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Heritability of Measures of Kidney Disease Among Zuni Indians: The Zuni Kidney Project

Jean W. MacCluer, PhD[1], **Marina Scavini, MD**[2,3,4], **Vallabh O. Shah, PhD**[2,5], **Shelley A. Cole, PhD**[1], **Sandra L. Laston, PhD**[1], **V. Saroja Voruganti, PhD**[1], **Susan S. Paine, MPH**[2], **Alfred J. Eaton, BS**[1], **Anthony G. Comuzzie, PhD**[1], **Francesca Tentori, MD**[3], **Dorothy R. Pathak, PhD**[2,6,7], **Arlene Bobelu, BS**[3], **Jeanette Bobelu**[2], **Donica Ghahate**[2], **Mildred Waikaniwa**[2], and **Philip G. Zager, MD**[2,3]

[1] Southwest Foundation for Biomedical Research, San Antonio, TX

[2] Department of Medicine, Division of Nephrology, University of New Mexico Health Sciences Center

[3] Dialysis Clinic Inc, Albuquerque, NM

[4] San Raffaele Scientific Institute, Milan, Italy

[5] Biochemistry and Molecular Biology, University of New Mexico Health Sciences Center, Albuquerque, NM

[6] Department of Epidemiology, Michigan State University, East Lansing, MI

[7] Department of Family Medicine, Michigan State University, East Lansing, MI

Abstract

Background—The long-term goal of the GKDZI (Genetics of Kidney Disease in Zuni Indians) Study is to identify genes, environmental factors, and genetic-environmental interactions that modulate susceptibility to renal disease and intermediate phenotypes.

Study Design—A community-based participatory research approach was used to recruit family members of individuals with kidney disease.

Setting & Participants—The study was conducted in the Zuni Indians, a small endogamous tribe located in rural New Mexico. We recruited members of extended families, ascertained through a proband with kidney disease and at least 1 sibling with kidney disease. 821 participants were recruited, comprising 7,702 relative pairs.

Predictor Outcomes & Measurements—Urine albumin-creatinine ratio (UACR) and hematuria were determined in 3 urine samples and expressed as a true ratio. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation modified for American Indians. Probands were considered to have kidney disease if UACR was ≥0.2 in 2 or more of 3 spot urine samples or estimated GFR was decreased according to the CRIC (Chronic Renal Insufficiency Cohort) Study criteria.

Results—Kidney disease was identified in 192 participants (23.4%). There were significant heritabilities for estimated GFR, UACR, serum creatinine, serum urea nitrogen, and uric acid and

Address correspondence to Philip G. Zager, MD, University of New Mexico, Department of Medicine–Nephrology ACC5, Albuquerque, NM 87131-5271. pzag@unm.edu.

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a variety of phenotypes related to obesity, diabetes, and cardiovascular disease. There were significant genetic correlations of some kidney-related phenotypes with these other phenotypes.

Limitations—Limitations include absence of renal biopsy, possible misclassification bias, lack of direct GFR measurements, and failure to include all possible environmental interactions.

Conclusions—Many phenotypes related to kidney disease showed significant heritabilities in Zuni Indians, and there were significant genetic correlations with phenotypes related to obesity, diabetes, and cardiovascular disease. The study design serves as a paradigm for the conduct of research in relatively isolated, endogamous, underserved populations.

INDEX WORDS

Genetics; heritability; American Indians; kidney diseases; risk factors; glomerular filtration rate; urine albumin-creatinine ratio (UACR); creatinine; serum urea nitrogen (SUN); uric acid

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The Zuni Indians are experiencing an epidemic of chronic kidney disease (CKD). The prevalence of end-stage renal disease is 20.0-, 4.4-, and 5.6-fold higher than in European and African Americans and the composite estimate for American Indians, respectively.[1,2] Earlier studies, which were not population based, attributed most kidney disease to mesangiopathic glomerulonephritis.[3–6] Presently, >95% of end-stage renal disease is attributable to diabetic nephropathy.

To decrease the burden of CKD, the Zuni Pueblo established the Zuni Kidney Project in partnership with the Indian Health Service, University of New Mexico, Southwest Foundation for Biomedical Research, and Dialysis Clinic Inc.[2] We conducted a population-based cross-sectional survey that showed high prevalence estimates, age-and sex-adjusted to the Zuni population, for decreased estimated glomerular filtration rate (eGFR),[7] albuminuria, and hematuria.[8] Prevalence estimates for albuminuria and hematuria were higher for diabetic than nondiabetic participants.[8,9]

The GKDZI (Genetics of Kidney Disease in Zuni Indians) Study was initiated to identify genes, environmental factors, and genetic-environmental interactions that modulate susceptibility to CKD and intermediate phenotypes. This report presents heritability estimates and genetic correlations for CKD, diabetes, and cardiovascular disease phenotypes.

METHODS

Study Design

GKDZI is a community-based participatory research project. Institutional review boards from each institution approved the study, and informed consent was obtained. We recruited 821 members of extended families ascertained through probands with CKD and 1 or more affected sibling(s).

Setting

The Zuni Pueblo in rural New Mexico is relatively endogamous. The tribe has approximately 10,000 members, and 80% live in the pueblo. Median age is 26 years.[10] Most adult tribal members work as artisans making jewelry, pottery, and fetishes, which are a contemporary art form that represents animals and icons important to the Zuni.

Participants

Probands were identified from Zuni Kidney Project survey participants.[7–9,11,12] Eligibility criteria for probands and affected siblings included age 18 years or older and evidence of CKD, for example, urine albumin-creatinine ratio (UACR) ≥0.2 in at least 2 of 3 urine samples or decreased eGFR.[13] We used parental identities to construct family trees and determine the relatedness of individual pairs. We recruited first-, second-, and third-degree relatives of probands and their spouses. First-degree relatives are parents, siblings, and offspring; second-degree relatives are aunts and uncles, nieces and nephews, grandparents, and grandchildren; and third-degree relatives are first cousins, great aunts, great uncles, etc. All family members with CKD were eligible. We used PEDSYS (Southwest Foundation for Biomedical Research, http://pedsys.sfbrgenetics.org)[14] for data entry, quality control, report generation, and preparation of data files for statistical genetic analysis, and PedigreeDraw,[15] a family tree drawing program (Jurek Software, www.pedigree-draw.com).

Variables

Participants were considered to have diabetes if they met at least 1 of the following conditions: (1) history of diabetes, (2) plasma glucose level ≥200 mg/dL, (3) hemoglobin A_{1c} (HbA_{1c}) level >7.0%,[16,17] or (4) receiving diabetes medication(s). Diabetes status in participants with HbA_{1c} level of 6.0%–7.0%, plasma glucose level <200 mg/dL, and no history of diabetes was considered "indeterminate."[7] Participants were classified as hypertensive if they met at least 1 of the following conditions: (1) history of hypertension; (2) systolic or diastolic blood pressure ≥140 and ≥90 mm Hg, respectively;[18] or (3) using antihypertensive medication(s). Blood was drawn for chemistry profile, HbA_{1c},[17] serum creatinine (SCr),[19] and, in a subset, serum cystatin C (SCysC) measurement.[20] Buffy coats were obtained by centrifugation for DNA isolation. We assessed phenotypes related to CKD (eGFR, UACR, SCr, and serum urea nitrogen [SUN]) or diabetes and cardiovascular disease (weight, body mass index [BMI], HbA_{1c}, diabetes status, hypertension status, serum triglycerides, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and total cholesterol) in artisans and nonartisans.

Data Sources and Measurement

Questionnaire Data and Biological Measurements Made in the Home—We administered a questionnaire[2] that ascertained birth dates, parents' identities, education, occupation, tribal affiliation, language spoken, and medical history. Height and weight were measured.[2] We identified overweight (BMI 25–29 kg/m^2) and obese (BMI ≥30 kg/m^2) participants. We measured systolic and diastolic blood pressure 3 times separated by 1-minute intervals and used the respective average values to classify hypertension status.

Reducing Bias in Biological Samples—To minimize classification bias, we attempted to obtain 3 urine samples from each participant. The median interval between urine collections was 2 days. We compared classifications of albuminuria and hematuria using the first versus the mode of 3 urine samples. UACR was classified as normal (<0.03), incipient (0.03–0.19), or overt (≥0.20). If all 3 samples were discordant, we used the median value. Urine albumin was measured using nephelometry.[21–23] The presence of 3 or more red blood cells per high-power field was considered evidence of hematuria.

Reducing Bias in eGFR—We used the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation, modified for use in American Indians,[7,8,24] and a SCysC-based equation (both formulas are given in the notes to the third table in this article) to estimate GFR based on a single serum sample.[25–28] Limitations of these equations include need for race-specific coefficients and lack of widespread calibration in SCr and SCysC assays.[25]

SCr level is influenced by muscle mass. eGFR may underestimate GFR in people with near-normal kidney function.[25–28] We categorized eGFR using the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI)[29] and the CRIC (Chronic Renal Insufficiency Cohort) Study age-specific criteria.[13]

Study Size

Study size was derived from previous studies of genetic effects on complex diseases in Mexican American,[30,31] American Indian,[32,33] and Alaskan Eskimo[34,35] extended families. The GKDZI sample size was similar to these studies, in which we obtained significant heritabilities.

Statistical Methods

Questionnaire data were entered into a Microsoft Access database using double data entry and computerized range checks. Discrepancies were resolved by direct comparison with the questionnaire. Initial data entry error rates were low (2.1%) and decreased to <0.5%. Laboratory data were transferred electronically to the database.

Statistical analyses were conducted using SOLAR (Southwest Foundation for Biomedical Research, http://solar.sfbrgenetics.org).[36,37] Data were expressed as mean ± standard error. For tests of differences between groups and calculation of heritabilities and correlations, all traits were inverse normalized. Observations were ranked and replaced by the expected value for that rank from a standard normal distribution. Multiple UACR measurements from an individual were evaluated using the Friedman nonparametric test for repeated measures. Phenotypic correlations of eGFR calculated using the MDRD Study equation modified for American Indians ($eGFR_{MDRD\text{-}AI}$) versus $eGFR_{SCysC}$ were computed in SOLAR. Categorical classifications by $eGFR_{MDRD\text{-}AI}$ and $eGFR_{SCysC}$ were compared using a weighted κ, 95% confidence interval (CI), and symmetry tests. Differences were considered statistically significant for $P < 0.05$.

Heritability Estimation and Quantitative Genetic Analysis

We estimated the heritability (h^2) of $eGFR_{MDRD\text{-}AI}$, UACR, and other intermediate phenotypes and genetic correlations using maximum likelihood variance decomposition methods[36,38] in SOLAR. Heritability is the ratio of the additive genetic variance to the total phenotypic variance.[39,40] We calculated heritabilities using residual variances after accounting for effects of covariates. We constructed 2 sets of models, the first including age, sex, and their higher order terms and interactions as covariates and the second including these covariates plus diabetes, hypertension, and artisan status. We estimated the proportion of variance attributable to covariates by comparing models with and without covariates. Covariates were included on the basis of their biological, rather than statistical, significance. We computed Kullback-Leibler R^2 values for dichotomous traits. We used family relationships and phenotypic measures in family members to infer the proportion of phenotypic variance attributable to the additive effects of genes and the genetic correlation between pairs of phenotypes. The calculations do not require information for specific genotypes. If other nonadditive sources of genetic variation exist, for example, dominance or epistasis, the reported heritabilities and correlations would represent lower bounds. We did not include household membership, which may fluctuate. Only if the exposure pattern for an environmental variable or of shared household membership mimicked Mendelian transmission would the heritability and correlation estimates be inflated by nongenetic factors.

Using the variance component model, P values for heritabilities were obtained by comparing the likelihood of a model in which h^2 is estimated to the likelihood of a model in which h^2 is

constrained to zero. Twice the difference in the natural log likelihoods is asymptotically distributed as a ½:½ mixture of a χ^2 distribution with 1 *df* and a point mass at zero. This approach allows an explicit test of whether correlations among family members are caused in part by additive genetic effects.

Bivariate analyses yield genetic and environmental correlations among phenotypes. Genetic correlations indicate the extent to which the additive effects of the same set of genes influence more than 1 phenotype. Environmental correlations include environmental effects and nonadditive genetic effects.

RESULTS

Participants

We recruited 821 participants from 30 families, of which 19 contained 3 or more generations and 11 contained 2 generations. After linking participants through offspring and marriage, 805 merged into 1 family. Among 821 participants, there were 7,702 relative pairs (Table 1). Median age was 36.7 years, and interquartile range was 21.1 years. Of the participants, 405 (49.3%) were female, 446 (54.3%) reported 12 or more years of education, 463 (56.4%) were artisans, and 686 (83.6%) spoke Shiwi, the Zuni language.

Evidence of Kidney Disease in Diabetic and Nondiabetic Participants

Participants were considered to have CKD if they had a UACR >0.03 on 2 or more urine samples or decreased eGFR according to age-specific criteria used in CRIC. Hematuria was not used in the classification of CKD because we did not ascertain its cause. CKD was present in 192 participants (23.4%). Of these, 83 had diabetes, 108 did not have diabetes, and 1 had indeterminate diabetes status. Albuminuria was present in 105 (97.2%) nondiabetic and 73 (98.7%) diabetic participants with CKD stages 1–4 ($P < 0.001$). eGFR was decreased in 24 (28.9%) diabetic and 7 nondiabetic (6.5%) participants with CKD stages 1–5. Many nondiabetic participants with albuminuria and/or decreased eGFR (n = 108) had features of metabolic syndrome, for example, hypertension (52.8%), overweight (37.0%), and obesity (45.4%). All 12 participants with end-stage renal disease had diabetes. Inclusion of hematuria as a diagnostic criterion would have yielded an additional 32 participants with CKD.

Prevalence of Kidney Disease in Multigenerational Families

CKD was present in 2 or more generations in 23 families. In nondiabetic participants, 4, 3, and 2 generations were present in 1, 3, and 10 families, respectively. Two generations of diabetic participants with CKD were present in 10 families, and 3 generations, in 1 family.

UACR, Hematuria, and eGFR

Urine Albumin-Creatinine Ratio—Three urine samples or 2 concordant samples were obtained for 798 participants. Classifications using the initial versus the mode of 3 urine samples were similar (Table 2; weighted κ, 0.89 [95% CI, 0.85–0.92]).[41] The symmetry test (s = 6.0; $P = 0.1$) showed no directional bias. However, the initial UACR tended to overestimate the prevalence of albuminuria. In participants with incipient albuminuria on the initial urine sample, 18 (15%) subsequently had 2 normal UACR determinations. Three participants (5%) with overt albuminuria on the initial urine sample subsequently had 2 normal UACR determinations. In participants with an initial normal UACR, 9 (1.5%) subsequently were reclassified as incipient, and 1 (0.2%), as overt albuminuria.

Hematuria—We determined the mode for the presence of red blood cells in 3 urine samples in 739 participants. The initial urine sample had 3 or more red blood cells per high-power field in 86 (11.6%) participants. However, using the mode of 3 urine samples, only 44 (51.2%) of these participants had 3 or more red blood cells per high-power field. In 653 (88.4%) participants without hematuria on the initial urine sample, only 12 (1.8%) had a mode of 3 or more red blood cells per high-power field (McNemar test, s = 16.7; $P < 0.001$). Despite modest agreement ($\kappa = 0.58$ [95% CI, 0.48–0.68]), the lack of symmetry indicated a bias toward a false-positive result of a single test for hematuria. Of 192 participants classified as having kidney disease using UACR or decreased $eGFR_{MDRD-AI}$, only 24 (12.5%) had 3 or more red blood cells per high-power field.

Estimated GFR—We compared the classification of kidney disease obtained using the MDRD Study equation modified for use in American Indians[26,42] and the SCysC eGFR equation[43] in 245 participants. There was moderately good agreement ($\kappa = 0.50$ [95% CI, 0.37–0.63]) using KDOQI stages.[29] Agreement for the age-specific CRIC criteria[13] was modest ($\kappa = 0.39$ [95% CI, 0.00–0.78]). Using KDOQI criteria, Tidman et al[44] also reported good agreement between $eGFR_{MDRD}$ and $eGFR_{SCysC}$. Although the MDRD Study equation modified for American Indians tended to classify low GFR more often than the SCysC eGFR equation, the difference was not significant ($P = 0.1$). Phenotypic correlations between the $eGFR_{MDRD-AI}$ and $eGFR_{SCysC}$ were moderately strong in the study sample as a whole and in groups stratified by age, sex, and diabetes status (Table 3). The Bland-Altman plot showed a slight bias because at lower values, the $eGFR_{MDRD-AI}$ tended to be lower than the $eGFR_{SCysC}$. The opposite was true at higher values (Fig 1). Overall, differences between the $eGFR_{MDRD-AI}$ and $eGFR_{SCysC}$ were small. Therefore, we used $eGFR_{MDRD-AI}$, which was less expensive to measure, in subsequent analyses. Hemodialysis patients were not included in the comparison of GFR-estimating equations because neither SCr nor SCysC concentrations are in steady state.

Intermediate Phenotypes

Of the participants, 277 (33.7%) were classified as overweight (BMI, 25–29 kg/m^2), and 325 (39.6%), as obese (BMI ≥ 30 kg/m^2). There were 140 diabetic (17.1%) participants, of whom 17 (12.1%) were newly diagnosed. Hypertension was present in 286 (34.8%) participants. Of these, 105 (36.7%) were using an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and 93 (32.5%) were not previously aware of their hypertension.

Intermediate phenotypes related to CKD, obesity, diabetes, and cardiovascular disease stratified by sex (Table 4), diabetes (Table 5), and hypertension status (Table 6) are shown. There were significant differences by sex for $eGFR_{MDRD-AI}$, SCr, uric acid, hematuria, weight, BMI, HbA_{1c}, systolic blood pressure, diastolic blood pressure, LDL cholesterol, and total cholesterol (Table 4). $eGFR_{MDRD-AI}$, UACR, SUN, uric acid, weight, BMI, HbA_{1c}, systolic blood pressure, HDL cholesterol, LDL cholesterol, and triglycerides differed among diabetic versus nondiabetic participants (Table 5). HDL and LDL cholesterol were similar in hypertensive and nonhypertensive participants; however, all other phenotypes differed by hypertension status (Table 6).

Approximately half the participants were artisans. Distributions of UACR, SUN, uric acid, systolic blood pressure, diastolic blood pressure, HDL cholesterol, LDL cholesterol, and total cholesterol were significantly higher in artisans (Table 7).

Heritability and Genetic Correlations of Intermediate Phenotypes

Heritability estimates and proportions of variance attributable to covariates for phenotypes related to CKD and cardiovascular disease are listed (Table 8). Heritabilities for $eGFR_{MDRD-AI}$, UACR, SCr, SUN, uric acid, SCysC, weight, BMI, HbA_{1c}, systolic blood pressure, diastolic blood pressure, hypertension status, HDL cholesterol, LDL cholesterol, triglycerides, and total cholesterol were significantly different from zero. Heritabilities for hematuria and diabetes status failed to reach statistical significance. Inclusion of additional covariates in model 2 did not substantially change the estimated heritabilities. The proportion of total phenotypic variance attributable to covariates increased as the number of covariates increased. Proportions of variance attributable to covariates for model 2 ranged from 0.044 for LDL cholesterol to 0.437 for systolic blood pressure.

Genetic correlations indicate the extent of pleiotropy, or shared genetic effects, among phenotypes. There were no significant genetic correlations, indicating no detectable shared genetic effects, among kidney-related phenotypes. Genetic and environmental correlations of CKD phenotypes with obesity, diabetes, and cardiovascular disease phenotypes are listed (Table 9). Information about specific genotypes is not required to estimate genetic correlations. Genetic and environmental correlations correspond to partitioning of the covariance into the additive genetic component and a component subsuming environment and nonadditive genetic effects.

Genetic correlations of UACR with systolic blood pressure, diastolic blood pressure, and hypertension status indicate that some genes of the hypertension axis influence UACR. The genetic correlation between SUN and HbA_{1c} reflects the pleiotropic effects of genes involved in ambient glucose levels and/or glycosylation. There were no significant genetic correlations and no evidence for pleiotropy for $eGFR_{MDRD-AI}$, SCr, or uric acid with any phenotypes related to cardiovascular disease, diabetes, or obesity. There was no evidence of pleiotropy for BMI, weight, HDL cholesterol, LDL cholesterol, total cholesterol, or triglycerides with any intermediate phenotypes for CKD; thus, these may represent genetically independent phenotypes.

Environmental correlations with traits related to obesity, diabetes, and blood pressure tended to be lower than the genetic correlations, but were more likely to attain statistical significance. Environmental and genetic correlations with $eGFR_{MDRD-AI}$ and SCr tended to be opposite in sign. For UACR, all genetic and environmental correlations were positive, and correlations with HbA_{1c}, systolic blood pressure, and hypertension status were statistically significant.

DISCUSSION

This study shows the value of studying extended families to assess the heritability of CKD and intermediate phenotypes in an endogamous population. The significant heritability estimates obtained and the proportion of phenotypic variance contributed by covariates support our hypothesis that genetic and environmental factors modulate susceptibility to kidney disease in the Zuni.

Heritability measures the proportion of phenotypic variance attributed to the additive effects of genes within a population, and the sources, nature, and magnitude of phenotypic variance differ between populations. Therefore, comparisons of heritabilities between populations must be interpreted with caution. Familial clustering and heritability estimates for kidney function and related phenotypes in the GKDZI were similar to those in other studies.[32,45–51] Significant heritabilities for eGFR have been observed in European Americans (0.25–0.31)[49] and African Americans (0.17).[47] In the Framingham Heart Study, there were

significant heritabilities for eGFR (0.36)[48] and log-transformed systolic blood pressure in unadjusted models (0.38) and models adjusted for sex, BMI, and alcohol consumption (0.47).[46] In hypertensive families of African descent, heritability estimates adjusted for age and sex for measured and Cockcroft-Gault–estimated creatinine clearance were 0.52 and 0.82, respectively.[45] In American Indians in the Strong Heart Study, heritability estimates for diastolic blood pressure and BMI were 0.34 and 0.44, respectively.[32]

Heritabilities have been reported for traits related to diabetic nephropathy.[50,52–57] The heritability of UACR was 0.21 in Pima Indians[50] and as reported in Fogarty et al[52] and Krolewski et al[54], 0.27 and 0.23, respectively, in non-Hispanic white families. In Finnish families, heritability for albuminuria was 0.30.[53] Fogarty et al[52] found significant genetic correlations of UACR with systolic and diastolic blood pressure. Studies in non-Hispanic whites with type 2 diabetes yielded high heritabilities for eGFR (0.75) and UACR (0.46).[55] However, these traits were not genetically correlated.[56] The high prevalence of albuminuria in nondiabetic Zuni Indians with hypertension and obesity is in concert with observations in Australian Aborigines.[58]

Genetic factors contribute to the variance in renal function and intermediate phenotypes in many populations. Genetic signals for traits related to diabetic nephropathy have been detected in non-Hispanic whites, African Americans, Mexican Americans, and American Indians. Imperatore et al,[50] using segregation analysis, reported evidence for a major gene influencing susceptibility to diabetic nephropathy in Pima Indians. Other analyses have focused on candidate chromosomal regions,[59–61] genome-wide microsatellite markers,[54,57,62–69] and single-nucleotide polymorphism markers.[70]

In the present study, there were no significant genetic correlations between diabetes status and CKD-related intermediate phenotypes. There was a significant genetic correlation between HbA_{1c} and SUN. There were no significant genetic correlations of HbA_{1c} with SCr, eGFR, or UACR. Given the increased risk of CKD in diabetic patients, the significant heritability of HbA_{1c} and the strong genetic correlation between HbA1c and SUN, genes that influence glycemic control may influence kidney function.[71] The genetic correlations of UACR with systolic blood pressure, diastolic blood pressure, and hypertension status indicate the pleiotropic effects of genes that influence these traits. This may explain in part why albuminuria is a strong predictor of cardiovascular disease.[72] There were no significant genetic correlations among the kidney-related phenotypes.

Although some differences in intermediate phenotypes among participants stratified by sex, diabetes, hypertension, and artisan vocation achieved statistical significance, they may not be clinically significant. Heavy metals used by artisans may have contributed to the observed differences in several intermediate phenotypes, for example, uric acid, systolic blood pressure, diastolic blood pressure, LDL cholesterol, and total cholesterol. We previously showed high levels of cadmium and lead in household dust of Zuni artisans.[73] Environmental lead exposure is a risk factor for the onset[70,74–76] and progression of CKD.[77] Environmental cadmium exposure is associated with diabetes[78] and CKD.[79] Jewelry, pottery, and fetish making occurs primarily in the home. We cannot determine what differences in selected variables reflect genetic versus nongenetic factors until genetic analyses have been completed.

The present study has several limitations. First, given the high prevalence of diabetes and absence of kidney biopsies, there are 2 potential sources of misclassification bias: (1) nondiabetic kidney disease in diabetic participants and (2) diabetic kidney disease in participants who have not yet met diagnostic criteria for diabetes. No participants with diabetes and kidney disease were classified as having nondiabetic kidney disease. We may

have underestimated the prevalence of nondiabetic kidney disease and the number of generations with nondiabetic kidney disease in a given family. Second, despite the agreement between $eGFR_{MDRD\text{-}AI}$ and $eGFR_{SCysC}$, absence of a direct measure of GFR represents a significant limitation, especially because eGFR was based on a single SCr or SCysC determination. Third, the high prevalence of CKD increased anxiety, thus limiting the willingness of many to participate. Fourth, not all genetic-environmental interactions were assessed.

The study also has several strengths: (1) a community-based participatory research study design, (2) large multigenerational extended families, (3) 3 urine samples to classify UACR and hematuria, (4) comparison of $eGFR_{MDRD\text{-}AI}$ and $eGFR_{SCysC}$, and (5) collection of vocational data.

In summary, many phenotypes related to kidney disease show significant heritabilities in Zuni Indians, and there are significant genetic correlations with phenotypes related to obesity, diabetes, and cardiovascular disease. The study design serves as a paradigm for the conduct of research in relatively isolated, endogamous, and under-served populations.

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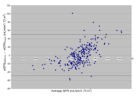

Figure 1.
Bland-Altman plot shows the difference between glomerular filtration rate estimated using the Modification of Diet and Renal Disease Study equation modified for American Indians ($eGFR_{MDRD-AI}$) and serum cystatin C–based formula ($eGFR_{SCysC}$) plotted against the average of the $eGFR_{MDRD-AI}$ and $eGFR_{SCysC}$.

Table 1

Distribution of Relative Pairs Among GKDZI Study Participants

Relationship	Zuni Relative Pairs
Parent-offspring	530
Siblings	448
Half siblings	352
Avuncular (eg, uncle-niece)	966
Grand avuncular	370
Grandparent-grandchild	158
1st cousin	987
1st cousin once removed	1,244
2nd cousin	790
Other relationship	1,857
Total	7,702

Note: N = 821.

Abbreviation: GKDZI, Genetics of Kidney Disease in Zuni Indians.

Table 2

Comparison of UACR Classified by Initial Versus Mode of 3 Urine Samples

	Mode of 3 Samples		
Initial Sample	**Normal**	**Incipient**	**Overt**
Normal	607	9	1
Incipient	18	97	6
Overt	3	2	55

Abbreviation: UACR, urinary albumin-creatinine ratio.

Table 3

Correlations between $eGFR_{MDRD\text{-}AI}$ and $eGFR_{SCysC}$

	No. of Participants	Correlation ± SE[a]
All participants	245	0.449 ± 0.05
Age		
Younger	123	0.479 ± 0.07
Older	122	0.405 ± 0.08
Sex		
Female	135	0.431 ± 0.05
Male	110	0.494 ± 0.05
Diabetes status		
Diabetic	52	Not computable[b]
Nondiabetic	193	0.407 ± 0.06

Note: $eGFR_{MDRD\text{-}AI}$ was calculated in milliliters per minute per 1.73 m^2 using the 4-variable MDRD (Modification of Diet and Renal Disease) Study equation modified for American Indians[42]: $186 \times ([SCr]^{-1.154}) \times (age^{-0.203}) \times 0.742$ [if female] × 1.106. $eGFR_{SCysC}$ was calculated in milliliters per minute per 1.73 m^2 as: $33.7 + (-0.047 \times age) + (68.4/SCysC)$.

Abbreviations: eGFR, estimated glomerular filtration rate; SCr, serum creatinine; SCysC, serum cystatin C; SE, standard error.

[a] All correlations, $P < 0.05$.

[b] Correlations between $eGFR_{MDRD\text{-}AI}$ and $eGFR_{SCysC}$ in diabetic participants could not be computed due to small sample size (n = 52).

Table 4

Traits Related to Kidney Disease, Diabetes, and CVD in GKDZI Study Participants, by Sex

Trait	All Participants	No. (women/men)	Women	Men	P^a
$eGFR_{MDRD-AI}$ (mL/min/1.73m^2)	116.14 ± 28.7	396/411	113.53 ± 31.2	118.65 ± 25.9	0.002
UACR	129.28 ± 566.1	397/413	100.68 ± 417.5	156.77 ± 678.3	0.3
SCr (mg/dL)	0.916 ± 0.88	404/416	0.864 ± 0.99	0.968 ± 0.77	<0.001
SUN (mg/dL)	12.29 ± 6.4	404/415	12.52 ± 7.6	12.06 ± 5.1	0.7
Uric acid (mg/dL)	5.92 ± 1.7	403/415	5.17 ± 1.4	6.64 ± 1.6	<0.001
Hematuria[b]	2.18 ± 10.6	397/412	3.04 ± 14.6	1.34 ± 3.3	<0.001
Weight (lb)	166.99 ± 40.6	405/416	161.81 ± 38.8	172.04 ± 41.8	<0.001
BMI (kg/m^2)	29.44 ± 6.8	405/416	30.99 ± 7.4	27.93 ± 5.9	<0.001
HbA_{1c} (%)	5.81 ± 1.4	405/416	5.91 ± 1.4	5.72 ± 1.3	0.02
SBP (mm Hg)	122.54 ± 16.6	405/416	117.78 ± 15.0	127.17 ± 16.8	<0.001
DBP (mm Hg)	77.70 ± 11.5	405/416	75.07 ± 10.0	80.27 ± 12.3	<0.001
HDL-C (mg/dL)	49.47 ± 16.1	385/387	48.30 ± 14.5	50.64 ± 17.4	0.07
LDL-C (mg/dL)	98.29 ± 31.2	350/361	94.54 ± 27.5	101.93 ± 34.0	0.01
Triglycerides (mg/dL)	171.50 ± 131.4	402/414	169.35 ± 108.8	173.59 ± 150.3	0.5
Total cholesterol (mg/dL)	180.15 ± 38.3	402/414	175.16 ± 35.2	184.99 ± 40.5	<0.001

Note: Unless otherwise indicated, values shown are mean ± standard error.

Abbreviations and definitions: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; $eGFR_{MDRD-AI}$, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease Study equation modified for American Indians; GKDZI, Genetics of Kidney Disease in Zuni Indians; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SCr, serum creatinine; SUN, serum urea nitrogen; UACR, urinary albumin-creatinine ratio.

[a] All traits were inverse normalized to test differences between the 2 groups.

[b] Hematuria is defined as 3 or more red blood cells per high-power field.

Table 5

Traits Related to Kidney Disease, Diabetes, and CVD in GKDZI Study Participants, by Diabetes Status

Trait	No. (no DM/DM)[a]	Participants Without DM	Participants With DM	P[b]
$eGFR_{MDRD-AI}$ (mL/min/1.73 m^2)	679/128	117.89 ± 26.2	106.79 ± 38.5	<0.001
UACR	678/131	59.23 ± 242.5	492.57 ± 1,236.6	<0.001
SCr (mg/dL)	680/140	0.82 ± 0.30	1.39 ± 2.0	0.08
SUN (mg/dL)	679/140	11.23 ± 3.7	17.40 ± 12.0	<0.001
Uric acid (mg/dL)	678/140	5.98 ± 1.7	5.59 ± 1.6	0.001
Hematuria[c]	677/131	2.16 ± 11.3	2.09 ± 5.2	0.4
Weight (lb)	680/140	164.62 ± 38.5	179.01 ± 47.6	<0.001
BMI (kg/m^2)	680/140	28.91 ± 6.5	32.08 ± 7.5	<0.001
HbA_{1c} (%)	680/140	5.37 ± 0.41	7.96 ± 2.2	<0.001
SBP (mm Hg)	680/140	120.87 ± 15.9	130.77 ± 17.8	<0.001
DBP (mm Hg)	680/140	77.49 ± 11.4	78.77 ± 12.0	0.9
HDL-C (mg/dL)	639/133	50.29 ± 16.3	45.55 ± 14.4	0.004
LDL-C (mg/dL)	594/117	99.31 ± 30.8	93.14 ± 32.6	0.03
Triglycerides (mg/dL)	676/140	158.95 ± 106.4	232.11 ± 204.6	<0.001
Total cholesterol (mg/dL)	676/140	180.35 ± 37.3	179.16 ± 42.9	0.2

Note: Unless otherwise indicated, values shown are mean ± standard error.

Abbreviations and definitions: BMI, body mass index; DBP, diastolic blood pressure; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; $eGFR_{MDRD-AI}$, estimated glomerular filtration rate calculated using the Modification of Diet and Renal Disease Study equation modified for American Indians; GKDZI, Genetics of Kidney Disease in Zuni Indians; HbA_{1c}, glycated hemoglobin (based on American Diabetes Association criteria); HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SCr, serum creatinine; SUN, serum urea nitrogen; UACR, urinary albumin-creatinine ratio.

[a] Diabetes status could not be determined in 1 participant.

[b] All traits were inverse normalized to test differences between the 2 groups.

[c] Hematuria is defined as 3 or more red blood cells per high-power field.

Table 6

Traits Related to Kidney Disease, Diabetes, and CVD in GKDZI Study Participants, by HTN Status

Trait	No. (no HTN/HTN)	Participants Without HTN	Participants With HTN	*P*[a]
$eGFR_{MDRD-AI}$ (mL/min/1.73 m^2)	533/274	119.15 ± 26.6	110.27 ± 31.6	<0.001
UACR	533/277	36.75 ± 148.4	307.32 ± 921.1	<0.001
SCr (mg/dL)	534/286	0.799 ± 0.18	1.13 ± 1.5	<0.001
SUN (mg/dL)	533/286	11.26 ± 3.5	14.20 ± 9.5	<0.001
Uric acid (mg/dL)	532/286	5.74 ± 1.6	6.24 ± 1.7	<0.001
Hematuria[b]	532/277	2.45 ± 12.7	1.66 ± 4.2	0.05
Weight (lb)	535/286	159.73 ± 35.9	180.57 ± 45.2	<0.001
BMI (kg/m^2)	535/286	28.35 ± 6.4	31.48 ± 7.0	<0.001
HbA_{1c} (%)	535/286	5.48 ± 0.88	6.43 ± 1.9	<0.001
SBP (mm Hg)	535/286	115.34 ± 11.2	136.00 ± 16.8	<0.001
DBP (mm Hg)	535/286	73.65 ± 8.3	85.29 ± 12.8	<0.001
HDL-C (mg/dL)	501/271	49.46 ± 15.6	49.49 ± 16.9	0.6
LDL-C (mg/dL)	464/247	96.37 ± 28.3	101.90 ± 35.7	0.1
Triglycerides (mg/dL)	530/286	152.92 ± 105.0	205.94 ± 164.6	<0.001
Total cholesterol (mg/dL)	530/286	175.7 ± 35.4	188.39 ± 41.9	<0.001

Note: Unless otherwise indicated, values shown are mean ± standard error.

Abbreviations and definitions: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; $eGFR_{MDRD-AI}$, estimated glomerular filtration rate calculated using the Modification of Diet and Renal Disease Study equation modified for American Indians; GKDZI, Genetics of Kidney Disease in Zuni Indians; HbA_{1C}, glycated hemoglobin (based on American Diabetes Association criteria); HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SCr, serum creatinine; SUN, serum urea nitrogen; UACR, urinary albumin-creatinine ratio.

[a] All traits were inverse normalized to test differences between the 2 groups.

[b] Hematuria is defined as 3 or more red blood cells per high-power field.

Table 7

Traits Related to Kidney Disease, Diabetes, and CVD in GKDZI Study Participants, by Heavy Metal Exposure

Trait	No. (nonartisans/artisans)	Participants Who Were Not Artisans	Participants Who Were Artisans	P^a
$eGFR_{MDRD-AI}$ (mL/min/1.73m^2)	348/459	118.15 ± 29.8	114.61 ± 27.8	0.2
UACR	349/461	78.26 ± 315.2	167.91 ± 696.4	0.009
SCr (mg/dL)	358/462	0.94 ± 1.1	0.90 ± 0.68	0.2
SUN (mg/dL)	358/461	12.87 ± 7.3	11.83 ± 5.7	0.002
Uric acid (mg/dL)	357/461	5.69 ± 1.7	6.09 ± 1.6	0.005
Hematuria[b]	349/460	2.29 ± 14.8	2.09 ± 5.4	0.9
Weight (lb)	358/463	166.30 ± 41.7	167.53 ± 39.8	0.1
BMI (kg/m^2)	358/463	29.81 ± 7.2	29.15 ± 6.5	0.7
HbA_{1c} (%)	358/463	5.79 ± 1.5	5.83 ± 1.3	0.3
SBP (mm Hg)	358/463	119.43 ± 15.9	124.94 ± 16.8	<0.001
DBP (mm Hg)	358/463	75.17 ± 10.9	79.67 ± 11.6	0.003
HDL-C (mg/dL)	335/437	48.05 ± 15.6	50.57 ± 16.3	0.02
LDL-C (mg/dL)	311/400	93.25 ± 26.9	102.21 ± 33.6	0.001
Triglycerides (mg/dL)	356/460	172.05 ± 141.4	171.08 ± 123.3	0.9
Total cholesterol (mg/dL)	356/460	174.16 ± 35.6	184.78 ± 39.6	<0.001

Note: Unless otherwise indicated, values shown are mean ± standard error.

Abbreviations and definitions: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; $eGFR_{MDRD-AI}$, estimated glomerular filtration rate calculated by the Modification of Diet and Renal Disease Study equation modified for American Indians; GKDZI, Genetics of Kidney Disease in Zuni Indians; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SCr, serum creatinine; SUN, serum urea nitrogen; UACR, urinary albumin-creatinine ratio.

[a] All traits were inverse normalized to test differences between the 2 groups.

[b] Hematuria is defined as 3 or more red blood cells per high-power field.

Table 8

Heritabilities of Traits Related to Kidney Disease and to Obesity, Diabetes, and CVD

	Model 1				Model 2			
Trait	**No.**	**h^2 ± SE**	***P***	**PVC**	**No.**	**h^2 ± SE**	***P***	**PVC**
$eGFR_{MDRD-AI}$	818	0.32 ± 0.07	<0.001	0.233	818	0.33 ± 0.07	<0.001	0.233
UACR	797	0.28 ± 0.08	<0.001	0.074	796	0.25 ± 0.08	<0.001	0.161
SCr	809	0.23 ± 0.07	<0.001	0.274	809	0.24 ± 0.07	<0.001	0.274
SUN	807	0.22 ± 0.07	<0.001	0.133	807	0.20 ± 0.08	0.001	0.159
Uric acid	816	0.29 ± 0.07	<0.001	0.223	816	0.32 ± 0.07	<0.001	0.244
Hematuria	761	0.07 ± 0.06	0.1	0.113	715	0.06 ± 0.06	0.2	0.114
SCysC	245[a]	0.50 ± 0.13	<0.001	0.235	245[a]	0.46 ± 0.13	<0.001	0.260
Weight	816	0.58 ± 0.08	<0.001	0.077	815	0.53 ± 0.08	<0.001	0.137
BMI	817	0.51 ± 0.08	<0.001	0.108	816	0.44 ± 0.08	<0.001	0.174
HbA_{1c}	807	0.25 ± 0.07	<0.001	0.133	806	0.28 ± 0.07	<0.001	0.322
Diabetes status	819	0.07 ± 0.15	0.3	0.213[b]	819	0.16 ± 0.16	0.1	0.304[b]
SBP	818	0.31 ± 0.07	<0.001	0.272	817	0.15 ± 0.06	0.003	0.437
DBP	818	0.24 ± 0.07	<0.001	0.201	817	0.31 ± 0.06	0.007	0.363
HTN status	820	0.58 ± 0.15	<0.001	0.168[b]	819	0.60 ± 0.15	<0.001	0.236[b]
Triglycerides	809	0.27 ± 0.07	<0.001	0.029	809	0.27 ± 0.07	<0.001	0.089
HDL-C	770	0.39 ± 0.07	<0.001	0.033	770	0.37 ± 0.07	<0.001	0.063
LDL-C	667	0.31 ± 0.09	<0.001	0.023	667	0.30 ± 0.09	<0.001	0.044
Total cholesterol	813	0.37 ± 0.07	<0.001	0.070	813	0.36 ± 0.07	<0.001	0.085

Note: Glucose excluded because many participants were not fasting. Model 1: adjusted for age, sex, age^2, age × sex, and age^2 × sex. Model 2: adjusted for age, sex, age^2, age × sex, age^2 × sex, plus being an artisan and diabetic and HTN status. For diabetes, diabetes status was not used as a covariate; for HTN, SBP and DBP, hypertension status was not used as a covariate.

Abbreviations and definitions: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; $eGFR_{MDRD-AI}$, estimated glomerular filtration rate calculated using the Modification of Diet and Renal Disease Study equation modified for American Indians; GKDZI, Genetics of Kidney Disease in Zuni Indians; h^2, heritability; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; PVC, proportion of variance due to covariates; SBP, systolic blood pressure; SE, standard error of variance; SCr, serum creatinine; SCysC, serum cystatin C; SUN, serum urea nitrogen; UACR, urinary albumin-creatinine ratio.

[a] Pilot study only.

[b] For dichotomous traits, Kullback-Leibler R^2 replaces PVC.

Table 9

Genetic and Environmental Correlations Between Intermediate Phenotypes Related to Kidney Disease and Traits Related to Obesity, Diabetes, and CVD

Trait 1	Trait 2	$\rho_g \pm$ SE	*P*	$\rho_e \pm$ SE	*P*
$eGFR_{MDRD-AI}$	BMI	0.155 ± 0.16	0.3	−0.099 ± 0.09	0.3
	Weight	0.086 ± 0.15	0.6	−0.084 ± 0.09	0.4
	HbA_{1c}	−0.194 ± 0.19	0.3	0.089 ± 0.07	0.2
	SBP	0.166 ± 0.17	0.3	−0.101 ± 0.07	0.2
	DBP	0.161 ± 0.19	0.4	−0.012 ± 0.07	0.9
	HTN status (yes/no)	0.305 ± 0.19	0.1	−0.135 ± 0.07	0.07
	HDL-C	0.094 ± 0.16	0.6	0.227 ± 0.07	0.004
	Total cholesterol	−0.029 ± 0.17	0.9	0.076 ± 0.08	0.3
	Triglycerides	0.036 ± 0.19	0.9	−0.182 ± 0.07	0.01
UACR	BMI	0.212 ± 0.16	0.2	0.004 ± 0.09	0.9
	Weight	0.110 ± 0.15	0.5	0.045 ± 0.09	0.6
	HbA_{1c}	0.204 ± 0.20	0.3	0.173 ± 0.07	0.02
	SBP	0.421 ± 0.15	0.02	0.177 ± 0.07	0.02
	DBP	0.478 ± 0.18	0.02	0.107 ± 0.07	0.1
	HTN status (yes/no)	0.563 ± 0.16	0.003	0.264 ± 0.06	<0.001
	HDL-C	0.063 ± 0.17	0.7	0.082 ± 0.08	0.3
	Total cholesterol	0.185 ± 0.17	0.3	0.095 ± 0.08	0.2
	Triglycerides	0.070 ± 0.20	0.7	0.111 ± 0.07	0.1
SCr	BMI	−0.187 ± 0.18	0.3	0.077 ± 0.08	0.3
	Weight	−0.182 ± 0.18	0.3	0.093 ± 0.09	0.3
	HbA_{1c}	0.231 ± 0.20	0.3	−0.083 ± 0.07	0.2
	SBP	−0.103 ± 0.19	0.6	0.013 ± 0.07	0.8
	DBP	−0.193 ± 0.20	0.4	−0.020 ± 0.06	0.8
	HTN status (yes/no)	−0.261 ± 0.21	0.2	0.076 ± 0.07	0.3
	HDL-C	−0.011 ± 0.18	0.9	−0.220 ± 0.07	0.003
	Total cholesterol	0.080 ± 0.19	0.7	−0.085 ± 0.07	0.2
	Triglycerides	−0.011 ± 0.21	0.9	0.148 ± 0.07	0.03
SUN	BMI	0.044 ± 0.18	0.8	0.008 ± 0.09	0.9

Trait 1	Trait 2	$\rho_g \pm$ SE	*P*	$\rho_e \pm$ SE	*P*
	Weight	0.135 ± 0.17	0.4	−0.027 ± 0.09	0.8
	HbA_{1c}	0.664 ± 0.23	0.005	−0.022 ± 0.07	0.7
	SBP	−0.379 ± 0.20	0.06	−0.048 ± 0.07	0.5
	DBP	−0.273 ± 0.21	0.2	−0.072 ± 0.07	0.3
	HTN status (yes/no)	−0.372 ± 0.21	0.08	0.171 ± 0.08	0.02
	HDL-C	−0.227 ± 0.18	0.2	−0.289 ± 0.07	<0.001
	Total cholesterol	0.059 ± 0.19	0.8	−0.159 ± 0.07	0.03
	Triglycerides	−0.169 ± 0.23	0.5	0.145 ± 0.07	0.04
Uric acid	BMI	0.296 ± 0.14	0.06	0.198 ± 0.08	0.02
	Weight	0.267 ± 0.14	0.07	0.186 ± 0.09	0.05
	HbA_{1c}	0.223 ± 0.19	0.3	−0.052 ± 0.07	0.5
	SBP	0.290 ± 0.17	0.1	0.123 ± 0.07	0.09
	DBP	0.124 ± 0.19	0.5	0.220 ± 0.07	0.001
	HTN status (yes/no)	0.188 ± 0.19	0.3	0.092 ± 0.07	0.2
	HDL-C	−0.303 ± 0.15	0.06	−0.094 ± 0.08	0.2
	Total cholesterol	0.134 ± 0.17	0.4	0.138 ± 0.07	0.7
	Triglycerides	0.325 ± 0.17	0.09	0.190 ± 0.07	0.009

Note: Glucose excluded because many participants were not fasting. No significant genetic or environmental correlation with LDL-C.

Abbreviations and definitions: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; $eGFR_{MDRD\text{-}AI}$, estimated glomerular filtration rate calculated by the Modification of Diet and Renal Disease Study equation modified for American Indians; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; ρ_g, genetic correlation coefficient; ρ_e, environmental correlation coefficient; SBP, systolic blood pressure; SCr, serum creatinine; SE, standard error of variance; SUN, serum urea nitrogen; UACR, urinary albumin-creatinine ratio.