/MH. Therefore, to support endocrine and general health, lower birthweight and L/MH might be taken as additional indicators combined with others to monitor men at risk of intensified sex steroid decline. Identification of susceptible men for intensified age-related sex steroid decline through a predictive set of markers and the subsequent monitoring might enable appropriate interventions such as psychological or lifestyle interventions or hormone supplementation to be applied before the age-related sex steroid decline significantly impairs health and quality of life.

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DISCLOSURE OF INTEREST

The authors report no conflict of interests.

AUTHORS' CONTRIBUTIONS

AW contributed to the design of the study and the data collection, analysis, and interpretation of the data and wrote the first draft of the manuscript together with SH. SH contributed to the data collection, analysis, and interpretation of the data and wrote the first draft of the manuscript together with AW. PLM critically revised the manuscript and contributed with substantial intellectual content. UE contributed to the design of the study and critically revised the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section at the end of the article:

Appendix S1 Supplementary Material.