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ORIGINAL ARTICLE

D-dimer and the risk of hypertension: The REasons for Geographic And Racial Differences in Stroke Cohort Study

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Abstract

Background: Reasons for increased risk of hypertension in Black compared with White people are only partly understood. D-dimer, a thrombo-inflammatory marker higher in Black individuals, is also higher in people with hypertension. However, the impact of D-dimer on racial disparities in risk of incident hypertension has not been studied.

Objectives: To assess whether D-dimer is associated with the risk of incident hypertension, whether the association between D-dimer and the risk of incident hypertension differs by race, and whether the biology reflected by D-dimer explains racial disparities in the risk of incident hypertension.

Methods: This study included 1867 participants in the REasons for Geographic And Racial Differences in Stroke cohort study without baseline hypertension and with a second visit 9.4 years after baseline. Risk ratios of incident hypertension by baseline D-dimer level were estimated, a D-dimer–by–race interaction was tested, and the mediating effect of D-dimer (which represents underlying biological processes) on the association of race and hypertension risk was assessed.

Results: The risk of incident hypertension was 47% higher in persons in the top quartile than in those in the bottom quartile of D-dimer (risk ratio [RR]: 1.47; 95% CI: 1.23-1.76). The association was partly attenuated after adjusting for sociodemographic and adiposity-related risk factors (RR: 1.22; 95% CI: 1.02-1.47). The association of D-dimer and hypertension did not differ by race, and D-dimer did not attenuate the racial difference in the risk of incident hypertension.

Conclusion: D-dimer concentration reflects pathophysiology related to the development of hypertension. Specific mechanisms require further study and may involve adiposity.

KEYWORDS
biomarkers, D-dimer, hypertension, inflammation, racial groups

Essentials

- We studied whether D-dimer, a factor reflecting clotting and inflammation, related to the risk of hypertension.
- D-dimer levels were measured in 1867 people followed for 10 years for hypertension development.
- A higher D-dimer level was associated with a higher risk of hypertension.
- Future research should examine biological pathways linking D-dimer to hypertension.

1 | INTRODUCTION

Using the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure definition for hypertension (>140/90 mm Hg) [1], in 2017-2018, 31.7% of US adults aged ≥18 years had hypertension, with a disproportionate impact on non-Hispanic Black adults (40.1%) compared with non-Hispanic White adults (32.7%) [2]. Hypertension is a leading contributor to cardiovascular disease burden; however, the underlying causes of essential hypertension, which accounts for 95% of all cases [3], are still ill-defined. Previous studies have suggested that hypertension confers a prothrombotic state [4,5].

Development of hypertension is linked to abnormalities of the vascular wall and inflammation through several potential mechanisms [6,7]. Vessel wall damage confers a procoagulant state by enabling the initiation of coagulation and production of thrombin [6]. Thrombin has numerous pathologic roles, including promotion of vascular constriction [8], which may increase peripheral resistance and blood pressure. A recent experimental study in hypertensive mice and rats showed that the factor XI–dependent thrombin generation feedback loop amplified coagulation and promoted vascular inflammation. Inhibition of the thrombin–factor XI loop with an antisense oligonucleotide against factor XI reduced vascular dysfunction and attenuated arterial hypertension. These findings suggest that the coagulation-inflammation circuit involving thrombin generation is an important regulator of hypertension [9].

Thrombin also converts fibrinogen to the insoluble product fibrin, which provides structural support for thrombi [10]. Following thrombus formation, plasmin-mediated degradation of fibrin enables thrombus resolution. D-dimer is a byproduct of fibrin breakdown, and although it does not have enzymatic activity, in epidemiology studies, its measurement has proven useful in identifying pathways of disease risk related to thrombo-inflammation. Specifically, thrombin, fibrin, and D-dimer are intertwined with inflammatory responses and inflammatory-mediated disease [11,12]. Higher D-dimer is associated with adverse levels of C-reactive protein (CRP), interleukin 6, interleukin 8, and soluble CD14, indicating that it is a marker of amplified inflammatory responses [13]. Inflammation promotes hypertension by causing endothelial damage, triggering oxidative stress, and activating the sympathetic nervous system [14], and indeed, inflammatory biomarkers are related to hypertension risk [15,16].

Evidence linking D-dimer with hypertension comes mostly from cross-sectional studies [17–20]. A single longitudinal study evaluated the association between D-dimer and incident hypertension in a US clinical trial population [21]. However, this study only included male physicians (primarily White men), and racial differences were not analyzed. Because Black adults have higher D-dimer levels than White adults [22] and they are at substantially greater risk of hypertension, studying race differences in the association between D-dimer and hypertension risk and determining whether D-dimer as a marker of biological pathways involved in racial disparities in hypertension risk is essential.

Consequently, this study aimed to address the following questions: (1) whether individuals with higher D-dimer levels are at a higher risk of developing hypertension, (2) whether the association of D-dimer with the risk of incident hypertension differs between Black and White individuals, and (3) whether the biology represented by D-dimer might mediate racial differences in the risk of incident hypertension. To generate hypotheses for future work, we also tested the interaction of gender and D-dimer on hypertension risk.

2 | METHODS

The REasons for Geographic And Racial Differences in Stroke (REGARDS) study is a national, population-based, longitudinal study whose main objectives focus on racial and geographic disparities in stroke mortality. From 2003 to 2007, the study enrolled 30,239 Black and White participants, aged ≥45 years, by oversampling of the Black population and residents of the Stroke Belt region of the United States (North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas). At baseline, participants were interviewed using computer-assisted telephone interview technology, completed a self-administered questionnaire, and were assessed in an in-home evaluation. Telephone interviews have been performed at 6-month intervals to identify potential cardiovascular events and assess cognitive functioning. Further details on the methodology have previously been published [23]. The REGARDS study was reviewed and approved by all institutional review boards at all participating universities. All participants provided written consent.

From 2013 to 2016, the REGARDS study participants were invited to undergo repeat evaluation using computer-assisted telephone interview technology, self-administered questionnaires, and in-home assessments. Individuals who chose not to participate in the second phase remained active in the ongoing 6-month telephonic assessments.

From the 13,912 participants attending both in-home visits, a nested sex- and race-stratified cohort of 4400 participants—the Biomarkers as Mediators of Racial Disparities in Risk Factors (BioMedioR) study—was selected as previously described [24]. The group comprised 50% men, 50% women, 50% Black participants, and 50% White participants. Goals of the BioMedioR study were to assess the association between biomarkers and incident hypertension and to determine the effects of biomarkers on racial disparities in hypertension risk. The BioMedioR study measured baseline biomarkers, including D-dimer, that were selected because of known race differences in levels and known cross-sectional associations with hypertension and/or diabetes.

2.1 | Data collection and variables

Trained examiners conducted the 2 in-home visits. At each visit, 2 blood pressure measurements were obtained using a standard aneroid sphygmomanometer following specific procedures [25]. Quality monitoring was performed by the examination of digit preference and retraining personnel, when necessary [23]. Height, weight, and waist circumference were measured using specific methods. In-home examiners also performed phlebotomy and collected blood samples in serum separator tubes, EDTA plasma tubes, and sample collection/anticoagulant tubes (SCAT-1; Haematologic Technologies). Centrifugation was performed within 2 hours, and serum and plasma were separated. Mailer tubes were placed on frozen gel ice and shipped overnight to the University of Vermont Laboratory for Clinical Biochemistry Research. These were recentrifuged at 4°C for 30,000 × *g*-minutes and analyzed or stored at −80°C [26].

2.2 | Outcome of interest

The main outcome was incident hypertension between the 2 assessments, where hypertension was defined, at both visits, using the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines (systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg) or self-reported use of antihypertensive medications [1]. Sensitivity analyses used the American Heart Association (AHA) and the American College of Cardiology (ACC) 2017 definition of hypertension (systolic blood pressure of ≥130 mm Hg, diastolic blood pressure of ≥80 mm Hg, or self-reported use of antihypertensive medications) [27].

2.3 | Covariates

Demographic confounding variables at baseline included self-reported age, sex, race, education, and income. Income levels were grouped into <$20,000, ≥$20,000 and <$35,000, ≥$35,000 and <$75,000, and ≥$75,000. Nonreported income was classified in a separate category. Lifestyle factors included smoking status (current, past, or never) [28] and physical activity (defined as activity sufficient to sweat 4 or more times per week, 1-3 times per week, or none) [29]. Adiposity variables were body mass index (BMI; weight [kg] divided by height squared [m^2]) and waist circumference.

Clinical factors included diabetes, baseline systolic blood pressure, and total cholesterol. Diabetes was defined as fasting plasma glucose of ≥126 mg/dL (or a random plasma glucose of ≥200 mg/dL among those failing to fast) or use of insulin or oral diabetes medication [30]. Total cholesterol was measured in serum using the Ortho Vitros Clinical Chemistry System 950IRC instrument (Johnson & Johnson Clinical Diagnostics). CRP is considered an inflammatory marker related to hypertension [15] and was measured by high-sensitivity particle-enhanced immunonepholometry on the BNII nephelometer (N High Sensitivity CRP, Dade Behring Inc). Diet characteristics were not considered in the analysis because they were not correlated with D-dimer (data not shown) and had high missingness (23%).

2.4 | Exposure of interest

D-dimer was measured in the SCAT-1 plasma on the STAR automated coagulation analyzer (Diagnostica Stago) using an immunoturbidometric assay (Liatest D-DI; Diagnostica Stago). The interassay coefficient of variation ranged from 5% to 14%. Correlation of D-dimer drawn using the REGARDS study processing methods with the standard methods was excellent [26].

2.5 | Statistical analysis

After excluding participants with baseline hypertension and those with missing D-dimer values, the analytical sample size was 1867 participants. The complete data sample, which excluded all participants with missing values on covariates of interest, comprised 1813 participants (Figure).

All analyses were weighted to account for the gender- and race-stratified selection of participants into the sample (sampling design) and, thus, reflect the entire REGARDS cohort [24]; baseline characteristics are described by D-dimer quartiles. Because of weighting, baseline characteristics are expressed as proportions instead of absolute numbers. Poisson regression was used to calculate risk ratios (RRs) of hypertension associated with baseline D-dimer, both continuously with standardized log transformation (D-dimer was not normally distributed) and categorically across quartiles. Besides a crude model, we examined an additional 5 adjusted models where demographic, lifestyle factors, adiposity-related factors, clinical factors, and CRP were sequentially added to the crude model.

To determine whether there were racial differences in the association of D-dimer and hypertension risk, interaction terms of D-dimer and race were added to the models, with a *P* value for interaction of ≤.10 indicating a racial difference.

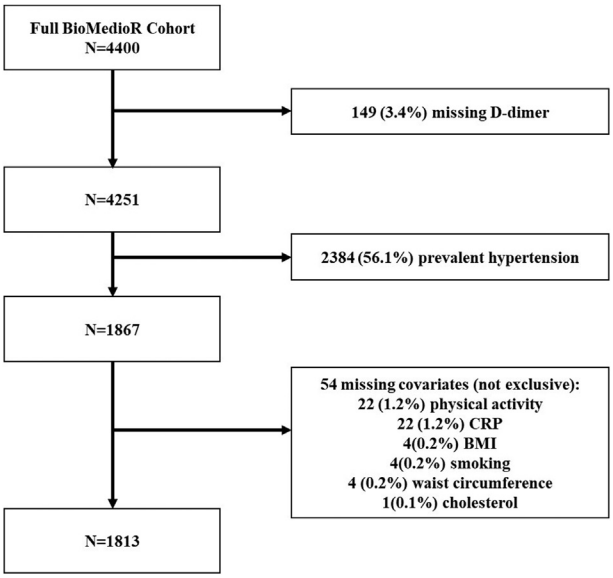

FIGURE Flow diagram shows the analytical (N = 1867) and complete data samples (N = 1813). Exclusion criteria for the analytical sample included missing D-dimer values and prevalent hypertension (JNC7 guidelines). BMI: body mass index; CRP: C-reactive protein; JNC7: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

2.6 | Mediation analysis

To assess whether D-dimer reflects biology that might mediate the association between race and hypertension, the inverse odds ratio weighting (IOWR) approach was used [31] in the crude and adjusted models. Mediation, here, is not intended to imply causation but to suggest biology, which might underly the observed differences in the population. Briefly, the IOWR assesses the natural direct and indirect effects of mediation using the odds ratio's invariance attribute. The exposure (race) was regressed on the mediator (log-transformed D-dimer) and confounding variables. The inverse of the exposure-mediator odds given confounders were used to weight the main regression analysis of hypertension (the outcome) on race. A coefficient was obtained from the weighted regression analysis and was used to determine the natural direct effects of race on hypertension. The total effects were evaluated by fitting regression models of race on hypertension. Then, the indirect effects, which quantify the amount of mediation, were captured by subtracting the direct effects from the total effects. The IOWR can support multiple mediators and is appropriate for any standard regression model. The 95% CIs were estimated nonparametrically, using 1000 iterations of bootstrapping.

To ascertain the proportion of incident hypertension that can be attributed to D-dimer in the fourth quartile, the attributable risk fraction was calculated as follows:

$$\frac{Prevalence_{\text{Elevated D-dimer}} \times (RR - 1)}{1 + [Prevalence_{\text{Elevated D-dimer}} \times (RR - 1)]}$$

2.7 | Sensitivity analysis

Three sensitivity analyses were performed. The first utilized the AHA/ACC 2017 definition of hypertension. In the second, mediation was assessed by calculating percent attenuation [32] using the following formula:

$$\frac{RR_{\text{without D-Dimer}} - RR_{\text{with D-Dimer}}}{RR_{\text{without D-Dimer}} - 1}$$

RR represents the risk ratio [32] of incident hypertension associated with being Black compared with being White. The 95% CIs percent attenuation were calculated using 1000 bootstrap iterations. Last, we assessed the impact of inflammation on the association of D-dimer with hypertension by adding CRP to model 1 (ie, before other nondemographic risk factors that relate to inflammation were added).

All statistical analyses were performed using R 3.6.0. A priori α levels of 0.05 for marginal effects and 0.10 for interaction terms were used.

3 | RESULTS

The mean (SD) follow-up time was 9.4 (1.0) years. Hypertension incidence was 35.3% (95% CI: 33.2%-37.6%) for the entire population, 46.3% (95% CI: 42.6%-50.4%) in Black participants, and 31.7% (29.1%-34.4%) in White participants. A greater percentage of Black participants (68.1%) were excluded for prevalent hypertension, compared with White participants (44.1%).

Table 1 presents baseline characteristics by quartiles of D-dimer. The median (IQR) of D-dimer was 0.36 (0.25-0.55) μg/mL; it was 0.42 (0.28-0.65) μg/mL in Black individuals and 0.35 (0.24-0.53) μg/mL in White individuals. Participants who were older, women, Black, smoked cigarettes, had less exercise, were less educated, and had lower income had higher levels of D-dimer. Higher BMI and CRP levels were also associated with higher D-dimer levels.

Table 2 shows that in the unadjusted model, there was a higher risk of hypertension with increasing D-dimer quartile (P trend < .001). Participants in the fourth quartile had a 47% higher risk of developing hypertension than those in the first quartile (RR: 1.47; 95% CI: 1.23-1.76). Adjustment for demographic, lifestyle, and adiposity-related variables (model 3) decreased the fourth vs first quartile risk of hypertension by 14.3% (RR: 1.26; 95% CI: 1.05-1.52). Additional adjustment for clinical covariates and CRP did not further attenuate the estimated RR. A similar pattern was observed when assessing the risk of hypertension by continuous D-dimer. In the unadjusted model, each SD higher log D-dimer was associated with a 10% higher risk of hypertension, whereas the risk of hypertension was 4% higher per SD higher log D-dimer in the model adjusted for demographic, lifestyle, and adiposity-related variables. Further adjustment for clinical factors and CRP did not reduce the risk. In the sensitivity analysis, using the AHA/ACC 2017 definition of hypertension, there was no material difference in the results (Supplementary Table 1). When CRP was

TABLE 1 Baseline characteristics by D-dimer, weighted to account for sampling design (unweighted N = 1867).[a]

	Baseline D-dimer (μg/mL)[b]			
Covariates Mean (SD) or %	**Quartile 1 0.01-0.25 μg/mL**	**Quartile 2 0.25-0.36 μg/mL**	**Quartile 3 0.36-0.55 μg/mL**	**Quartile 4 0.53-20.1 μg/mL**
Unweighted N	455	468	477	467
Weighted N	1575	1576	1578	1581
Demographic				
Age (y)	59.0 (7.0)	61.0 (7.8)	63.1 (8.7)	64.1 (8.3)
Sex (% female)	45.1	52.5	57.4	65.8
Black race (%)	18.4	22.8	26.9	31.2
Education (%)				
Less than high school	3.5	5.5	5.1	6.7
High school graduate	18.1	16.0	20.1	25.0
Some college	27.1	24.8	28.8	24.3
College graduate and beyond	51.3	53.7	46.1	44.0
Income (%)				
<$20,000	6.7	9.8	10.8	13.0
$20,000-$34,000	16.9	16.6	19.6	19.8
$35,000-$74,000	33.9	34.2	36.5	32.0
>$75,000	31.7	28.0	24.5	22.7
Not reported	10.7	11.4	8.55	12.6
Lifestyle				
Physical activity (%)				
≥4 times/wk	37.6	33.7	34.4	32.0
1-3 times/wk	39.1	39.7	42.0	39.7
None	23.3	26.7	23.6	28.3
Smoking				
Current	8.82	8.32	9.44	11.9
Former	32.9	43.7	38.3	37.6
Never	58.3	47.9	52.2	50.5
Adiposity Factors				
BMI (kg/m^2)	26.8 (4.6)	27.6 (5.2)	27.6 (5.1)	28.6 (5.8)
Waist circumference (cm)	89.8 (13.4)	91.7 (19.2)	91.2 (14.3)	93.0 (14.8)
Clinical Factors				
Diabetes (%)	8.3	11.5	8.4	8.3
Systolic blood pressure (mm Hg)	117 (11)	118 (11)	119 (11)	120 (11)
Total cholesterol (mg/dL)	196 (36)	196 (36)	199 (39)	196 (37)
CRP (mg/L)	2.0 (2.8)	3.1 (5.4)	3.3 (5.9)	4.8(8.6)

BMI, body mass index; CRP, C-reactive protein.

[a]The unweighted sample size reflects the number of BioMedioR participants in the analysis, and the weighted sample size reflects the number of participants in the entire REGARDS (REasons for Geographic And Racial Differences in Stroke) population at the risk of incident hypertension.

[b]The weighted median (IQR) D-dimer for the entire sample was 0.36 (0.25-0.55) μg/mL. The weighted median (IQR) D-dimer for Black participants was 0.42 (0.28-0.65) μg/mL. The weighted median (IQR) D-dimer for White participants was 0.35 (0.24-0.53) μg/mL.

TABLE 2 Association of D-dimer with hypertension risk, overall and by race group.

	Risk ratios of incident hypertension (95% CI)[a]						
	Per SD ln D-dimer 0.72 log μg/mL	Q1 0.01-0.25 μg/mL	Q2 0.25-0.36 μg/mL	Q3 0.36-0.55 μg/mL	Q4 0.55-20.1 μg/mL	*P* value for linear trend across quartiles of D-dimer	*P* value for race* D-dimer
All 680 cases/1867 participants (36.4%)							
Model 0	1.10 (1.04, 1.17)	1.0	1.17 (0.96, 1.42)	1.15 (0.94, 1.39)	1.47 (1.23, 1.76)	<.001	NA
Model 1	1.06 (1.00, 1.13)	1.0	1.14 (0.94, 1.38)	1.08 (0.89, 1.32)	1.36 (1.13, 1.63)	.004	.6
Model 2	1.06 (1.00, 1.13)	1.0	1.16 (0.95, 1.41)	1.10 (0.90, 1.34)	1.36 (1.13, 1.64)	.004	.5
Model 3	1.04 (0.98, 1.11)	1.0	1.12 (0.92, 1.36)	1.06 (0.87, 1.29)	1.26 (1.05, 1.52)	.03	.6
Model 4	1.02 (0.96, 1.09)	1.0	1.09 (0.91, 1.32)	1.05 (0.87, 1.27)	1.21 (1.01, 1.46)	.07	.7
Model 5	1.03 (0.97, 1.10)	1.0	1.08 (0.90, 1.31)	1.05 (0.87, 1.27)	1.22 (1.02, 1.47)	.06	.6
Black participants 302 cases/674 participants (44.8%)	0.81 log μg/mL						
Model 0	1.07 (0.99, 1.17)	1.0	1.07 (0.81, 1.42)	0.98 (0.74, 1.29)	1.32 (1.03, 1.69)	.07	NA
Model 1	1.04 (0.96, 1.14)	1.0	1.04 (0.79, 1.37)	0.96 (0.73, 1.27)	1.24 (0.96, 1.60)	.2	NA
Model 2	1.04 (0.95, 1.14)	1.0	1.03 (0.79, 1.35)	0.94 (0.71, 1.24)	1.22 (0.94, 1.59)	.2	NA
Model 3	1.03 (0.94, 1.13)	1.0	0.98 (0.75, 1.29)	0.91 (0.69, 1.19)	1.16 (0.90, 1.51)	.4	NA
Model 4	1.02 (0.93, 1.12)	1.0	0.96 (0.74, 1.24)	0.94 (0.72, 1.22)	1.10 (0.86, 1.42)	.5	NA
Model 5	1.01 (0.92, 1.11)	1.0	0.94 (0.73, 1.22)	0.93 (0.71, 1.21)	1.07 (0.84, 1.38)	.6	NA
White participants 378 cases/1193 participants (31.7%)	0.69 log μg/mL						
Model 0	1.09 (1.00, 1.17)	1.0	1.17 (0.92, 1.50)	1.17 (0.91, 1.50)	1.42 (1.13, 1.80)	.005	NA
Model 1	1.08 (0.99, 1.17)	1.0	1.19 (0.93, 1.52)	1.15 (0.89, 1.47)	1.40 (1.10, 1.78)	.01	NA
Model 2	1.07 (0.99, 1.17)	1.0	1.22 (0.95, 1.56)	1.18 (0.91, 1.52)	1.41 (1.10, 1.80)	.01	NA
Model 3	1.04 (0.96, 1.14)	1.0	1.19 (0.93, 1.52)	1.14 (0.88, 1.46)	1.29 (1.01, 1.64)	.07	NA
Model 4	1.03 (0.95, 1.12)	1.0	1.17 (0.92, 1.48)	1.11 (0.87, 1.42)	1.26 (0.99, 1.60)	.1	NA
Model 5	1.05 (0.96, 1.14)	1.0	1.16 (0.92, 1.48)	1.12 (0.87, 1.44)	1.29 (1.01, 1.64)	.07	NA

Model 0: unadjusted; model 1: age, sex, race, education, and income; model 2: model 1 + smoking and physical activity; model 3: model 2 + body mass index and waist circumference; model 4: model 3 + diabetes mellitus, systolic blood pressure, and total cholesterol; model 5: model 4 + C-reactive protein. The *P* value of D-dimer*gender interaction was .6 (model 5).

ln, log-transformed; Q, quartile of D-dimer.

[a]Analyses were weighted by the sampling stratification factors.

added to model 1 (ie, before other risk factors, the fourth quartile RR was 1.45 [1.21, 1.75]).

Although the interaction between race and D-dimer was not significant (*P* values for interaction > .1 in all models), we observed a small difference in the RR estimates by race (Table 2). In the unadjusted model, the risk of hypertension in the fourth quartile compared to the first quartile was 32% higher (RR: 1.32; 95% CI: 1.03-1.69) for Black participants and 42% higher for White participants (RR: 1.42; 95% CI: 1.13-1.80). Adjusting for confounders attenuated the association to the null in Black people and modestly in White people. In the exploratory analysis, there was no difference in the association of D-dimer and hypertension risk in men compared with women (*P* value for interaction in model 5 = .6).

In the sensitivity analysis using the AHA/ACC 2017 hypertension definition (Supplementary Table 1), a reverse pattern was observed for the race by D-dimer interaction, but this was also not statistically significant (*P* interaction > .3 in all models). The adjusted RR, in the fourth quartile, in the final model was 1.07 (95% CI: 0.84-1.36) among White participants and 1.41 (95% CI: 0.96-2.05) among Black participants. Similarly, there was no difference in the association by sex.

Table 3 shows that D-dimer did not substantially mediate the association between race and hypertension risk. For all 5 models, the

TABLE 3 D-dimer as a mediator of the excess risk of hypertension in Black compared to White participants.[a,b]

	Total effects (direct and indirect effects)	Direct effects (association absent of D-dimer)	Indirect effects (potential mediation of D-dimer)	*P* value for indirect effects
Model 0	1.46 (1.30, 1.65)	1.47 (1.30, 1.66)	1.00 (0.97, 1.03)	.5
Model 1	1.40 (1.24, 1.58)	1.31 (1.13, 1.51)	1.07 (0.98, 1.17)	.5
Model 2	1.41 (1.25, 1.60)	1.31 (1.13, 1.52)	1.08 (0.98, 1.19)	.5
Model 3	1.32 (1.16, 1.49)	1.26 (1.08, 1.47)	1.04 (0.95, 1.17)	.5
Model 4	1.20 (1.07, 1.36)	1.15 (0.98, 1.35)	1.05 (0.94, 1.20)	.5
Model 5	1.20 (1.06, 1.36)	1.16 (0.98, 1.36)	1.04 (0.94, 1.17)	.5

Model 0: unadjusted; model 1: age, sex, race, education, and income; model 2: model 1 + smoking and physical activity; model 3: model 2 + body mass index and waist circumference; model 4: model 3 + diabetes mellitus, systolic blood pressure, and total cholesterol; model 5: model 4 + C-reactive protein.

[a]Analyses were weighted by the sampling stratification factors.

[b]Direct effects refer to the unmediated effects of race on hypertension. Indirect effects are the mediated effects (through D-dimer) of race on hypertension, and total effects encompass both direct and indirect effects.

indirect effects were not significant (P = .5). Assessing the mediation by calculating percent attenuation confirmed that D-dimer was a negligible mediator of racial differences in hypertension risk (Supplementary Table 2). Sensitivity analyses that used the AHA/ACC 2017 definition for hypertension did not change the interpretation of the results (Supplementary Tables 3 and 4).

Using a final RR of 1.22, the proportion of incident hypertension attributable to D-dimer in the fourth quartile was 5.2%.

4 | DISCUSSION

In this longitudinal cohort study of Black and White US adults, the risk of incident hypertension over 9 years was 47% greater in the fourth quartile than in the first quartile of D-dimer in an unadjusted model. This association was less on controlling for sociodemographic and adiposity-related risk factors but remained significant, with a 22% higher risk of incident hypertension relative to the first quartile. This yielded an attributable risk of 5.2%. There was no difference in the association of D-dimer with hypertension by race, and the biology reflected by D-dimer did not mediate the excess risk of incident hypertension among Black compared with White participants.

Our findings, of some attenuation of the association of D-dimer with hypertension by adiposity measures, are similar to other findings and suggest that the relationship between dysregulated coagulation and adiposity may be relevant, in part, to the pathogenesis of hypertension. In a case-control study nested within the Physicians' Health Study, the risk of hypertension in the third and fourth (≥0.11 μg/mL) quartiles compared with the first quartile of D-dimer was 52% to 81% higher. Adjusting for BMI attenuated the relationship from 38% to 68% higher [21]. Education, income, and waist circumference were not adjusted for, which might explain the larger risk estimates than those observed in our study.

Elevated BMI [33,34] and waist circumference [35] are associated with a higher risk of hypertension, and D-dimer is associated with leptin [36], an adipokine. Leptin is a hormone primarily secreted by white adipose tissue, and its levels are proportional to body fat. Leptin regulates several physiological processes, including energy homeostasis, neuroendocrine function, and metabolism. Leptin dysfunction results in metabolic abnormalities, including obesity [37].

Biological pathways underlying the associations between D-dimer, adiposity, and hypertension remain unclear. Dysfunctional adiposity due to excessive weight gain promotes inflammation, and pro-inflammatory responses induce endothelial dysfunction [38]. Vascular endothelial damage contributes to a hypercoagulable state, which, in turn, can lead to hypertension [39]. The findings in mice and rats indicate that the coagulation-inflammation circuit involving thrombin generation is a key regulator of hypertension [9]. Interestingly, when we adjusted for CRP first before adiposity measures, the risk of hypertension was not attenuated (data not shown). This indicates that there are other mechanisms that explain the relationship between D-dimer, adiposity, and hypertension. Evidence has consistently shown that Black people have higher D-dimer level [19,40,41] and a higher risk for incident hypertension [42–44] than White people. Despite this, we observed no clear difference in the association of D-dimer with hypertension by race in this study. In both racial groups, adjustment for confounders shifted risk estimates toward the null, further supporting the argument that dysregulated clotting mechanisms leading to hypertension are partly mediated by other risk factors.

Some limitations of this study require discussion. First, D-dimer was measured at 1 time point, creating potential for misclassification because of biovariability and measurement error. However, biovariability of D-dimer is quite acceptable for use in epidemiologic research, suggesting that a single baseline D-dimer is a reasonable reflection of a person's true level [45]. The measurement of D-dimer at >1 time point to obtain an average level could reduce this misclassification; however, this is not practical in most epidemiologic studies (especially in a study like REGARDS with 30,239 participants). Misclassification of D-dimer could lead to bias to the null hypothesis; thus, our reported estimates of the association may underestimate the true association. Second, given that D-dimer can be influenced by

many factors, longitudinal change as an exposure would be interesting to study, but this could not be done here. Third, some demographic and lifestyle confounders were self-reported; thus, they are subject to recall or reporting bias. Fourth, as in all epidemiologic studies, residual confounding is possible, and there might be unmeasured confounders we did not consider. Fifth, even with the large initial sample size, the higher prevalence of hypertension at baseline among Black compared with White persons resulted in a smaller sample size of Black participants at the risk for incident hypertension during follow-ups. This may have reduced the power to detect the small racial differences in the association between D-dimer and incident hypertension that was observed. Sixth, between the baseline and follow-up visits, 22% of participants died and 24% withdrew or opted not to participate, raising questions about selective attrition [24]. To address this, a previous REGARDS study on causes of racial disparities in incident hypertension found no evidence of quantifiable selection bias due to the differences in attrition; baseline covariates, including race and sex, did not significantly affect study withdrawal [46]. This suggests that the findings would be comparable between a complete case analysis and methods that incorporate study withdrawal [24]. Seventh, we were unable to measure some key factors related to fibrinolytic function due to the blood sample collection method used in the REGARDS study [26]. Future research in other cohorts could address this. Finally, this study was limited to Black and White participants aged ≥45 years; therefore, findings may not be applicable to younger individuals and other racial groups. Notwithstanding these limitations, the REGARDS cohort offers a large, national representative sample of Black and White individuals with a high retention over nearly 10 years, and blood pressure along with critical confounders such as height and weight were carefully measured using standard methods. To our knowledge, no other prospective studies in the United States have assessed the racial differences in the association between D-dimer and hypertension.

To summarize, the association between D-dimer and hypertension risk was moderate. Racial differences in the association were not seen. Thrombotic mechanisms may play a role in the pathogenesis of hypertension partly via modifiable risk factors, namely, adiposity. Future research should determine pathways linking D-dimer, hypertension, and hypertension risk factors to uncover new targets for hypertension prevention and treatment.

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AUTHOR CONTRIBUTIONS

D.K.M.: design of study, analysis/interpretation of data, writing/revising, and final approval. B.G., L.L., S.E.J., L.A.M., N.A.Z., G.H., and M.C.: design of study; L.L., S.E.J., T.B.P., L.A.M., A.S.W., N.A.Z., and G.H.: analysis/interpretation of data, writing/revising, and final approval. All authors read and approved the final paper.

RELATIONSHIP DISCLOSURE

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REFERENCES

[1] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA*. 2003;289:2560–72.
[2] Rana J, Oldroyd J, Islam MM, Tarazona-Meza CE, Islam RM. Prevalence of hypertension and controlled hypertension among United States adults: evidence from NHANES 2017-18 survey. *Int J Cardiol Hypertens*. 2020;7:100061.
[3] Carretero OA, Oparil S. Essential hypertension. Part I: definition and etiology. *Circulation*. 2000;101:329–35.
[4] Lip GY. Hypertension and the prothrombotic state. *J Hum Hypertens*. 2000;14:687–90.
[5] Dielis AW, Smid M, Spronk HM, Hamulyak K, Kroon AA, ten Cate H, et al. The prothrombotic paradox of hypertension: role of the renin-angiotensin and kallikrein-kinin systems. *Hypertension*. 2005;46:1236–42.

[6] Beevers G, Lip GY, O'Brien E. ABC of hypertension: the pathophysiology of hypertension. *BMJ*. 2001;322:912–6.
[7] De Miguel C, Rudemiller NP, Abais JM, Mattson DL. Inflammation and hypertension: new understandings and potential therapeutic targets. *Curr Hypertens Rep*. 2015;17:507.
[8] Hirano K. The roles of proteinase-activated receptors in the vascular physiology and pathophysiology. *Arterioscler Thromb Vasc Biol*. 2007;27:27–36.
[9] Kossmann S, Lagrange J, Jäckel S, Jurk K, Ehlken M, Schönfelder T, et al. Platelet-localized FXI promotes a vascular coagulation-inflammatory circuit in arterial hypertension. *Sci Transl Med*. 2017;9:eaah4923.
[10] Pieters M, Wolberg AS. Fibrinogen and fibrin: an illustrated review. *Res Pract Thromb Haemost*. 2019;3:161–72.
[11] Bao W, Qi X, Li H, Hou F, Zhang X, Wang R, Guo X. Correlation of D-dimer level with the inflammatory conditions: a retrospective study. *AME Med J*. 2017;2:27–35.
[12] Jennewein C, Tran N, Paulus P, Ellinghaus P, Eble JA, Zacharowski K. Novel aspects of fibrin(ogen) fragments during inflammation. *Mol Med*. 2011;17:568–73.
[13] Kamin Mukaz D, Gergi M, Koh I, Zakai NA, Judd SE, Sholzberg M, et al. Thrombo-inflammatory biomarkers and D-dimer in a biracial cohort study. *Res Pract Thromb Haemost*. 2021;5:e12632.
[14] Dinh QN, Drummond GR, Sobey CG, Chrissobolis S. Roles of inflammation, oxidative stress, and vascular dysfunction in hypertension. *Biomed Res Int*. 2014;2014:406960.
[15] Lakoski SG, Cushman M, Siscovick DS, Blumenthal RS, Palmas W, Burke G, et al. The relationship between inflammation, obesity and risk for hypertension in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Hum Hypertens*. 2011;25:73–9.
[16] Plante TB, Long DL, Guo B, Howard G, Carson AP, Howard VJ, et al. C-reactive protein and incident hypertension in black and white Americans in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort study. *Am J Hypertens*. 2021;34:698–706.
[17] Khaleghi M, Saleem U, McBane RD, Mosley TH Jr, Kullo IJ. African-American ethnicity is associated with higher plasma levels of D-dimer in adults with hypertension. *J Thromb Haemost*. 2009;7:34–40.
[18] Lip GY, Blann AD, Jones AF, Lip PL, Beevers DG. Relation of endothelium, thrombogenesis, and hemorheology in systemic hypertension to ethnicity and left ventricular hypertrophy. *Am J Cardiol*. 1997;80:1566–71.
[19] Zakai NA, McClure LA, Judd SE, Kissela B, Howard G, Safford M, et al. D-dimer and the risk of stroke and coronary heart disease. The REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Thromb Haemost*. 2017;117:618–24.
[20] Lammertyn L, Schutte AE, Pieters M, Schutte R. D-dimer relates positively with increased blood pressure in black South Africans: the SABPA study. *Thromb Res*. 2014;133:1152–7.
[21] Sesso HD, Jiménez MC, Wang L, Ridker PM, Buring JE, Gaziano JM. Plasma inflammatory markers and the risk of developing hypertension in men. *J Am Heart Assoc*. 2015;4:e001802.
[22] Lutsey PL, Cushman M, Steffen LM, Green D, Barr RG, Herrington D, et al. Plasma hemostatic factors and endothelial markers in four racial/ethnic groups: the MESA study. *J Thromb Haemost*. 2006;4:2629–35.
[23] Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, et al. The REasons for Geographic And Racial Differences in Stroke study: objectives and design. *Neuroepidemiology*. 2005;25:135–43.
[24] Long DL, Guo B, McClure LA, Jaeger BC, Tison SE, Howard G, et al. Biomarkers as MEDiators of racial disparities in risk factors (BioMedioR): rationale, study design, and statistical considerations. *Ann Epidemiol*. 2022;66:13–9.
[25] Howard VJ, Woolson RF, Egan BM, Nicholas JS, Adams RJ, Howard G, et al. Prevalence of hypertension by duration and age at exposure to the stroke belt. *J Am Soc Hypertens*. 2010;4:32–41.
[26] Gillett SR, Boyle RH, Zakai NA, McClure LA, Jenny NS, Cushman M. Validating laboratory results in a national observational cohort study without field centers: the REasons for Geographic And Racial Differences in Stroke cohort. *Clin Biochem*. 2014;47:243–6.
[27] Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71:e127–248.
[28] Parekh TM, Wu C, McClure LA, Howard VJ, Cushman M, Malek AM, et al. Determinants of cigarette smoking status in a national cohort of black and white adult ever smokers in the USA: a cross-sectional analysis of the REGARDS study. *BMJ Open*. 2019;9:e027175.
[29] McDonnell MN, Hillier SL, Hooker SP, Le A, Judd SE, Howard VJ. Physical activity frequency and risk of incident stroke in a national US study of blacks and whites. *Stroke*. 2013;44:2519–24.
[30] Carson AP, Muntner P, Kissela BM, Kleindorfer DO, Howard VJ, Meschia JF, et al. Association of prediabetes and diabetes with stroke symptoms: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Diabetes Care*. 2012;35:1845–52.
[31] Nguyen QC, Osypuk TL, Schmidt NM, Glymour MM, Tchetgen Tchetgen EJ. Practical guidance for conducting mediation analysis with multiple mediators using inverse odds ratio weighting. *Am J Epidemiol*. 2015;181:349–56.
[32] MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. *Annu Rev Psychol*. 2007;58:593–614.
[33] Shihab HM, Meoni LA, Chu AY, Wang NY, Ford DE, Liang KY, et al. Body mass index and risk of incident hypertension over the life course: the Johns Hopkins Precursors Study. *Circulation*. 2012;126:2983–9.
[34] Forman JP, Stampfer MJ, Curhan GC. Diet and lifestyle risk factors associated with incident hypertension in women. *JAMA*. 2009;302:401–11.
[35] Folsom AR, Prineas RJ, Kaye SA, Munger RG. Incidence of hypertension and stroke in relation to body fat distribution and other risk factors in older women. *Stroke*. 1990;21:701–6.
[36] Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Adiposity, adipokines, and risk of incident stroke in older men. *Stroke*. 2013;44:3–8.
[37] Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. Narrative review: the role of leptin in human physiology: emerging clinical applications. *Ann Intern Med*. 2010;152:93–100.
[38] Vilahur G, Ben-Aicha S, Badimon L. New insights into the role of adipose tissue in thrombosis. *Cardiovasc Res*. 2017;113:1046–54.
[39] Blann AD. How a damaged blood vessel wall contibutes to thrombosis and hypertenasion. *Pathophysiol Haemost Thromb*. 2003;33:445–8.
[40] Cushman M, Folsom AR, Wang L, Aleksic N, Rosamond WD, Tracy RP, et al. Fibrin fragment D-dimer and the risk of future venous thrombosis. *Blood*. 2003;101:1243–8.
[41] Pieper CF, Rao KM, Currie MS, Harris TB, Cohen HJ. Age, functional status, and racial differences in plasma D-dimer levels in community-dwelling elderly persons. *J Gerontol A Biol Sci Med Sci*. 2000;55:M649–57.
[42] Balfour PC Jr, Rodriguez CJ, Ferdinand KC. The role of hypertension in race-ethnic disparities in cardiovascular disease. *Curr Cardiovasc Risk Rep*. 2015;9:18.
[43] Lackland DT. Racial differences in hypertension: implications for high blood pressure management. *Am J Med Sci*. 2014;348:135–8.
[44] Thomas SJ, Booth III JN, Dai C, Li X, Allen N, Calhoun D, et al. Cumulative incidence of hypertension by 55 years of age in blacks and whites: the CARDIA study. *J Am Heart Assoc*. 2018;7:e007988.
[45] Sakkinen PA, Macy EM, Callas PW, Cornell ES, Hayes TE, Kuller LH, et al. Analytical and biologic variability in measures of hemostasis, fibrinolysis, and inflammation: assessment and implications for epidemiology. *Am J Epidemiol*. 1999;149:261–7.

[46] Long DL, Howard G, Long DM, Judd S, Manly JJ, McClure LA, et al. An investigation of selection bias in estimating racial disparity in stroke risk factors. *Am J Epidemiol*. 2019;188:587–97.

SUPPLEMENTARY MATERIAL

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