Consequences of Exposure to Prenatal Famine on Estimated Glomerular Filtration Rate and Risk of Chronic Kidney Disease Among Survivors of the Great Ethiopian Famine (1983-85): A Historical Cohort Study

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Abstract

Background: The impact of an adverse prenatal environment such as famine exposure on development of adulthood non communicable chronic illnesses, including diabetes and hypertension has been well articulated in the recent past and supported by evidence. However, there exist a limited number of longitudinal studies on long term consequences of prenatal famine on adulthood kidney function. Hence, we set out to examine whether prenatal exposure to the Ethiopian Great Famine (1983–1985) was associated with changes in estimated glomerular filtration rate (GFR) and risk of developing chronic kidney disease (CKD) during adulthood.

Methods: The study was conducted in 219 famine exposed and 222 non exposed cohorts in Raya Kobo district, North Wollo Zone, Northern Ethiopia. Estimated GFR was computed using the CKD Epidemiology Collaboration (The CKD-EPI) equation. CKD was defined as eGFR= <60 mL/min per 1.73 m^2. Linear and logistic regression analyses were employed to examine the independent effect of prenatal famine exposure on eGFR and CKD respectively.

Results: The mean (SD) serum creatinine of exposed and non-exposed groups were 0.78 (0.2) and 0.75 (0.2) respectively. The mean (SD) eGFR of exposed groups was 107.95 (27.49) while the non-exposed 114.48 (24.81) ml/min. In linear regression, unadjusted model to examine the association between famine exposure and eGFR resulted in a significant negative beta coefficient (β = -0.124: 95% CI: -11.43, -1.64). Adjusting the exposure for outstanding covariates of kidney health, including systolic blood pressure, fasting blood sugar and blood glucose did not alter the inverse relationship (β = -.114 95% CI:-10.84, -1.17). In binary unadjusted logit model, famine exposure resulted in nearly 2.7 times increased odds of developing CKD (OR: 2.68, 95% CI: 1.16, 6.2). The odds remained equivalent after adjusting for systolic blood pressure, fasting blood glucose and BMI (OR= 2.61: 95% CI: 1.120, 6.09).

Conclusion: prenatal exposure to the Great Ethiopian Famine was associated with decreased eGFR and greater risk of CKD among survivors. These findings may imply that famine in early life may play significant role in the development of kidney dysfunction in adulthood.

Background

Mortality and burden of *disease* related to suboptimal kidney functioning are the major contributors of global ill health [1]. The world health organization (WHO) reported an *estimated* 5– *10* million people die annually from *kidney disease [2]*. According to Global Burden of Ddisease (GBD) estimates, in 2017 alone, with a global prevalence of 9.1%, chronic kidney disease (CKD) alone resulted in 1.2 million deaths [3]. Contrary to what the socio- demographic index (SDI) indicates, most of the burden of CKD disproportionately affects low-and middle-income countries, where detection rates remain low [1, 3-4]. Despite one in three people in the general population are at increased risk of CKD, 90% of those with CKD are unaware of their condition [5].

Direct measurement of GFR to determine CKD status is complicated in clinical as well as survey setting as it requires substantial time and resources [3, 6-7]. Alternatively, GFR can be estimated from a blood sample by using equations (eGFR) based on the plasma concentration of creatinine or cystatin C, while the latter is the better [9].Yet, estimated glomerular filtration rate is the best indicator of kidney function and to determine to stage of kidney disease [7-9]. According to many guidelines, CKD is defined as decreased kidney function shown by glomerular filtration rate (GFR) of less than 60 ml/min per 1·73 m^2, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause [3-10].

Although often considered as comorbidity of diabetes or hypertension, CKD has numerous complex causes [1-5]. Spanning in the life-course, important risk factors for kidney disease are documented as environmental, infection and lifestyle factors [2-4]. Atypically, common etiologies in low income countries have been documented as diarrheal diseases, HIV infection, low birth weight, malaria and preterm birth [2-3]. Furthermore, data in recent decades also showed correlation between suboptimal kidney health and contextual risk factors such as prenatal unhealthy environment [11-18].

The impact of adverse prenatal famine or starvation on late adulthood chronic illness including diabetes, hypertension and CVD has been well articulated in the recent past and supported by evidence [14-16]. As it was explained by the Barker hypothesis (1990), an adverse nutrition in early life, including prenatally as measured by birth weight, increased susceptibility to the metabolic syndrome, which includes obesity, diabetes, insulin insensitivity, hypertension, and hyperlipidemia and complications that include coronary heart disease and stroke [16]. In line with Barker, famine studies also documented higher proportion of diabetes, hypertension and changes in metabolic markers among survivors during adulthood [16, 20-21]. However, a limited number of longitudinal studies were done to investigate the long term consequence of perinatal famine on the kidney function. Yet, the available studies, conducted among Chines and the Dutch famine survivors reported an increased risk of CKD and or suboptimal kidney functional markers such as protein urea among prenatal famine exposed groups [11-14].

If risk groups are identified early, chronic kidney disease can be prevented and or worsening of kidney function can be slowed or averted by known interventions [1-4]. WHO indicates that the timely identification and management of population at risk for CKD represent the most effective strategy to address the growing global burden of chronic noncommunicable diseases [2]. In line with this, we used “the great Ethiopian famine” as a natural experiment setting to explore the impact of perinatal starvation on adulthood anthropometric metabolic and cognitive changes. In our earlier attempt, we have reported results of the metabolic and cognitive changes among the exposed group elsewhere [22-23]. Here, we aimed to assess whether prenatal exposure to the Ethiopian Great Famine (1983–1984) was associated with changes in glomerular filtration rate (GFR) and risk of CKD (EGFR<60 ml/min per 1.73 m^2) among adults in Wollo, North East part of Ethiopia.

Methods And Materials

Study setting, design and period

The study was conducted in 36 Kebeles of Raya Kobo district, North Wollo Zone, Northern Ethiopia. The district covers an area of 2,001.57 square kilometers and has a total population of 228,798 of which 147,837 are females [24]. A historical cohort study design was employed from March 15, to April 30, 2019 to investigate the effect of prenatal famine exposure on estimated glomerular filtration rate and risk of chronic kidney disease.

Study Participants, Sample size determination and sampling procedure

Famine exposed groups were adults who were conceived or born between August 8, 1983 and August 30, 1985. The post-famine cohorts (non- exposed) was those who were born between 8 September 1987 and 8 October, 1988 GC. Exclusions were made for subjects with history of household displacement during the famine period, physical disability including deformity (Kyphosis, Scoliosis, limb deformity) and pregnancy. The sample size was calculated by applying two population proportion assuming a prevalence of type two diabetes mellitus as proxy risk factor for CKD in fetal exposed group to be (22.6%) and non-exposed group (9.8%) [25]. Accordingly, the total sample size was 456 (228 exposed and 228 non- exposed). Details of participants' selection procedure were reported elsewhere [22] (suppl. 1).

Measurements

Biochemical measurements were conducted for fasting total cholesterol; plasma glucose; triglycerides and high-density lipoproteins. Five milliliters of venous blood were collected from each participant in plane test tubes after overnight fasting (8-12 hours). High density lipoprotein-cholesterol (HDL-c), triglyceride and fasting glucose using A-25 bio-system® clinical chemistry analyzer. Low density lipoprotein (LDL) level was determined using Freidwald formula [27]. Anthropometric measurements were taken using a standardized protocol using portable battery operated Seca® digital scale, Seca stadiometer constant tension tapes (Seca®, Germany). Blood pressure (BP) was measured in the left arm three times with 5 min interval and the average of the three readings was recorded.

Data Processing and Analysis

Data were double-entered using EpiData 3.1 and exported to SPSS for windows version 25 ([SPSS Inc. version 25, Chicago, Illinois] for cleaning and analysis. The data were cleaned by checking outliers and missing values. Categorical variables were described as frequencies and percentages and compared using the Pearson chi-square test. Continuous variables with a normal distribution were described using the relevant indicators of central tendency and spread (mean ± SD or median and IQR). Student's t - test

was used to evaluate the mean score difference between prenatal famine exposed and non-exposed cohorts.

Estimated GFR was computed using The CKD-EPI creatinine equation where eGFR (estimated glomerular filtration rate) expressed as ml/min/1.73 m^2

eGFR= 141 x min(SCr/κ, 1)α x max(SCr /κ, 1)-1.209 x 0.993Age x 1.018 [if female] x 1.159 [if Black].

Where S_{Cr} (standardized serum creatinine) in mg/dL, κ = 0.7 (females) or 0.9 (males), α = -0.329 (females) or -0.411 (males), min = indicates the minimum of S_{Cr}/κ or 1, max = indicates the maximum of S_{Cr}/κ or 1, age = years

Linear and logistic regressions were employed to examine the relationship between famine exposure in prenatal life and eGFR or CKD respectively. In order to account for the effect of outstanding biologic covariates four different regression models were evaluated. The first models in both regressions present unadjusted coefficients while model two, three and four were adjusted in a stepwise approach for fasting blood glucose, systolic hypertension and body mass index, respectively. Hosmer-Lemeshow χ2 greater than 0.05 and maximum standard errors (SE) greater than 2 were used to check model fitness and multi-collinearity, respectively. Potential effect modification was assessed by interaction terms. All analyses were two sided and p value of 0.05 was used to declare a significant difference. The results were expressed as adjusted odds ratio and 95%confidence interval.

Results

The socio-demographic details of the study participant were published elsewhere [22] (sup. 1). Table 1 presents comparisons of the outstanding variables between 222 non exposed and 219 exposed individuals. The mean (SD) serum creatinine of exposed and non-exposed groups were 0.78 (0.2) and 0.75 (0.2) respectively. The mean (SD) eGFR of exposed groups was 107.95 (27.49) while the non-exposed 114.48 (24.81). There existed significant mean differences between the two groups in terms of eGFR, TG and Creatinine.

Table 1
Comparison of prenatal famine exposed and non-exposed groups on selected parameters. Wollo, Ethiopia, Independent samples T test.

	Exposed Mean(SD)	Non exposed Mean(SD)	Mean difference 95(CI)
eGFR	107.95 (27.49)	114.48(24.8)	-6.53(-11.43, -1.63)*
BMI	23.03(3.82)	22.64(3.94)	0.39 (-0.34, 1.11)
Triglycerides	107.26 (57)	91.67(49.95)	17.33 (7.33, 27.33)*
Fasting blood glucose	86.44 (20.01)	82.91(17.58)	3.13 (-0.39, 6.64)
Total cholesterol	138.17(56.3)	130.69(51.0)	7.48 (-2.57, 17.53)
HDL Cholesterol	44.21 ± 12.28	45.24(12.31)	-0.83 (-3.09, 1.43)
Creatinine	0.78(0.2)	0.75(0.20)	0.03 (0.003, 0.07)*
Systolic BP (MmHg)	114.45 (12.50)	112.61(11.99)	1.49 (-0.78, 3.75)

* Significant at P < 0.01, eGFR; estimated glomerular filtration rate, CI: confidence interval, BMI: body mass index, HDL; High density lipoprotein, BP; blood pressure

Out of the famine exposed cohorts 8 participants and 20 for the non-exposed has CKD. Chi square test indicates a significant difference between the groups' in terms of proportion of CKD (Table 2).

Table 2
Prevalence of CKD among prenatal famine exposed and non-exposed cohorts, Wollo, Ethiopia.

			Non Exposed	Exposed	Total	P-value
CKD	Yes	Count	8	20	28	*0.029
		% within CKD	0.29	0.71	1.00	
	No	Count	214	199.00	413	
		% within CKD	0.52	0.48	1.00	
	Total	Count	222	219	441	

Chi square test: *significant at P < 0.05, CKD; Chronic Kidney disease

In linear regression, unadjusted model to examine the association between famine exposure and eGFR resulted in significant negative beta coefficients (β = − .124: 95% CI: -11.43, -1.64) (model 1). In model 2, adjusted for fasting blood sugar, GFR is reduced by − .115 with the exposure (β = − .12, 95% CI:-10.88, -1.17). In model three further adjustment was made for fasting blood glucose in addition for systolic blood pressure where exposure to famine remained to have a negative beta coefficient (β = − .109, 95% CI: -10.62,-.89). The last model, adjusted for fasting blood sugar, systolic blood pressure and BMI resulted in a reduction of eGFR by − .114 with prenatal famine (β = − .114, 95% CI:-10.84, -1.17).) (Table 3).

Table 3
Association of prenatal famine exposure and eGFR among adults, a linear regression analysis, Wollo, Ethiopia.

Models	Beta	95.0% CI
Model 1 (unadjusted)	− .124	-11.43, -1.63*
Model 2 (Adjusted for FBG)	− .115	-10.88, -1.17**
Model 3 (Adjusted for FBG and systolic BP)	− .109	-10.62, − .891**
Model 4 (Adjusted for FBG, systolic BP and BMI)	− .114	-10.84,-1.17**
*Significant at P < 0.01, **significant at P < 0.05, fasting blood sugar, BMI; body mass index, BP; blood pressure		

In binary logit, unadjusted model to examine the association between famine exposure and developing CKD resulted in positive odds, where exposure to famine resulted in nearly 2.7 times increased likelihood of having CKD (OR: 2.7, 95% CI: 1.16, 6.2) (model 1). Model two and three also showed in almost equivalent positive odds of having CKD with exposure (OR 2.63, 95% CI: 1.13, 6.13) and (OR: 2.61, 95% CI: 1.12, 6.11) respectively. In the final model, adjusted for systolic BP, fasting blood sugar and BMI resulted in equivalent odds with model 2 and 3; OR (CI): 2.61 95% CI: (1.12, 6.09) (Table 4).

Table 4
Association of prenatal famine exposure and CKD among adults, a linear regression analysis, Wollo, Ethiopia.

Models	Beta	95.0% CI
Model 1 (unadjusted)	2.68	1.16, 6.24
Model 2 (Adjusted for FBG)	2.63	1.13, 6.12
Model 3 (Adjusted for FBG and systolic BP)	2.61	1.12, 6.10
Model 4 (Adjusted for FBG, systolic BP and BMI)	2.61	1.12, 6.09
**significant at P < 0.05, FBG; fasting blood sugar, BMI; body mass index,BP; blood pressure		

Discussion

In our previous studies in the same study setting, we have reported the positive association between prenatal exposure to famine in early life and the risk of metabolic syndrome and cognitive malfunctioning late in adulthood [22–23]. Furthermore, we have also identified anthropometric assaults associated with prenatal famine exposure, such as reduction in adulthood height and increased waist to height ratio [24]. Presently, we have results that show exposure to famine in the fetal period associated with declined eGFR and raised prevalence of CKD. These findings may provide further evidence that an adverse nutrition event has long-lasting impact on the risk of chronic disease development later in life.

The present finding indicates that exposure to prenatal famine had an association with reduction in eGFR. We also found that, compared to non-exposed groups, adults who were exposed to famine in their fetal period had a higher proportion of CKD. In both of the above case scenarios, adjusting for classic outstanding covariates of CKD [2–4] (fasting blood glucose, BMI and systolic blood pressure) did not alter this association. This phenomenon may indicate the independence of the association between fetal malnutrition and impaired kidney function during adulthood.

Our findings were consistent with Chinese study, which reported lower EGFR (Beta = − 1.47, 95%CI − 2.81, − 1.13] and greater risk of having CKD (OR 2.85, 95%CI 1.25, 6.50) among famine exposed groups compared to controls [12]. However, the effect measures in Chines studies appear larger compared to our finding. This could be explained by the difference in the participant characteristics of the two studies where the chines cohorts were older in age than our participants. Interestingly, surrogate to our eGFR marker, the Dutch famine study reported two fold of microalbuminuria among famine exposed cohorts during mid-gestation (OR 2.1, 95% CI 1.0, 4.3) [28]. A similar finding was also reported from another Chinese study which indicates famine exposure was linked to a greater risk (OR 1.54, 95% CI 1.04, 2.28) of higher protein urea among women rural participants [14]. Corroborating the above findings, a recent systematic review reported unfavorable changes with kidney structure and function, measured by kidney volume, proteinuria, eGFR and mean creatinine clearance in the offspring of mothers with folate, vitamin A, and total energy deficiencies during pregnancy [29].

Apart from observational studies, findings from reviews of animal experimental studies reported that exposure to maternal global nutritional restriction during pregnancy to have unfavorable effects such as decreased kidney weight, lower nephron endowment, larger glomerular size, and lower GFR [30]. Taking low birth weight as surrogate to nutrition restrictions on human, large scale studies such as the Helsinki Birth Cohort Study (1924–1944) reported a positive association of smaller body size at birth with increased risk for developing CKD [31]. Similarly, in many other studies, reduction in kidney mass, volume or nephron number was reported as adverse outcomes associated with low birth weight [32–34]. Nonetheless, as described in the recent systematic review of 34 studies, there still remained reports of null effect of low birth weight on nephrogenesis, which may warrant the need for further investigation [35].

The implication of our findings should be interpreted considering the prevalent under nutrition in low income countries, which could have close or similar consequences on the health of the kidney during adulthood. Careful monitoring of CKD in hunger spots should be critical undertaking through early kidney disease detection programs and appropriate treatment of CKD risk factors such as obesity, high systolic blood pressure and elevated glucose levels.

This study has some limitations. Fasting blood glucose and creatinine was obtained based on single measurement, so the prevalence of CKD might be overestimated. We also estimated GFR using CKD-EPI equation as we don’t have any locally adapted equation.

Conclusion

Prenatal exposure to the Great Ethiopian Famine of 1984-85 was associated with decreased eGFR and greater risk of CKD among survivors, which may indicate that famine in early life may play an important role in latter development of kidney dysfunction.

Abbreviations

CI: Confidence interval

OR: Odds ratio

CKD: Chronic kidney disease

eGFR: estimated glomerular filtration rate

BMI: Body Mass Index

SD: Standard Deviation.

FBG: Fasting blood sugar

SBP: systolic BP

Declarations

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Availability of data and materials

The data supporting the conclusions of this article is included within the article (and its Additional file.

Authors’ contributions

All stated authors KHA, GA, MY and MMA are involved in the study from the inception to design, acquisition of data, analysis and interpretation and drafting of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not Applicable.

Ethics approval and consent to participate

Permission to conduct the study was obtained from the Institutional Review Board of Jimma University, Institute of Health Sciences, Ethiopia (reference no. JHRPGD/660/2019). Detailed description of the study was given to community leaders and households with the aim of sensitizing and mobilizing the local population. Informed verbal and written consent was taken from each participating household heads.

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