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A cross-sectional study of the association of age, race and ethnicity, and body mass index with sex steroid hormone marker profiles among men in the National Health and Nutrition Examination Survey (NHANES III)

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ABSTRACT

Objectives: Since sex hormone markers are metabolically linked, examining sex steroid hormones singly may account for inconsistent findings by age, race/ethnicity and body mass index (BMI) across studies. First, these markers were statistically combined into profiles to account for the metabolic relationship between markers. Then, the relationships between sex steroid hormone profiles and age, race/ethnicity and BMI were explored in multinomial logistic regression models.

Design: Cross-sectional survey.

Setting: The US Third National Health and Nutrition Examination Survey (NHANES III).

Participants: 1538 Men, >17 years.

Primary outcome measure: Sex hormone profiles.

Results: Cluster analysis was used to identify four statistically determined profiles with Blom-transformed T, E, sex hormone binding globulin (SHBG), and 3-α diol G. We used these four profiles with multinomial logistic regression models to examine differences by race/ethnicity, age and BMI. Mexican American men >50 years were associated with the profile that had lowest T, E and 3-α diol G levels compared to other profiles ($p<0.05$). Non-Hispanic Black, overweight (25–29.9 kg/m^2) and obese (>30 kg/m^2) men were most likely to be associated with the cluster with the lowest SHBG ($p<0.05$).

Conclusion: The associations of sex steroid hormone profiles by race/ethnicity are novel, while the findings by age and BMI groups are largely consistent with observations from single hormone studies. Future studies should validate these hormone profile groups and investigate these profiles in relation to chronic diseases and certain cancers.

ARTICLE SUMMARY

Article focus

- Using cluster analysis, can unique groups of sex steroid hormones be formed among a nationally representative sample of men which would take into account that these hormone marker levels are related?
- In multinomial logistic regression models rather than linear models, are age, race/ethnicity and body mass index (BMI) groups more strongly associated with different statistically determined sex steroid hormone clusters?
- How do the associations from multinomial logistic regression models compare to findings between sex steroid hormones and age, race/ethnicity and BMI groups using linear regression models?

Key messages

- To take into account the fact that sex steroid hormone marker levels are related, four distinct sex steroid hormone profiles were statistically determined using cluster analysis, described as: 'low sex hormone binding globulin (SHBG)', 'high 3-α diol G', 'high T, E and SHBG' and 'low T, E, and 3-α diol G' profiles.
- Mexican American men >50 years were associated with the profile that had lowest T, E and 3-α diol G levels compared to other profiles ($p<0.05$). Non-Hispanic Black, overweight (25–29.9 kg/m^2) and obese (>30 kg/m^2) men were most likely to be associated with the cluster with the lowest SHBG ($p<0.05$).
- The associations of sex steroid hormone profiles by race/ethnicity are novel, while findings by age and BMI groups are largely consistent with results from single hormone studies. Future studies should examine hormone profiles in relation to chronic disease risk.

INTRODUCTION

Sex steroid hormones, testosterone (T) and 17-β estradiol (E), along with sex hormone binding globulin (SHBG), a carrier protein

ARTICLE SUMMARY

Strengths and limitation of this study

- Nationally representative sample of men in the USA where minority groups were oversampled to ensure adequate representation in study analyses.
- Hormone marker values were used from a single measurement and covariates like diet and smoking were taken from self-reported data.

of T and E and androstanediol glucuronide (3-α diol G), a metabolite used as a marker for T and dihydrotestosterone (DHT) metabolism, play critical roles in sexual development and body function.[1–5] These hormone markers are involved in muscle and bone growth, adipose tissue function and distribution.[6–8] Differences in the levels of sex hormone markers have been hypothesised to contribute to differences in several chronic diseases and prostate cancer rates observed by age, race/ethnicity and body mass index (BMI).[9–20] Yet, differences in sex steroid hormone marker levels by age, race/ethnicity and BMI groups have yet to be fully clarified in the literature.[21–35]

Many previous studies have investigated single sex hormone marker levels in linear regression models by age, race/ethnicity and BMI. Typically, with increasing age, T and E levels decline and SHBG increases, although there was evidence to suggest that some older men have hormone marker levels similar to younger men.[19 21 22 26 28 29 35–39] By race/ethnicity, higher hormone levels have been reported among non-Hispanic Black men compared to non-Hispanic Whites, although this finding was not consistent across studies; and, studies sex hormone markers among other racial/ethnic groups were scant.[5 8 30 34 35 40–42] With increasing BMI, T has been reported to decline and E and SHBG increase, yet these findings are not consistent across studies.[8 21 24 26–28 40] On the basis of somewhat inconsistent findings across these studies, it is possible that investigating factors that influence sex steroid hormone marker levels singly was inadequate.

Sex hormone markers E, T, SHBG and 3-α diol G are known to be related through sex steroid metabolism. Since sex hormone markers are related, then differing hormone levels may be related to each other as well. Cluster analysis can identify underlying statistical patterns among sex hormone markers, which may be indicative of general patterns of sex steroid hormone markers among men. Investigating statistically related sex steroid hormone profiles may produce different associations with age, race/ethnicity and BMI groups than investigating these markers singly in linear models. Therefore, we used cluster analysis to statistically determine which mean hormone marker levels cluster together to form specific hormone profiles, and multinomial logistic regression to determine whether age, BMI and race/ethnicity groups were more likely to be associated with different sex steroid hormone marker profiles.

MATERIALS AND METHODS

Study population

We utilised data from the National Health and Nutrition Examination Survey (NHANES) III conducted by the National Center for Health Statistics (NCHS), and these methods have been described previously.[43 44] Briefly, NHANES III was collected in two phases, and this study used the phase I data from 1988 to 1991. This cross-sectional survey was designed as a multistage stratified, clustered probability sample, the sampling frame includes US residents ≥2 months of age, civilian, non-institutionalised population and NHANES III over sampled those >65 years, Non-Hispanic Blacks and Mexican Americans.

The NHANES III study population was used to derive the analysis cohort. A total of 16 295 men were interviewed of which n=14 781 completed a mobile examination component (MEC) exam.[43 44] The NHANES III morning portion of the survey phase I (1988–1991), included n=2417 men and n=1637 that provided blood samples. We removed the males who were under 17 years of age and four outliers with high 17-β estradiol levels identified by box and whisker plot analysis for a final analysis cohort of n=1528 men.

Exposure variables

Age, race/ethnicity and BMI were the exposures of interest. The NHANES III data obtained age and race/ethnicity information from the US Census survey 1990 to draw the sampling frame, so this information was 100% complete and was verified during the adult interview survey screening by NHANES III field staff.[43 44] Continuous age (in years) was categorised into the following groups: 17–29, 30–49, 50–69 and 70 and over. Race/ethnicity was categorised as White non-Hispanic, Black non-Hispanic, Mexican Americans and All others. Asian, American Indian/Alaskan Native, or Pacific Islanders were included in the other group. Whites and Blacks in the analysis reported non-Hispanic ethnicity. Mexican American is considered an ethnicity, and may also report any race group (White, Black, Asian, American Indian/Alaskan Native or Pacific Islander). Hispanics other than Mexican Americans were included in the other group, since there were few. BMI (weight in kg divided by height in m^2) was obtained from body measurements taken during the MEC. BMI information is available for 99.5% (n=1524) of men in the analysis cohort. Categories of BMI were constructed based on WHO guidelines: underweight <18.5, normal weight 18.5–24.9, overweight 25–29.9 and obese ≥30 kg/m^2.[45]

Outcome variable

Laboratory measurement methods in NHANES III have been described previously.[43 44] Briefly, NHANES III

selected a random subset of n=1637 men over 12 years of age during the 1988–1991 phase I survey collection, where morning blood samples were collected to measure serum levels of T, E, SHBG and 3-α diol G using standard procedures. As described previously, samples were centrifuged, serum was aliquotted and stored at −70°C. Samples were randomly ordered and technicians were blinded to identity, age and race/ethnicity. The lowest detection limits by the electrochemiluminescence immunoassays on the 2010 Elecsys autoanalyser for the samples were: T 0.02 ng/ml, E 5.0 pg/ml, and SHBG 0.35 nmol/l. Enzyme immunoassays were used for 3-α diol G and the lowest detection limits were 0.33 ng/ml. The functional sensitivity, or the lowest analyte concentration that can be reproduced with a coefficient of variation ≥20% for T was 0.12 ng/ml and 12 pg/ml for E. Control samples were run at the start of the day, after every 100 samples, at the end of the day, once per reagent kit and after calibration. Control samples fell within 2 SD at the start of the sample runs, but 3 SD were tolerated at prior control points. Hormone marker data were included as continuous variables in the NHANES III dataset.

Blom-transformations of the laboratory results for T, E, SHBG and 3-α diol G were used in this analysis. Blom-transformed hormone marker variables were chosen for cluster analysis since these are rank approximations, and were unit-free, which makes the distribution of the four markers comparable.[46] The Blom-transformed marker variables were moderately correlated ($r_{Spearman}$<0.50) indicating that the unweighted observations are independent, and can be used for cluster analysis.

Model covariates

To adjust the regression models for lifestyle and dietary factors, we used data from the NHANES III adult, examination and laboratory files. Alcohol intake, smoking status, exercise amount, zinc, total calorie, total fat, total monosaturated fat, total polysaturated fat, total saturated fat, fibre, were taken from 24 h recall surveys, which captured food intake from the past 24 h.[43 44] Lycopene intake was from blood samples since it was not available from 24 h recall surveys. Alcohol intake (grams) was combined into three groups (non-drinkers, drinkers and missing). Smoking status was categorised into four levels, as men who do not smoke, men who smoke, but not every day and men who are current everyday smokers of <35 cigarettes/day or ≥35 cigarettes/day. The exercise variable combined the total days per month a person participated in exercise activities. Serum lycopene concentration was measured in blood samples, and if levels were below detection (0.63 µg/ml) 0 was recorded. Exercise per month, lycopene concentrations, other food intake variables were grouped into quartiles.

The medical exam variables used in the models, included fasting status, exam day of the week, blood cholesterol level, aspartate aminotransferase and alanine aminotransferase were from the MEC data. Fasting compliance was determined prior to blood and urine collection via questionnaire, and was not followed uniformly, for instance: <1% fasted for 20 h or more, 91.8% fasted for 10.01–19.99 h, 7.5% fasted for 10 h or less and <0.1% either did not fast or no value was available. No minimum detection limits were presented for cholesterol, aspartate aminotransferase and alanine aminotransferase. Cholesterol, aspartate aminotransferase and alanine aminotransferase were categorised into quartiles for analysis.

Data analysis

All data analysis was conducted using SAS V.9.2 (Cary, North Carolina, USA). K-means cluster analysis was chosen to create cluster profiles using Blom-transformed T, E, SHBG and 3-α diol G over other exploratory methods, since it assigns each observation only to one group, is based on least squares, tends to find clusters with roughly the same number of observations, and is robust to outliers in the data. The k-means procedure calculates statistics that can be used to determine the best number of k clusters, including: an approximate overall R^2 value, pseudo F-statatistics and Cubic Clustering Criteria (CCC). These statistics were employed to compare exploratory cluster solutions using four to eight cluster groups on the unweighted data, since survey procedures were not available for cluster analysis in SAS V.9.2.

Multinomial logistic regression models using survey procedures (accounting for weighted and stratified data) were employed to examine how age, race/ethnicity and BMI were associated with the constructed sex hormone profiles. Low SHBG served as the reference group since mean hormone values were most similar to the total population. Models were reduced by investigating the exposure variables (age, race/ethnicity and BMI) for a 10% change in the ORs. Covariates included in the full models included age, race/ethnicity, BMI, exam day of the week, hours of fasting, aspartate aminotransferase, alanine aminotransferase, cholesterol levels, exercise level, smoking and drinking status, total calories, total fat, monosaturated fats, polyunsaturated fats, saturated fat, fibre, lycopene and zinc intake.

RESULTS

We calculated the percentages (%) and 95% CIs for age, race/ethnicity and BMI (n=1528) (table 1). The majority of men in the cohort were 30–49 years (42.25%), followed by 17–29 years (29.05%), 50–69 years (21.18%) and over 70 years (7.52%). By race/ethnicity, men self-reported to be, non-Hispanic White (77.36%), and non-Hispanic Blacks (9.75%), Mexican American (5.25%) and all other races (7.64%). The highest proportions of men were either overweight, BMI 25–29.9, (39.73%) or normal weight, BMI 18.5–24.9 (38.45%), while 20.38% of men were considered obese, BMI ≥30.

Table 1 Demographic information among men, US NHANES III 1988–1991

Demographic information	Total (n)	Percentage
Age		
17–29	365	29.1
30–49	516	37.3
50–69	388	21.2
70 and over	259	7.5
Race/ethnicity		
Non-Hispanic White	689	77.4
Non-Hispanic Black	378	9.8
Mexican American	402	5.3
Other	59	7.6
Body mass index (kg/m^2)		
<18.5	21	1.4
18.5–24.9	555	38.5
25.0–29.9	623	39.7
≥30	328	20.4
Missing	1	<0.01

US NHANES III, US National Health and Nutrition Examination Survey III.

Table 2 Blom-transformed sex steroid hormone marker mean levels in the total population and hormone marker profiles among American men, US NHANES III 1988–1991

Hormone marker group	Total (N)	Mean	SD
Population total			
Testosterone	1527	0.13	0.04
17-β Estradiol	1524	0.06	0.06
Sex hormone binding globulin	1517	−0.15	0.05
Androstanediol glucuronide	1505	0.16	0.04
Low SHBG profile			
Testosterone	415	−0.25	0.04
17-β Estradiol	417	0.32	0.06
Sex hormone binding globulin	412	−1.10	0.06
Androstanediol glucuronide	407	0.20	0.06
High 3-α diol G profile			
Testosterone	327	−0.02	0.04
17-β Estradiol	326	−0.67	0.07
Sex hormone binding globulin	324	−0.08	0.05
Androstanediol glucuronide	324	0.78	0.06
High T, E and SHBG profile			
Testosterone	484	1.00	0.05
17-β Estradiol	480	0.68	0.05
Sex hormone binding globulin	480	0.53	0.04
Androstanediol glucuronide	476	0.15	0.05
Low T, E, and 3-α diol G			
Testosterone	298	−0.79	0.07
17-β Estradiol	298	−0.71	0.10
Sex hormone binding globulin	298	0.25	0.07
Androstanediol glucuronide	295	−0.98	0.04

N/A, not applicable; SHBG, sex hormone binding globulin; US NHANES III, US National Health and Nutrition Examination Survey III.

We used cluster analysis to create hormone profiles from Blom-transformed T, E, SHBG and 3-α diol G laboratory values, and only the four and five level cluster solutions performed well (data not shown). The pseudo F-statistic was improved over the five cluster solution, and the CCC value was positive (1.2) for the four cluster solution (data not shown). The four cluster solution was used to create hormone profiles (table 2).

We examined the mean levels of Blom-transformed T, E, SHBG and 3-α diol G for the hormone profiles and the total population to determine how the mean levels differed (table 2). The first cluster had lowest mean SHBG level of the groups, but the mean level of T, E and 3-α diol G was most similar to the total cohort (hereafter referred to as the 'low SHBG profile'). The second cluster had the highest mean 3-α diol G level compared to the other clusters (referred to as the 'high 3-α diol G profile'). The third cluster had the highest mean levels of T, E and SHBG (hereafter referred to as the 'high T, E and SHBG profile'). The fourth cluster had lowest mean levels of T, E and 3-α diol G compared to the other groups ('low T, E and 3-α diol G profile').

Associations with hormone profiles and age, race/ethnicity and BMI groups using weighted multinomial logistic regression models were examined (table 3). The younger men (17–29 years) were associated with the 'low SHBG profile'. Men in the 'low T, E and 3-α diol G profile' were most associated with 50–69 years (OR=11.5, 95% CI 4.74 to 27.68) and 70 years or over (OR=24.3, 95% CI 7.71 to 76.82). Non-Hispanic Black men had higher odds of being in the 'low SHBG profile' (OR=2.5, 95% CI 1.30 to 4.35) and Mexican American men were more strongly associated with the 'low T, E and 3-α diol G profile' (OR=3.1, 95% CI 1.69 to 5.68). Obese men (BMI ≥30) were most likely to be associated with the referent 'low SHBG profile' compared to men with a normal BMI (18.5–24.9) in all other profiles.

DISCUSSION

This is the first study to examine statistically determined sex steroid hormone marker profiles by age, BMI and race/ethnicity groups. Applying our novel approach in studying sex steroid hormone levels among US men, we created four statistically determined clusters, described as: 'low SHBG', 'high 3-α diol G', 'high T, E and SHBG' and 'low T, E and 3-α diol G'. Examining hormone profiles by age and BMI, our results largely agree with single hormone studies.[5 16 21 24 30 40 47] This study also found new evidence supporting differences in sex steroid hormone levels for non-Hispanic Blacks and Mexican American men using hormone profiles, and these observations differed from single hormone studies.

Men in our study associated with the 'low SHBG' profile were more likely to be younger (<17–29 years), obese (BMI ≥30) and non-Hispanic Black (table 3). Our findings indicate that the 'low SHBG profile' was more commonly associated with younger men (17–29 years),[5 16 30 40] and lower SHBG levels were reported among obese men in single hormone studies.[21 24 47] By contrast, the

Table 3 Hormone profile associations with age, race/ethnicity and body mass index (BMI) (kg/m^2) in reduced multinomial regression model†,‡,§ US NHANES III

Demographic characteristics	High 3-α diol G OR (95% CI)	High T, E, SHBG OR (95% CI)	Low T, E, 3-α diol G OR (95% CI)
Age (years)			
17–29	0.4* (0.2 to 0.7)	0.4* (0.3 to0.6)	0.3* (<0.1 to 1.0)
30–49†	1.0	1.0	1.0
50–69	1.9 (0.9 to 4.1)	2.3* (1.3 to 4.2)	11.5*(4.7 to 27.7)
70 and over	2.2* (1.0 to 4.7)	4.2* (1.9 to 8.9)	24.3*(7.7 to 76.8)
Race/ethnicity group			
non-Hispanic White†	1.0	1.0	1.0
non-Hispanic Black	0.4* (0.2 to 0.8)	1.0 (0.5 to 1.9)	0.7 (0.4 to 1.4)
Mexican American	1.5 (0.7 to 3.4)	1.4 (0.8 to 2.7)	3.1* (1.7 to 5.7)
Other	0.8 (0.3 to 2.2)	0.4* (0.2 to 0.8)	1.8 (0.7 to 4.4)
BMI (kg/m^2)			
<18.5	2.1 (0.8 to 5.3)	1.9 (0.2 to 24.6)	1.0 (0.1 to 13.6)
18.5–24.9†	1.0 (N/A)	1.0 (N/A)	1.0
25–29.9	0.6 (0.3 to 1.1)	0.3* (0.2 to 0.5)	0.4* (0.2 to 0.7)
≥30	0.2* (0.1 to 0.4)	0.05* (0.03 to 0.1)	0.1* (0.1 to 0.2)

*Statistically significant, p<0.05.
†Low sex hormone binding globulin (SHBG) profile is the reference group for multinomial logistic regression models.
‡The reduced model is adjusted for: age, race/ethnicity, BMI, exam day of the week, fasting in hours, liver enzyme levels, exercise level, smoking status, total calories, total fat, monosaturated fats, polyunsaturated fats, saturated fat, fibre, lycopene and zinc intake.
§Models used appropriate strata and weighting for national representation.
US NHANES III, National Health and Nutrition Examination Survey III.

observations that non-Hispanic Blacks were more likely to be associated with a 'low SHBG profile' compared to non-Hispanic Whites and Mexicans were new. This result does not agree with previous single hormone studies, which have dominantly reported no differences or higher levels of SHBG among non-Hispanic Blacks compared to non-Hispanic Whites.[5 16 30 31 40]

The 'high 3-α diol G profile' associations with age and BMI were somewhat ambiguous compared to other profiles, while the 'high 3-α diol G profile' was more strongly associated with non-Hispanic Whites. Past studies investigating 3-α diol G have reported higher 3-α diol G activity among older men with a higher BMI.[8 32 33 41 42 48–53] However, much stronger associations with older age and obesity were seen with other profiles compared to this profile.[8 32 33 41 42 48–53] Some single hormone studies reported no difference in 3-α diol G levels by race among younger men,[41] yet in other studies older men have reported higher 3-α diol G activity in non-Hispanic Whites compared to non-Hispanic Blacks which agrees with the findings in this study.[5 41 42 50 51] The reasons why hormone studies were largely consistent for higher 3-α diol G levels seen among older non-Hispanic White men, while findings for other race/ethnicity groups were inconsistent was still unclear.[5 9 16 30 31 34 40 42 50]

The men in the 'high T, E and SHBG profile' were older than the first two profiles, were most likely to have a normal BMI, and there were not any differences between the race/ethnicity groups. Previous cross-sectional studies investigating T alone have reported high T levels among young men, yet other studies have indicated that high T levels were not found exclusively among young men.[19 22 26 36–39 54–57] The results for the 'high T, E and SHBG' profile were consistent with single hormone studies that reported higher T and SHBG among men with a normal BMI.[58 59] Past studies have hypothesised that higher sex steroid hormones (T and E) were responsible for the racial disparities observed in the rates of prostate cancer.[9 22 30 35 40] Despite a higher proportion of non-Hispanic Black men found in the 'high T, E and SHBG profile', non-Hispanic Black men were not associated with this profile (data not shown). These findings do not support this previously considered hypothesis that sex steroid hormone levels are higher among non-Hispanic Black men compared to other race/ethnicity groups.[5 9 22 30 35 40 46]

The 'low T, E and 3-α diol G profile' was more likely to be associated with men over 70 years and Mexican American men, while findings by BMI were less defined compared to other profiles. Previous studies have suggested that lowered T and E metabolism, and increasing SHBG levels were associated with older ages.[19 22 26 36–39 54] This was in agreement with our results, since 74% of men are over 50 years in this profile, and associations were strongest with older age groups (table 3). Overweight and obesity have been associated with declines in T and SHBG, and despite the low T levels in this profile, the 'low SHBG profile' was more strongly associated with obesity.[24 58 59] Past single hormone studies specifically comparing T levels among Hispanics to non-Hispanics have conflicted, two reported no differences, one reported lower and another reported higher levels.[5 9 42 46] Although there

were few studies comparing sex steroid hormones among Mexican Americans compared to non-Hispanic Whites these findings from these studies conflict.[5 9 16 30 31 40 42]

This study has several strengths. NHANES III data was a nationally representative sample, so selection bias was minimised.[43 44] The NHANES III oversampled minorities and men over 65 years ensuring adequate numbers of men for analysis.[43 44] Our exposure variables were 99% complete.[43 44] Hormone levels were measured systematically using standard methods available at the time which did employ testing against control samples.[43 44] We were able to select only those men who provided blood samples in the morning to correct for daily hormone fluctuations, and control for day of the week the blood was drawn and fasting time.[43 44]

The study also has several limitations. The dietary information was from self-reported 24-h recall surveys, and may not reflect a man's true dietary behaviours.[43 44] Smoking status was also self-reported.[43 44] The study was only based on a single hormone measurement among men, which may not account for the daily complexity or serum hormone measurements over time. While the hormone profiles combine two major sex steroid hormones, a carrier protein and a metabolite, these profiles are still likely to be an oversimplification compared to hormone metabolism in the body.

In conclusion, specific sex steroid hormone marker profiles were more likely than others to be associated with one or more age, race/ethnicity or BMI groups. Our findings for non-Hispanic Blacks and Mexican Americans are novel, since these groups have often been suggested to be associated with higher sex steroid hormone levels, yet this study found the opposite. Our findings by age and BMI largely agreed with most single hormone studies. The observed race/ethnicity differences across the hormone profiles in the current analysis, suggest that when accounting for the relationship between sex steroid hormone markers, race/ethnicity differences become apparent. Further research is necessary to determine if sex steroid hormone profiles contribute to the increased risk of several cancers and chronic diseases observed by race/ethnicity.

Contributors All authors contributed to the project, this included: JR: concept and study design, performed data download from the internet and merged sets, input into and performed data cleaning and analysis including variable construction and statistical testing, manuscript drafting and revisions. WK: concept and study design, input into data cleaning and analysis particularly statistics and variable construction and inclusion, manuscript drafting and revisions. HZ: concept and study design, input into data cleaning and analysis particularly statistics, manuscript drafting and revisions. SS: concept and study design, input into data cleaning and analysis particularly variable construction and inclusion, manuscript drafting and revisions. TS-A: concept and study design, input into data cleaning and analysis particularly variable construction and inclusion, manuscript drafting and revisions.

Competing interests None.

Ethics approval University of South Carolina.

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