WITHDRAWN: Diagnosis of Gout is not Associated with Growth of Abdominal Aortic Aneurysms

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EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Introduction

Gout is a systemic inflammatory disease which has been associated with an increased risk of cardiovascular events but its association with abdominal aortic aneurysm (AAA) progression is unknown. The aim of this study was to investigate the association of gout with growth of small AAA.

Methods

Patients with initial AAA diameter measuring 30-54mm were recruited from surveillance programs at four Australian centres. Maximum AAA diameter was measured with a standardised and reproducible protocol to monitor AAA growth. Presence of gout was defined by clinical diagnosis by clinician or prescription of medications used to treat gout. Linear mixed effects modelling was performed to examine the independent association of gout with AAA growth.

Results

A total of 637 participants, including 66 (10.3%) diagnosed with gout, received a median of 4 (Inter-quartile range (IQR): 3, 6) scans over a median follow-up of 1.8 (IQR: 1.0, 3.0) years. In unadjusted analyses, participants with diagnosis of gout had a slower mean annual AAA growth of -0.3 mm/year (95% CI: -0.7, 0.2; p=0.25) than those without gout. After adjusting for potential confounders including initial AAA diameter, body mass index, prior stroke and anti-hypertensive medication prescription, gout was not significantly associated with AAA growth (-0.3 mm/year; 95% CI: -0.7, 0.2; p=0.24). Sensitivity analyses investigating the impact of initial AAA diameter on the association of gout with AAA growth found no interaction.

Conclusion

This study suggests diagnosis of gout is not associated with growth of small AAA.

Introduction

Abdominal aortic aneurysm (AAA) rupture is estimated to cause about 200,000 deaths per year worldwide [1]. Most AAA are asymptomatic prior to rupture and are identified through incidental imaging or ultrasound screening programs [2, 3]. AAA repair by open or endovascular surgery is the only established treatment to prevent AAA rupture [2, 3]. Small AAAs have a low risk of rupture and prior randomised trials show that early elective surgery does not reduce mortality [4]. Current guidelines therefore recommend that small asymptomatic AAAs (< 55mm in men and < 50mm in women) should be monitored by imaging surveillance [2, 3]. Most small AAAs continue to expand and ultimately about 70% of them require surgical repair at a later stage [4]. There are no established drug therapies to slow AAA growth [5]. Larger initial AAA diameter, current smoking and absence of diabetes are established risk factors for faster AAA

growth [6]. Discovering new risk factors for AAA growth may identify new treatment targets to limit AAA expansion.

Gout or hyperuricemia affects about 6.1 million adults in the United States [7]. Gout induces a low-grade systemic inflammatory state that has been associated with an increased incidence of cardiovascular events in some but not all observational studies [8–12]. Inflammation is strongly implicated in AAA pathogenesis and thus it is possible that gout could be associated with faster AAA growth [13]. No previous study has examined the association of diagnosis of gout with AAA growth. The current study aimed to assess whether people with current diagnosis of gout had faster AAA growth than those without gout.

Methods

Study Design

This study was a retrospectively designed analysis of an ongoing prospective cohort study that aims to identify risk factors associated with diagnosis and outcome of vascular disease. Patients with AAAs were recruited from four outpatient vascular services in Australia, including The Townsville University Hospital, the Mater Hospital Townsville, Gosford Vascular Services and The Royal Brisbane and Women's Hospital. Imaging data collected from patients during AAA surveillance between 2003 and 2018 were used. Written informed consent was obtained from all participants and the study was approved by the relevant human ethics committee (approval numbers HREC/14/QTHS/203; HREC/05/QTHS/29; HREC/09/QTHS/117; HREC/10/QRBW/11; HREC/10/QRBW/208; MHS20100201-01; SSA/10/QTHS/49; MEC/08/08/095; RA/4/1/5765; H5213; H5269 and H6028). The study was performed in accordance with the Declaration of Helsinki. All data regarding the study and participants were stored in a centralised digital database that was accessible by approved personnel only.

Study Population

For inclusion in the study, patients were required to have information available to ascertain diagnosis of gout at recruitment and also had at least two ultrasound scans during AAA surveillance. Gout was defined as either diagnosis by a physician (International Classification of Diseases (ICD)-9 274, ICD-10 M10) or current or prior prescription of allopurinol, colchicine, febuxostat, probenecid or a combination of these medications [14–17]. Follow-up data of included patients were considered for a maximum of six years.

Risk Factors And Medications

Patients were assessed by clinical interview and physical examination in order to collect risk factors and medication history. Risk factors data including age, sex, history of hypertension, diabetes, ischemic heart

disease (IHD), smoking and serum concentrations of cholesterol, triglyceride (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL) were collected. Prescriptions of medications, including aspirin, metformin, statins, angiotensin-II inhibitors, beta-blockers, calcium channel blockers, allopurinol and colchicine were also collected at recruitment. Smoking was defined as either ever (current or ex-smoker) or never smoked [18–20]. Hypertension, diabetes and stroke were defined by prior diagnosis or treatment of these conditions at study entry [18–20]. IHD was defined by a history of myocardial infarction, angina or treatment of IHD at study entry [18–20]. Body mass index (BMI) was measured as described previously [21].

Aaa Imaging

Maximum anterior to posterior and transverse infra-renal aortic diameters were measured by experienced sonographers who were unware of the participants diagnosis of gout. Aortic diameter was measured from outer wall to outer wall of the artery. AAA diameter were measured using ultrasound machines employed in the vascular laboratories at each centre including Toshiba Capasee (Toshiba Medical Systems, North Ryde, New South Wales, Australia), Philips HDI 5000 (Philips Medical Systems, Bothell, Washington, USA), GE LOGIQ 9 (GE Healthcare, Chicago, Illinois, USA), Siemens Acuson Antares™ (Siemens Healthcare, Bayswater, Victoria, Australia) and Philips IU22 (Philips Medical Systems) using a standard protocol, as described previously [22–24]. The reproducibility of aortic diameter measurements were assessed in each vascular laboratory, with inter-observer reproducibility coefficients being less than 4 mm as previously reported [22–25].

Data analysis

The primary aim of this study was to analyse the association between diagnosis of gout and AAA growth using linear mixed effects modeling. All continuous variables of the participant data were reported as mean ± standard deviation (S.D.) and categorical variables were reported as percentage (%). Normal distribution of all continuous variables were tested using Shapiro-Wilk normality test. Skewed data were log transformed prior to testing normality distribution. Statistical differences between paired groups of non-parametric data were determined using Wilcoxon test. Differences in nominal variables between groups were compared using chi square test. Continuous variables showed skewed distribution, therefore, Mann-Whitney U test was performed to test the differences between groups and data were reported as median and inter-quartile range (IQR).

Model Development

An unadjusted random intercept with slope model was used to examine the association between AAA growth and diagnosis of gout using unadjusted and multivariate adjusted models. Multivariate model included risk factors selected based on the bivariate comparisons between participants with or without gout that had a p value of < 0.10. Individual patients were treated as random effects in all models. Follow-

up period was treated as random effects in both adjusted and unadjusted random intercept with slope model. The interaction of follow-up period and patient group was used as the test statistic for all linear mixed effects (LME) analyses. Model fit was assessed by visual inspection of the standardised residual distribution and q-q norm plots, suggesting the presence of potentially influential outliers. Sensitivity analyses excluding outliers (defined as data points lying > 4 standard deviations from the mean of model residuals) were performed.

Predictions Using Lme Model

Following the model development, a new dataset with all possible combination of variables included in the model were extracted from the original dataset. The *predict* function was used to predict the AAA diameter using the unadjusted linear mixed effects model. The predicted AAA diameter was designed as a matrix using the *Model.matrix* function and diagonals were extracted to derive the 95% confidence intervals (CI). Predictions of mean (95% CI) annual increase in AAA diameter were provided for participants with and without gout.

Propensity Score Matched Cohort

A sub-analysis involving propensity-score matching was performed in an effort to balance participants with and without gout for potential confounding variables [26–30]. Propensity scores were estimated using a multivariate logistic regression model at a ratio of 1 and caliper diameter of 0.25 [31, 32]. The model included initial AAA diameter, body mass index (BMI), prior stroke, and angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARB) and calcium channel blockers (CCB) as covariates. A greedy matching algorithm was used to sequentially match each individual with gout to an individual without diagnosis of gout based on their propensity scores as previously described [31–33]. The balance of covariates was assessed by estimating standardised mean differences after matching the participants [33, 34]. An absolute standardised mean difference of < 0.1 was suggestive of limited covariate imbalance [31–33].

R program version 3.4.4 was used to perform the linear mixed effects modeling analysis and propensity-score matching using the ‘nlme’, ‘ggplot2’, ‘MatchIt’ and ‘survey’ packages [35–37]. Sample size estimate was performed using ‘longpower’ package. Statistical significance was assumed if p was ≤ 0.05.

Results

Participants

Of the total of 637 participants, 66 (10.3%) were diagnosed with presence of gout (Table 1). Risk factors assessed at entry including age, gender, ever smoked status, cholesterol, TG, HDL, LDL, initial AAA diameter, history of hypertension and stroke, and prescription of aspirin, statins, beta-blockers, and

metformin were not significantly different between participants with and without gout. Anti-hypertensive drugs including ACEI ($p = 0.04$), ARB ($p = 0.05$) and CCB ($p = 0.05$) were significantly more commonly prescribed in participants with gout than those without.

Table 1
Risk factors of included participants.

Continuous variables - Baseline	*No gout (n = 571)*	*Gout (n = 66)*	*p value*
Baseline continuous variables			
Age	74.3 (69.0-79.4) [1]	75.0 (71.0–81.0)	0.15
BMI	27.0 (23.3–30.6)	27.9 (25.2–31.8)	0.09
Cholesterol	4.2 (3.5–5.1) [42]	4.3 (3.4–4.9) [5]	0.94
TAGS	1.4 (1.0–2.0) [46]	1.5 (1.0-2.1) [5]	0.58
HDL	1.1 (0.9–1.4) [49]	1.1 (0.9–1.5) [6]	0.40
LDL	2.3 (1.7-3.0) [51]	2.2 (1.2–2.8) [8]	0.11
Initial AAA diameter	40.0 (35.0–44.0)	40.7 (35.0–44.0)	0.90
Nominal variables - Baseline			
Men	462 (80.9)	58 (87.9)	0.22
Ever smoker	497 (87.0)	59 (89.4)	0.72
Hypertension	427 (74.8)	54(81.8)	0.26
Diabetes mellitus	129 (22.6)	18 (27.3)	0.48
History of stroke	51 (8.9)	11 (16.7)	0.07
Ischemic heart disease	269 (47.1)	33 (50.0)	0.75
Aspirin	360 (36.0)	40 (60.6)	0.80
Statin	397 (69.5)	41 (62.1)	0.28
Beta blockers	208 (36.4)	27 (40.9)	0.56
ACE inhibitors	208 (36.4)	33 (50.0)	0.04
Angiotensin receptor blockers	124 (21.7)	22 (33.3)	0.05
Calcium channel blockers	148 (25.9)	25 (37.9)	0.05
Anti-coagulants	56 (9.8)	6 (9.1)	1.00
Metformin	72 (12.6)	10 (15.1)	0.70

Numbers in square brackets denote number of missing data points for that variable. Continuous variables expressed as median and interquartile range and are compared with the Mann-Whitney U test. Nominal variables expressed as count and percent - compared using chi-squared test. ACE, Angiotensin converting enzyme; BMI, Body mass index; HDL, High density lipoprotein; LDL, Low density lipoprotein; TAGS, Triglycerides.

Association Of Diagnosis Of Gout And Aaa Growth

Participants were followed by a median of 4 (Inter-quartile range (IQR): 3, 6) scans for a median period of 1.8 (IQR: 1.0, 3.0) years. The unadjusted random intercept and slope model showed a non-significantly slower mean annual AAA growth of -0.3 mm/year (95% CI: -0.7, 0.2; p = 0.25) in AAA patients diagnosed with gout compared to those with no gout diagnosis (Table 2). Bivariate comparisons of variables suggested that the model were to be adjusted for BMI, stroke history and prescription of ARB, ACE inhibitors and CCB. In addition, initial AAA diameter was also incorporated in models. The multivariate adjusted LME model suggested that the AAA patients with diagnosis of gout had a non-significant reduction in mean AAA growth of -0.3 mm/year (95% CI: -0.7, 0.2) as compared to patients that were not diagnosed with gout (p = 0.24) (Table 3). The linearity assumption of the model were tested using qqplot (Fig. 1). None of the included covariates had any two-way or three-way interaction with initial AAA diameter (Supplementary table 1). The model predictions of AAA diameter in patients diagnosed with and without gout were presented in Table 4.

Table 2
Association of diagnosis of gout and AAA growth assessed by linear mixed effects models: Summary of fixed effects

Covariates	*Estimates*	*Lower 95% CI*	*Upper 95% CI*	*p value*
Intercept	39.8	37.9	41.6	< 0.01
Past diagnosis of gout	-0.1	-1.7	1.5	0.91
Follow-up	1.8	1.3	2.3	< 0.01
Gout diagnosis * Follow-up	-0.3	-0.7	0.2	0.25
AAA, Abdominal aortic aneurysm; CI, Confidence interval				

Table 3
Linear regression model assessing the association of diagnosis of gout and AAA growth after adjusting for other risk factors

Predictors	*Estimates*	*95% CI (Lower - Upper)*	*p value*
(Intercept)	33.8	32.6–35.0	**< 0.001**
Past diagnosis of gout	-0.7	-1.5–0.1	0.08
Follow up	1.8	1.2–2.3	**< 0.001**
Initial AAA diameter tertile 2	6.8	6.2–7.4	**< 0.001**
Initial AAA diameter tertile 3	13.5	12.9–14.0	**< 0.001**
BMI	0.0	-0.05–0.01	0.28
Stroke	-0.4	-1.2–0.4	0.32
ACEI	0.4	-0.1–0.9	0.15
ARB	0.4	-0.2–1.0	0.16
CCB	0.2	-0.4–0.7	0.55
Patient group * Follow up	-0.3	-0.7–0.2	0.24
Random Effects			
σ^2	4.71		
$\tau_{00\ Patient\ ID}$	5.95		
$\tau_{11\ Patient\ ID*Follow\ up}$	1.42		
ICC	0.78		
$N_{\ Patient\ ID}$	636		
Marginal R^2 / Conditional R^2	0.58 / 0.91		

AAA, Abdominal aortic aneurysm; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers; BMI, Body mass index; CCB, Calcium channel blockers; CI, Confidence interval; ICC – Intraclass correlation coefficient; mm, millimetre; $N_{\ Patient.ID}$, Number of included patients; R^2, Correlation coefficient; $\tau_{11\ Patient.ID*Follow\ up}$, Random intercept and interaction variance; $\tau_{00\ Patient.ID}$, Random slope variance; σ^2, Residual variance.

Table 4
Unadjusted linear mixed effects predictions for participants with and without gout

	No prior gout diagnosis (n = 571)			*Prior gout diagnosis (n = 66)*			*LME results*
Time	*AAA diameter predictions*	*LCI*	*UCI*	*AAA diameter predictions*	*LCI*	*UCI*	*MD (95% LCI, UCI); p value*
Initial	39.7	37.5	41.9	39.6	37.3	41.9	-0.3 (-0.7, 0.2); 0.25
Final	43.3	41.1	45.5	42.6	40.3	44.9	

LCI, Lower confidence interval; LME, Linear mixed effects; MD, Mean difference; UCI, Upper confidence interval.

Propensity Score Matched Cohort Analysis

130 patients with (n = 65) and without (n = 65) gout were matched based on propensity scores as shown in Fig. 2. Standardised mean differences of < 0.1 was achieved for 6 out of 8 variables, suggesting adequate covariate balancing amongst most variables. Covariate balance (SMD < 0.1) could not be achieved for initial AAA diameter and history of prior stroke between individuals with and without gout despite propensity matching (Supplementary table 2). Within the propensity score matched cohort mean annual AAA (standard error) growth was not significantly different in AAA patients with and without gout: -0.10 (1.25) mm/ year, p = 0.93.

Discussion

The main finding of this study was that diagnosis of gout was not significantly associated with AAA growth. Participants in both groups were age and sex-matched with similar prevalence of comorbidities. Prescription of anti-hypertensive medications was significantly greater in participants diagnosed with gout than those without. To adjust for confounding factors, we performed both adjusted analyses and a sub-analysis using propensity-score matching. This confirmed the finding of the main analysis that diagnosis of gout was not associated with AAA growth.

A nationwide database of 474,725 participants suggested that hyperuricemia was an independent risk factor for death caused by aortic dissection or aneurysm [38]. The systemic inflammatory state associated with gout was suggested as the reason for this finding. A case control study including 164,463 participants with gout and 3,694,377 controls found that a diagnosis of gout was associated with increased relative risk of cardiovascular mortality of 1.71 (95% CI 1.66, 1.75) [39]. After adjustment for other risks the relative risk was reduced to 1.10 (95% CI 1.07, 1.13). In contrast, in a more recent analysis focused on patients with peripheral artery disease no independent association of prior diagnosis of gout with major adverse cardiovascular events or mortality was found [40]. Also, a recent retrospective observational study of 17,201 participants with coronary heart disease suggested a similar rates of PAD incidences in patients with and without gout (p = 0.279) [16]. The current study further reports that

diagnosis of gout was not associated with AAA growth after adjusting for confounders. Overall these findings suggest that amongst people with established cardiovascular disease, such as AAA and peripheral artery disease, gout is not an independent risk factor for disease progression. This might be because these individuals already have an established systematic inflammatory state associated with their cardiovascular disease. The situation in healthier individuals with less established vascular disease may be different.

This study has several limitations. The overall sample size and particularly the number of participants with gout was small. Prescription of anti-hypertensive medication was not balanced between groups although this was adjusted for in the multivariable models and propensity-score matching. It remains possible however that other factors which were not measured may have been unbalanced between groups. It therefore remains impossible to complete exclude residual bias. Uric acid levels were not measured on participants and the definition of gout relied on past diagnosis or treatment as has been used in multiple population-wide epidemiological studies [14–17]. Nevertheless, misclassification bias cannot be ruled out.

Conclusions

The results of this study suggest that diagnosis of gout is not associated with AAA growth.

Declarations

Ethics approval and consent to participate: Written informed consent was obtained from all participants and the study was approved by the relevant human ethics committee (approval numbers HREC/14/QTHS/203; HREC/05/QTHS/29; HREC/09/QTHS/117; HREC/10/QRBW/11; HREC/10/QRBW/208; MHS20100201-01; SSA/10/QTHS/49; MEC/08/08/095; RA/4/1/5765; H5213; H5269 and H6028).

Consent for publication: Not applicable

Availability of data and materials: All data generated during this study are included in this published article [and its supplementary information files]

Competing interests: The authors declare that they have no competing interests

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Author contribution: ST was involved in data cleaning, data analysis and manuscript preparation. JP was involved in assisting with data analysis and manuscript preparation. FQ, MB, BB, RV and JJ were

involved in data collection and manuscript editing. JG was involved with study conceptualisation, data collection, data analysis, funding acquisition and manuscript preparation.

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Figures

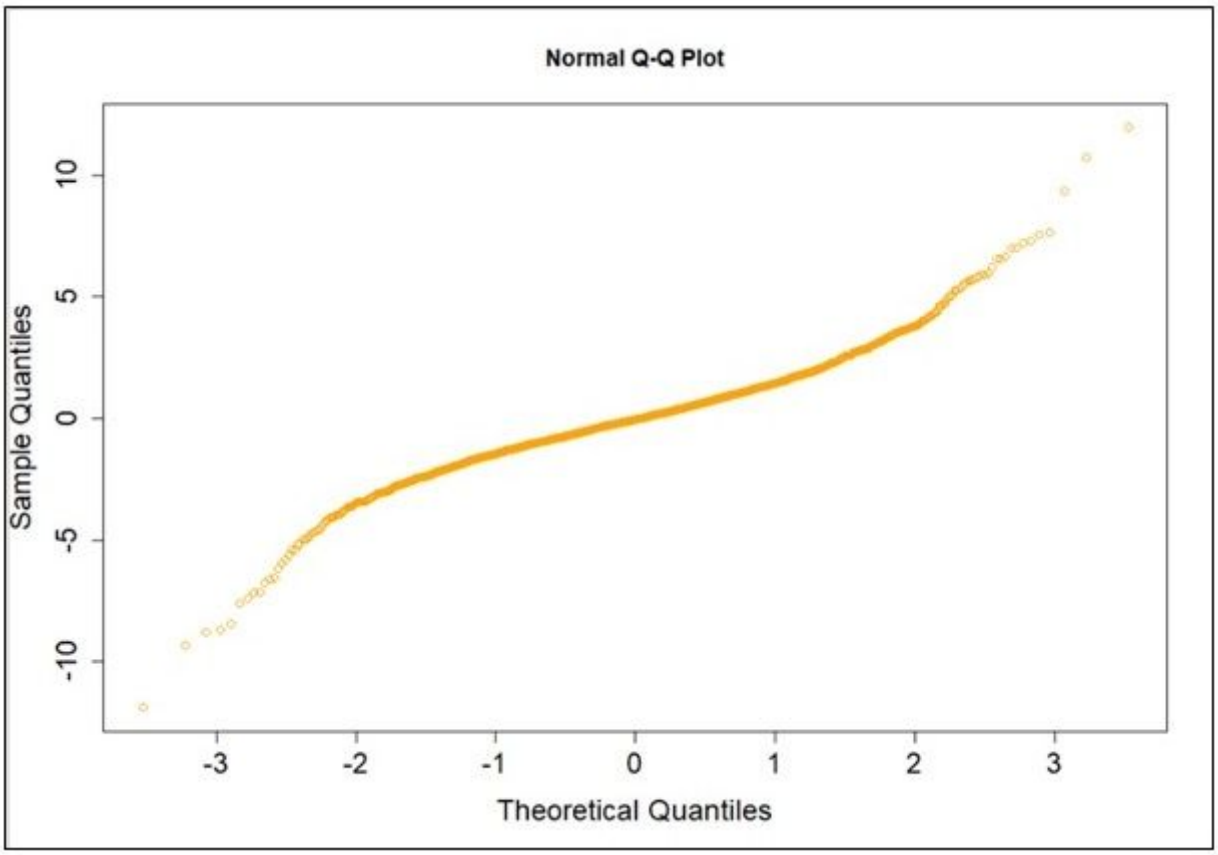

Figure 1

Quantile-quantile plot confirming the linearity of the assumed best fit model

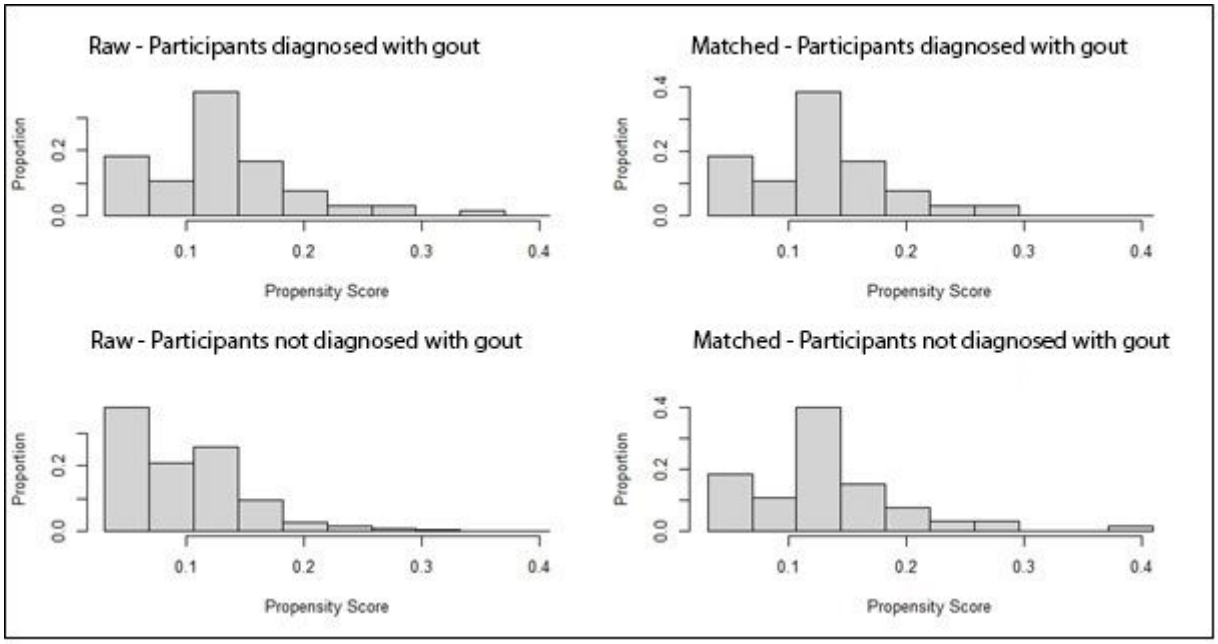

Figure 2

Histogram illustrating the cohorts before and after propensity score matching.

Supplementary Files

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- Supplementarymaterial.docx