# Reference Values and Factors Associated With Renal Resistive Index in a Family-Based Population Study

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***Abstract***—Increased renal resistive index (RRI) has been recently associated with target organ damage and cardiovascular or renal outcomes in patients with hypertension and diabetes mellitus. However, reference values in the general population and information on familial aggregation are largely lacking. We determined the distribution of RRI, associated factors, and heritability in a population-based study. Families of European ancestry were randomly selected in 3 Swiss cities. Anthropometric parameters and cardiovascular risk factors were assessed. A renal Doppler ultrasound was performed, and RRI was measured in 3 segmental arteries of both kidneys. We used multilevel linear regression analysis to explore the factors associated with RRI, adjusting for center and family relationships. Sex-specific reference values for RRI were generated according to age. Heritability was estimated by variance components using the ASSOC program (SAGE software). Four hundred women (mean age±SD, 44.9±16.7 years) and 326 men (42.1±16.8 years) with normal renal ultrasound had mean RRI of 0.64±0.05 and 0.62±0.05, respectively ($P$<0.001). In multivariable analyses, RRI was positively associated with female sex, age, systolic blood pressure, and body mass index. We observed an inverse correlation with diastolic blood pressure and heart rate. Age had a nonlinear association with RRI. We found no independent association of RRI with diabetes mellitus, hypertension treatment, smoking, cholesterol levels, or estimated glomerular filtration rate. The adjusted heritability estimate was 42±8% ($P$<0.001). In a population-based sample with normal renal ultrasound, RRI normal values depend on sex, age, blood pressure, heart rate, and body mass index. The significant heritability of RRI suggests that genes influence this phenotype. **(*Hypertension*. 2014;63:136-142.)** ● **Online Data Supplement**

**Key Words:** reference values ■ ultrasonography



Renal Doppler was introduced in the 1980s to screen for renovascular disease and detect renal artery stenosis.[1] It was also studied as a potential tool to improve the assessment of renal obstruction or transplant dysfunction.[2] The renal resistive index (RRI) obtained by the Doppler arterial waveform analysis is the most popular measure described in these pathologies.[3] It is a noninvasive and reproducible measure to investigate renal hemodynamics,[4] calculated from the peak systolic and end-diastolic velocities using the following equation: ([peak systolic velocity−end-diastolic velocity]/peak systolic velocity). RRI is based on the changes in flow velocity created by the pulsatile arterial perfusion and can be used as an estimate of renal arterial resistance. For instance, vasomotor stimuli such as sympathetic activation or fluid load can induce changes in the RRI that indirectly reflect changes in the renal vascular resistance.[5] Drugs affecting arteriolar vasomotor properties, such as nitroglycerine or captopril, have also been reported to change RRI.[6,7] However, a preserved vascular compliance seems to be necessary for vascular resistance to affect RRI.[8] Hence, with increasing downstream resistance, the diastolic velocity falls relative to systolic value, and RRI increases. In contrast, in the presence of a significant (>70%) main artery stenosis, the diastolic blood flow is less affected, but a slower systole with a dampened waveform (called parvus tardus) is observed, resulting in a decreased RRI value.[9]

Even with the widespread use of RRI, reference values and systematic factors influencing measurement values are not well known. Only small-sized studies have evaluated

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reference values in healthy adults, with a sample size of ≤194 participants.[4,5,10–16] Most of them have described an increase of RRI with age and even suggested a value >0.7 as being pathological without establishing normal values according to age. One study from the 1990s found RRI to be associated with heart rate,[10] but other factors have not been systematically explored in a population-based sample.

During the past 10 years, there has been an increasing interest in studying renal hemodynamics in patients with cardiovascular risk. In patients with hypertension, an increased RRI has been associated with target organ damage,[17–21] albuminuria, and aortic stiffness,[22] as well as adverse cardiovascular and renal outcomes.[23,24] In patients with diabetes mellitus, RRI predicted renal function decline, albuminuria, or arterial stiffness.[25–28] RRI has also been associated with renal damage at biopsy[29] and long-term progression of kidney disease in chronic renal failure.[30–34]

Despite the interest of RRI in the recent literature, there is a lack of reference values and exploration of associated factors based on a large population-based sample. Whether RRI aggregates in families is also unknown. The purpose of our study was, therefore, to analyze RRI, its associated factors, and heritability, as well as to determine normal values in a family-based population study.

## Material and Methods

Extended methods are available in the online-only Data Supplement. Swiss Kidney Project on Genes in Hypertension (SKIPOGH) is a family-based cross-sectional study exploring the role of genes and kidney hemodynamics in blood pressure (BP) regulation and kidney function in the general population.[35]

### Participant Selection

From December 2009 to March 2013, adult participants were recruited in 2 regions (Berne and Geneva) and 1 city (Lausanne) of Switzerland. A random sample of the inhabitants was drawn using different strategies. Inclusion criteria were (1) having a minimum age of 18 years; (2) being of European ancestry; (3) having ≥1 and ideally 3 first-degree family members willing to participate; and (4) providing a written informed consent. Pregnant or breastfeeding women were not included. The general participation rate was 27.1%. The SKIPOGH study was approved by the institutional ethical committees of each participating university hospitals.

### Study Visit

Participants were seen in the morning after an overnight fast. BP was measured in clinic after a resting period of ≥10 minutes in the sitting position with an appropriately sized arm cuff and a nonmercury manual auscultatory sphygmomanometer (A&D UM-101; A&D Company Ltd, Toshima Ku, Tokyo, Japan).

### Renal Doppler Ultrasound

In each center, the same experienced operator performed renal gray scale and color duplex ultrasounds according to a standardized procedure.[35] Participants were excluded from the present analysis in the presence of morphological kidney abnormalities, such as unilateral kidney, cysts, atrophy, stone, hydronephrosis, partial nephrectomy, horseshoe kidney, or any kidney malformation.

The assessment of the intrarenal vessels was made by duplex Doppler sonography. The RRIs were measured on 3 segmental arteries (superior, middle, and inferior) in each kidney. The values were then averaged to obtain the mean value for each participant. Participants with suspected renal artery stenosis were also considered as abnormal and excluded from the analysis.

The reproducibility of RRI measurements was assessed in a subgroup of 20 unrelated volunteers. We calculated inter- and intraobserver reproducibility using the Lin correlation coefficient for right and left RRI measurements. Inter- and intraobserver correlation coefficients for the right kidney were 0.75 and 0.89, respectively. For the left kidney, inter- and intraobserver correlation coefficients were 0.69 and 0.72, respectively.

### Collected Variables

#### *Laboratory Data*

Blood venous samples were drawn after an overnight fast. Blood glucose, electrolytes, kidney and liver function, serum cholesterol, and triglycerides were analyzed by standard clinical laboratory methods.

#### *Definitions*

Diabetes mellitus was defined as present when reported or treated or when fasting glycemia was ≥7 mmol/L. Hypertension was defined as mean office BP ≥140/90 mm Hg or treated hypertension. Pulse pressure (PP) was calculated as systolic BP (SBP) minus diastolic BP (DBP). The chronic kidney disease epidemiology collaboration formula was used to estimate the glomerular filtration rate (eGFR).[36] Chronic kidney disease (CKD) was defined as an eGFR <60 mL/min per 1.73 $m^2$.

### Statistics

All continuous variables are expressed as mean±SD and categorical variables as frequencies. Normal distribution was assessed graphically. Serum triglyceride levels were log transformed before statistical analysis. *t* Tests and $\chi^2$ tests were performed to compare baseline characteristics for continuous and categorical variables, respectively.

#### *Factors Associated With RRI*

We conducted univariate analyses to look for associations between RRI and the following variables of interest: age, body mass index (BMI), SBP, DBP, heart rate, PP, renal function (serum creatinine, continuous eGFR, eGFR tertiles, CKD stages, or CKD status), serum total cholesterol, serum triglycerides, smoking, diabetes mellitus, hypertension, and antihypertensive treatment. Spearman tests were conducted to obtain rank correlations.

To take familial correlations into account, we applied multivariable linear mixed regression models adjusted for study center to determine the independent association of each variable with RRI. Results of all linear analyses are presented as β coefficients and their 95% confidence intervals. Using a backward elimination approach, removing one by one the variable with the highest nonsignificant *P* value, only significant variables ($P<0.05$) were kept in the final model.

Analyses were performed first in all participants and then repeated after excluding the participants with diabetes mellitus, hypertension (office BP ≥140/90 mm Hg or treatment), and CKD to obtain associated factors and normal values in the healthy population. As we found the same factors associated with RRI, including similar effect sizes, when restricting the analyses to the left or right kidney, we only present combined analyses for both kidneys. Statistical significance was considered for a 2-sided $P<0.05$. Statistical analyses were conducted using STATA version 12.0 (StataCorp, College Station, TX).

#### *Reference Values for RRI According to Sex and Age*

Reference intervals for RRI by participants' age were computed using the LMS method.[37] These analyses were performed with R version 2.15.1 (R Core Team [2012], Vienna, Austria) using the GAMLSS package.[38] Sex- and age-specific reference values were computed for people without diabetes mellitus or hypertension.

#### *Heritability Estimates*

We estimated heritability of RRI using the ASSOC program in the Statistical Analysis for Genetic Epidemiology (SAGE) package, version 6.3, as described previously.[39] To estimate heritability, ASSOC uses a linear regression, allowing for covariates to be entered in the model. The main model included age, age$^2$, sex, and study center as covariates. Another model additionally included BMI, SBP, and heart rate. Heritability estimates are expressed as $h^2$ values with SE. Lambda coefficient ($\lambda'$) is a power transformation chosen to best approximate multivariate normal distribution of the residuals within pedigrees. As diabetes mellitus, hypertension, and CKD are heritable, the model was also built in healthy participants.

## Results

From December 2009 to October 2012, 1026 participants underwent a renal Doppler ultrasound. We excluded 273 (26.6%) examinations because of morphological anomalies or suspected renal artery stenosis (n=2). The presence of cyst was the most prevalent kidney abnormality (12%).We additionally excluded 27 (2.6%) participants having incomplete data for the covariables of interest. Finally, 726 (70.8%) participants, from 248 families and with complete information, remained for the present analysis.

The characteristics of the 326 men and 400 women included are presented in Table 1. Women were older and had higher RRI than men. Men had higher cardiovascular risk factors such as BMI (overweight and obesity), SBP, DBP, cholesterol, triglycerides, smoking, and diabetes mellitus. Women had higher heart rate and lower eGFR.

Compared with the included participants, those with kidney structural abnormalities (n=273) were more prone to have diabetes mellitus (8.8% versus 3.2%; $P<0.001$), arterial hypertension (34.3% versus 18.6%; $P<0.001$), lower renal function (eGFR, 88.8 versus 99.7 mL/min per 1.73 m$^2$; $P<0.001$), and higher BMI (26.0 versus 24.7 kg/m$^2$; $P<0.001$). They also had higher RRI (0.66±0.06 versus 0.64±0.06; $P<0.001$).

Participants with diabetes mellitus, hypertension, or CKD were excluded from the analysis to study healthy participants (n=572). Observed differences between men and women were similar as in the complete population. Their characteristics by sex are shown in Table S1 in the online-only Data Supplement. A flow chart of the study participants is depicted in Figure S1.

**Table 1. All Participant Characteristics According to Sex (N=726)**

| Variables | Women (n=400) | Men (n=326) | *P* Value |
|---|---|---|---|
| Hypertension (yes)* | 67 (16.8%) | 69 (21.2%) | 0.129 |
| Hypertension treatment | 44 (11%) | 45 (13.8%) | 0.58 |
| Diabetes mellitus (yes)* | 8 (2.0%) | 16 (4.9%) | 0.029 |
| eGFR <60 mL/min per 1.73 m$^2$ | 10 (2.5%) | 4 (1.2%) | 0.215 |
| Treated dyslipidemia (yes) | 14 (3.5%) | 14 (4.3%) | 0.580 |
| Smoking (yes) | 89 (22.3%) | 94 (28.8%) | 0.042 |
| BMI normal | 268 (67.0%) | 166 (50.9%) | <0.001 |
| BMI overweight | 88 (22.0%) | 122 (37.4%) | |
| BMI obesity | 44 (11.0%) | 38 (11.7%) | |
| Age, y | 44.9±16.7 | 42.1±16.8 | 0.027 |
| SBP, mm Hg | 113.4±16.6 | 118.9±14.9 | <0.001 |
| DBP, mm Hg | 73.0±9.6 | 77.4±9.3 | <0.001 |
| Pulse pressure, mm Hg | 40.4±11.4 | 41.4±11.4 | 0.208 |
| Heart rate, beats per min | 68.9±10.2 | 65.2±11.2 | <0.001 |
| BMI, kg/m$^2$ | 24.0±4.7 | 25.6±4.2 | <0.001 |
| RRI | 0.64±0.05 | 0.62±0.05 | <0.001 |
| Serum creatinine, μmol/L | 65.5±9.6 | 80.8±12.1 | <0.001 |
| eGFR mL/min per 1.73 m2 | 97.9±16.2 | 102.1±17.3 | 0.001 |
| Total cholesterol, mmol/L | 5.17±1.01 | 4.83±1.09 | <0.001 |
| Triglycerides, mmol/L | 0.92±0.46 | 1.13±0.73 | <0.001 |

Continuous variables are expressed as mean±SD and categorical ones as numbers and percentages (%). BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; RRI, renal resistive index; and SBP, systolic blood pressure.

*Arterial hypertension was defined as treated or BP ≥140/90 mm Hg and diabetes mellitus as treated or glycemia ≥7 mmol/L.

### Factors Associated With RRIs

In univariable analyses including all the participants (n=726), RRI was significantly higher in women than in men (0.64±0.05 versus 0.62±0.05; $P<0.001$), in diabetic than in nondiabetic participants (0.70±0.07 versus 0.63±0.05; $P<0.001$), and in hypertensive than in normotensive participants (0.66±0.06 versus 0.62±0.05; $P<0.001$), as illustrated in Figure S2. Participants treated for dyslipidemia or hypertension, smokers, and participants who were overweight or obese had significantly higher RRI than those without the corresponding characteristics (data not shown).

Stratifying by sex, we observed positive correlations of RRI with PP ($R=0.53$ and $R=0.47$; both $P<0.001$), SBP ($R=0.31$; both $P<0.001$), BMI ($R=0.19$ and $R=0.29$; both $P<0.001$), and triglycerides ($R=0.14$ and $R=0.15$; both $P<0.008$) in both women and men. RRI was also positively correlated with age in women and men (both $R=0.41$; $P<0.001$), although the relationship was not linear (age$^2$, $R=0.14$ and $R=0.16$; both $P<0.005$). We observed an inverse linear correlation of RRI with heart rate ($R=-0.14$ and $R=-0.15$; $P<0.008$) and eGFR ($R=-0.30$ and $R=-0.34$; both $P<0.001$). When stratified by sex, cholesterol, smoking, and DBP were not associated with RRI. Only age had a nonlinear (quadratic) association with RRI.

We built a multivariate model including all variables explored in the univariate analysis, taking into account the familial correlations and adjusting for study center. The final model is presented in Table 2 separately for men and women. In the fully adjusted model, eGFR, lipids, smoking, hypertension treatment, and diabetes mellitus were no longer associated with RRI in both women and men. After applying a backward stepwise regression, the final model was similar in women and men, with age, SBP, and BMI being positively associated with RRI, whereas heart rate and DBP were negatively associated. When PP was inserted into the model instead of SBP and DBP, it was also positively and independently associated with RRI (data not shown). Hypertension treatment was not associated with RRI when SBP and DBP were excluded from the model. Regarding the renal function, even after including in the model eGFR tertiles, CKD stages, or the presence of CKD defined as an eGFR<60 mL/min per 1.73 m$^2$, we could not find an association with RRI.

The analyses were repeated in healthy participants without diabetes mellitus, hypertension, or CKD. We found similar associations with coefficients in the same range (Table S2). Only BMI was not associated anymore with RRI in women in this subset.

Figure 1 shows the association of SBP, DBP, and PP with resistive index adjusted for all the variables included in the final models with the 95% confidence interval. We observed that the direction of association is similar in all (n=726) and healthy (n=572) participants.

### Reference Values for RRI According to Age and Sex

Reference values expressed as percentiles of RRI according to sex for a large age range in participants without hypertension, diabetes mellitus, or CKD (healthy, n=572) are shown

**Table 2. Factors Associated With Renal Resistive Index in Multivariable Linear Mixed Regression Models by Sex**

| | Final Model Women (n=400) | | | Final Model Men (n=326) | | |
|---|---|---|---|---|---|---|
| Variables | β Coefficient | 95% CI | *P* Value | β Coefficient | 95% CI | *P* Value |
| Age, per 10 y | 0.010 | 0.007 to 0.012 | <0.001 | 0.014 | 0.111 to 0.016 | <0.001 |
| Age$^2$, per 10 y | 0.002 | 0.001 to 0.03 | 0.001 | 0.004 | 0.003 to 0.006 | <0.001 |
| BMI, per 5 kg/m$^2$ | 0.005 | 0.001 to 0.009 | 0.018 | 0.009 | 0.004 to 0.013 | <0.001 |
| SBP, per 10 mm Hg | 0.014 | 0.01 to 0.018 | <0.001 | 0.015 | 0.011 to 0.018 | <0.001 |
| DBP, per 5 mm Hg | −0.012 | −0.015 to −0.009 | <0.001 | −0.011 | −0.014 to −0.008 | <0.001 |
| Heart rate, 10 per min | −0.005 | −0.009 to −0.001 | 0.008 | −0.009 | −0.012 to −0.005 | <0.001 |
| Intercept | 0.63 | 0.58 to 0.69 | <0.001 | 0.68 | 0.64 to 0.71 | <0.001 |

eGFR, total cholesterol, log triglycerides, smoking, diabetes mellitus, and hypertension treatment were entered in the first model but were not significantly associated with RRI over and above age, sex, BMI, SBP, DBP, and heart rate. Age$^2$ indicates age squared; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

in Figure 2. The distribution was similar in men and women, although women had slightly higher RRI values at all ages and presented a less pronounced J-shaped curve pattern. In both sexes, RRI values clearly increased after 40 years of age. The reference values were slightly higher when including patients with hypertension, diabetes mellitus, or CKD (Figure S3).

### Heritability Estimates

Adjusted heritability estimates for RRI are shown in Table 3. In the whole population, age-, sex-, and center-adjusted heritability was 38% with a sibship component and 41% otherwise (both $P<0.001$). Further adjustment for SBP, BMI, and heart rate hardly modified heritability estimates, which remained 40% to 42%. In the subset of healthy participants, heritability estimates were similar (37%–40%; $P<0.001$).

## Discussion

This study describes RRI in a large multicentric family-based population study and provides reference values according to sex and age in a large sample of healthy adults with morphologically normal kidneys. We found that female sex, higher age, SBP, and BMI were associated with higher RRI values and that higher DBP and heart rate were associated with lower RRI. In the multivariable analysis adjusted for age, BP, and BMI, neither renal function nor cardiovascular risk factors, such as diabetes mellitus, treated hypertension, smoking, or cholesterol, were independently associated with RRI. In addition, our data demonstrate that RRI is a heritable trait.

Although previous studies with smaller sample size did not describe or find any sex differences in RRI,[4,13] larger ones also found that women had higher values even when adjusting for other factors.[13,21,24] We do not have a satisfactory explanation for this observation, although hormonal differences might play a role.

Age is a known determinant of RRI. Some groups have specifically studied the age dependency of RRI in adults.[4,5,11,14,15] Nevertheless, to our knowledge, only 2 smaller studies provided continuous baseline values for the healthy population according to age,[11,16] but subjects were not randomly selected and the studies were not population based. We also showed that the relationship of RRI with age is nonlinear and that RRI increases sharply after 40 years of age. This age dependency is probably

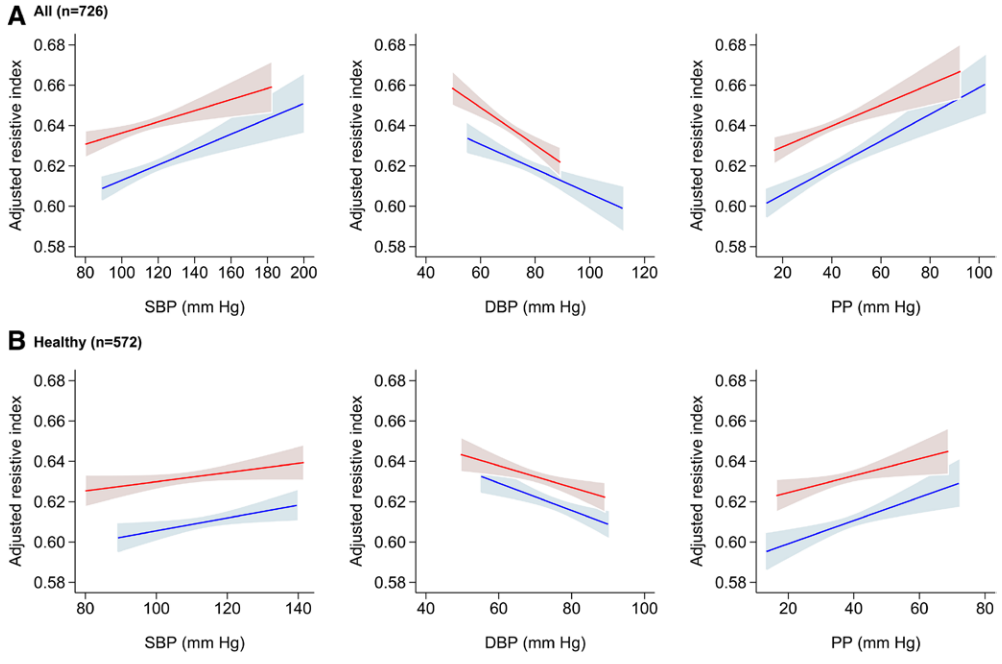


**Figure 1.** Association of blood pressure (BP) with adjusted renal resistive index according to sex in all (**A**) and healthy (**B**) participants. Women are denoted in red and men in blue. DBP indicates diastolic BP; PP, pulse pressure; and SBP, systolic BP.

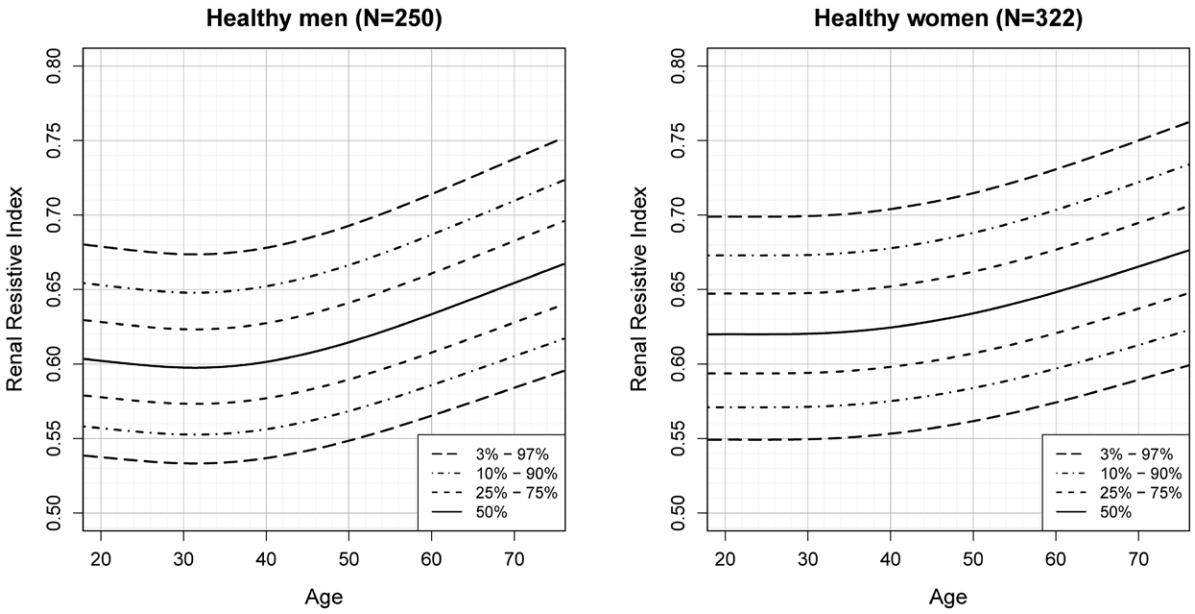


**Figure 2.** Normogram of renal resistive index according to age and sex in nondiabetic, nonhypertensive, and non-CKD (healthy) participants (n=572). CKD indicates chronic kidney disease.

at least partly because of the characteristics of the aging kidney with small vessel changes, because RRI has been associated with arteriosclerosis and fibrosis in kidney biopsy studies.[29,30,40] Another explanation might be the age-related change in vascular compliance. In our study, we observed a positive correlation of RRI with SBP and an inverse correlation with DBP. This underlines the importance of the PP as a determinant of the RRI. This has been demonstrated previously.[18,22,41–43] PP is a surrogate parameter of systemic arterial stiffness, and this parameter increases with age.[44] However, we found an age-independent effect of BP even in participants without hypertension. This observation supports the hypothesis that vascular compliance affects RRI more than vascular resistance.[8,42]

Many authors have used >0.70 as the cutoff to consider RRI values as abnormal. On the basis of our results, we think that RRI threshold values other than 0.7 might be appropriate depending on the age group. For instance, the 97th percentile among nondiabetic, nonhypertensive, and non-CKD participants presented in Figure 2 could serve as a suitable cutoff in settings similar to the Swiss one, considering the population-based and multicentric nature of our sample.

Our results on heart rate are also consistent with 1 previous report.[10] At a higher heart rate, the RRI measured is lower because of the higher end-diastolic velocity registered. This observation highlights the importance to interpret RRI cautiously in the presence of an abnormal heart rate.

The negative association of RRI with eGFR in univariate analyses resolved on adjustment for age. In multivariable analyses, we found no independent association of RRI with renal function (eGFR), diabetes mellitus, or hypertension treatment. This could be either because of the low number of patients with diabetes mellitus, hypertension, or CKD in our study or because of overadjustment if some of these variables lie in the causal pathway influencing RRI. It might also be a consequence of the exclusion from the analyses of adults with structural kidney abnormalities (n=273). Excluded participants presented higher RRI but had also a higher prevalence of diabetes mellitus and hypertension, higher BMI, and lower eGFR. In fact, whenever adults with abnormal kidneys were included in the multivariable analyses without stratifying by sex, arterial hypertension and diabetes mellitus were found to be significantly associated with RRI (data not shown). However, this

**Table 3. Heritability of Renal Resistive Index in All Participants and Those Without Diabetes Mellitus, Hypertension, or CKD (Healthy)**

| | Polygenic | | | | Polygenic+Sibling | | | |
|---|---|---|---|---|---|---|---|---|
| Models | $h^2$ | SE | *P* Value | $\lambda'$ | $h^2$ | SE | *P* Value | $\lambda'$ |
| All participants (n=726) | | | | | | | | |
| Age, age$^2$, sex, center adjusted | 0.41 | 0.08 | <0.0001 | 0.71 | 0.38 | 0.10 | <0.0001 | 0.71 |
| Age, age$^2$, sex, center+BMI, SBP, HR adjusted | 0.42 | 0.08 | <0.0001 | 0.85 | 0.40 | 0.09 | <0.0001 | 0.85 |
| Healthy participants (n=572) | | | | | | | | |
| Age, age$^2$, sex, center adjusted | 0.40 | 0.06 | <0.0001 | 0.71 | 0.38 | 0.07 | <0.0001 | 0.71 |
| Age, age$^2$, sex, center+BMI, SBP, HR adjusted | 0.40 | 0.06 | <0.0001 | 0.81 | 0.37 | 0.07 | <0.0001 | 0.81 |

Age$^2$ indicates age squared; BMI, body mass index; CKD, chronic kidney disease; $h^2$, heritability estimates; HR, heart rate; $\lambda'$ (lambda), power transformation chosen to best approximate multivariate normal distribution of the residuals within pedigrees; SBP, systolic blood pressure; and SE, standard error of $h^2$.

was not the case when stratifying by sex. For CKD, we only observed an association when eGFR was dichotomized into <60 or ≥60 mL/min per 1.73 $m^2$ in all adults and, when stratifying by sex, only in men. This underlines the importance of considering the presence of kidney abnormalities before interpreting RRI values and sex in further studies on RRI.

To our knowledge, this is the first study to demonstrate that RRI is a heritable trait. Because BP and arterial stiffness have been shown to be heritable, this finding is not surprising. However, this result was also confirmed in participants without diabetes mellitus, hypertension, or CKD. The clinical use of this finding is unclear, but we can imagine that families with lower RRI might have a slower deterioration of renal function with aging. Prospective studies are needed to test this hypothesis. This result justifies looking for genes involved in the control of RRI.

RRI has recently been identified as an important, noninvasive prognostic factor for the identification of target organ damage and risk of renal deterioration in patients with arterial hypertension, diabetes mellitus, or CKD.[17–28,30–34] To interpret this measure correctly, it is important to better understand its associated factors. Here, we identify key determinants of RRI, and our study allows the establishment of reference values based on a large sample of the general population. Other strengths are the use of the same standardized protocol across centers and the good observed reproducibility. The significant heritability estimates of RRI are also a good indicator of the quality of the data because noise (eg, generated by poor reproducibility) tends to increase the total phenotypic variance (ie, the denominator of the ratio used to estimate heritability) and not the additive genetic variance (ie, the numerator).

This study has some limitations. Its cross-sectional nature limits causal inferences. The effect sizes we found for the factors associated with RRI were rather small, which might be considered as not clinically relevant (ie, at the individual level). This, however, does not imply that such effects are not relevant from a public health perspective. For instance, small BP changes (2–3 mm Hg) may have a substantial effect on cardiovascular outcomes at the population level. An arteriography was not part of the protocol, and patients with renal stenosis, accessory, or multiple renal arteries might have been included in our study. All those variations tend to lower the RRI according to a previous study.[12] We only included participants of European ancestry, and therefore, our findings might not be generalizable to other populations. Race differences have not been studied in this field to date. Diabetes mellitus, hypertension, and kidney function were not found to be independently associated with RRI in our study. This could be because of the small number of patients with those pathologies after the exclusion of people with renal structural abnormalities. This does not mean that those factors do not have to be taken into account when interpreting RRI values, but our data suggest that their effect on RRI in patients with a normal ultrasound is low once adjusted for age and BP. Finally, although there was no difference in terms of age and sex between the participants and the sample from the general population from which it was drawn, the participation rate allows thinking that we might have a selection bias with a healthier participant effect. This probably prevents generalization of our results to sicker populations.

## Conclusions

In summary, this study shows that the main determinants of the RRI in the general population are sex, age, SBP, DBP, and heart rate. The age- and sex-specific reference values provided can be used to interpret RRI in similar populations and settings. We highlight a nonlinear association with age in both men and women with a steep age-related increase in RRI after 40 years of age. Finally, this family-based study demonstrates that resistive indexes are heritable, justifying the search for genes involved in the regulation of the RRI.

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## Disclosures

None.

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## Novelty and Significance

### What Is New?

- We provide age- and sex-specific reference values for the renal resistive index (RRI). We demonstrate that RRI is heritable in the general adult population.

### What Is Relevant?

- In the general population, many healthy subjects have RRI >0.7 after 40 years of age, questioning the use of this threshold value in the general population.
- The association of RRI with blood pressure highlights the importance of this parameter in the evaluation of RRI independently of hypertension treatment.

### Summary

Systolic and diastolic blood pressure, age, sex, and body mass index are independently associated with renal indexes. RRI is heritable. These findings could help in understanding the role of RRI as a prognostic factor in patients with hypertension.