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Retinal microvascular calibre and risk of incident diabetes: The multi-ethnic study of atherosclerosis

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Abstract

Aim—To prospectively examine the association of retinal microvascular signs with incident diabetes and impaired fasting glucose (IFG) in a multi-ethnic population-based cohort.

Methods—The multi-ethnic study of atherosclerosis comprised Caucasians, African-Americans, Hispanics and Chinese aged 45–84 years. Retinal vascular calibre and retinopathy were quantified from baseline retinal photographs. Incident diabetes and IFG were ascertained prospectively.

Results—After a median follow-up of 3 years, 243 (4.9%) people developed diabetes and 565 (15.0%) developed IFG. After adjusting for known risk factors, participants with wider retinal arteriolar calibre had a higher risk of developing diabetes [HR: 1.60; 95% CI: 1.12–2.29, $p = 0.011$ comparing highest with lowest arteriolar calibre tertile]. In ethnic subgroup analysis, the association between wider retinal arteriolar calibre and incident diabetes was stronger and statistically significant only in Caucasians [HR: 2.78; 95% CI: 1.37–5.62, $p = 0.005$]. Retinal venular calibre and retinopathy signs were not related to risk of diabetes or IFG.

Conclusion—Wider retinal arteriolar calibre is independently associated with an increased risk of diabetes, supporting a possible role for early arteriolar changes in diabetes development. This effect was largely seen in Caucasians, and not in other ethnic groups, and may reflect ethnic differences in susceptibility to diabetes from microvascular pathways.

Keywords

Retinal microvascular calibre; Retinopathy; Diabetes; Impaired fasting glucose

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Conflict of interest
The authors declare that they have no conflict of interest.

1. Introduction

Microvascular disease has been hypothesized to play a key role in the pathogenesis of diabetes [1] and pre-diabetic states such as impaired fasting glucose (IFG) [2]. However, the precise temporal sequence of microvascular disease to diabetes development remains uncertain [3].

An assessment of the retinal microvasculature may offer the opportunity to examine early microvascular changes that may precede diabetes development [4]. Cross-sectional studies suggest that persons with diabetes have wider retinal arterioles [5–8]. However, narrower retinal arterioles have been reported to predict an increased risk of developing diabetes in some prospective studies [9–11] but not in others, which found that diabetes risk was related to venular rather than arteriolar calibre changes [12]. A few studies have also reported that retinal vascular calibre was related to incident IFG [12,13].

Furthermore, isolated retinopathy signs in persons without diabetes have also been suggested to be markers of future diabetes risk [14], although most studies show that these retinopathy signs do not appear to be related to an increased risk of diabetes [15–17] except perhaps in younger individuals [16] and those with a family history of diabetes [15].

The majority of previous studies have been conducted in white populations, and no data are currently available to inform how these relationships may vary in different racial/ethnic groups. We therefore examined prospectively the relationship of retinal vascular calibre and retinopathy signs with incident diabetes and IFG in a multi-ethnic population-based cohort.

2. Methods

2.1. Study population

The multi-ethnic study of atherosclerosis (MESA) is a prospective cohort study of 6814 men and women aged 45–84 years without clinical cardiovascular disease living in six United States communities. The main objective of this study was to identify risk factors for subclinical and clinical cardiovascular disease progression. Sampling and recruitment procedures have been described in detail elsewhere [18]. In brief, 6814 participants comprising 4 ethnic groups (Caucasians, African-Americans, Hispanics and Chinese) were recruited between July 2000 and July 2002 from Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York City, New York; and St. Paul, Minnesota. Each field centre recruited approximately 1100 participants, with an approximately equal number of men and women from two or more of the ethnic groups to minimize confounding of ethnicity by site. The Tenets of the Declaration of Helsinki were followed and institutional review board approval was granted at all MESA sites. Written informed consent was obtained from each participant.

Retinal photography was performed at the second examination (August 2002–February 2004), which occurred immediately after the baseline examination. 6231 (91.6%) participants returned for this second examination, and 5946 (87.3%) and 5818 (85.4%) participants returned for the third (March 2004–September 2005) and fourth examinations (September 2005–May 2007), respectively.

For the purpose of this study, eligible participants were identified from the second examination, which was considered the baseline examination for this report. Incident diabetes and IFG were prospectively identified at the third and fourth examinations. Of the 6231 participants that returned for the second examination, 6176 (99.0%) had retinal photographs taken. Participants in the following categories, which are not mutually

exclusive, were excluded in separate models: those with prevalent diabetes or missing diabetes status, $n = 938$ (in incident diabetes prediction model); those with prevalent IFG, diabetes or missing diabetes status, $n = 2137$ (in incident IFG prediction model); and those with ungradable retinal photographs or missing data for retinal vessel calibre or retinopathy, $n = 283$ (Figs. 1 and 2).

2.2. Retinal photography and measurement of baseline retinal vascular calibre

Fundus photography was performed at each site using a standardized protocol described previously [19]. In brief, participants were seated in a darkened room and both eyes were photographed with a 45 degree 6.3 megapixel digital nonmydriatic camera. Two photographic fields were taken of each eye, the first centred on the optic disc and the second on the fovea. Images were sent from the six field centres to the University of Wisconsin, Madison, for measurement of retinal vascular calibre and quantification of retinopathy.

Retinal vascular calibre was measured using a computer-based program (IVAN, University of Wisconsin, Madison), based on a detailed protocol [20]. Trained graders, masked to participant characteristics performed these measurements. Optic-disc centred right eye photographs were selected for measurement; the left eye photograph was used if retinal vascular calibre could not be measured in the right eye. For each photograph, all arterioles and venules coursing through an area 0.5–1 disc diameter from the optic disc margin were measured, and using formulas developed by Hubbard et al. [21] and later modified by Knudtson et al. [22], these measurements were combined and summarized into a single central retinal artery equivalent (CRAE) and central retinal venular equivalent (CRVE). Reproducibility of these measurements has been reported, with intra- and intergrader intraclass correlation coefficients ranging from 0.78 to 0.99 [20].

2.3. Assessment of retinopathy signs

Assessment of retinopathy signs has been previously published [19]. In brief, retinopathy was considered to be present if any characteristic lesions as defined by the early treatment diabetic retinopathy study (ETDRS) [23] severity scale was present: microaneurysms, haemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading, and new vessels. These lesions were defined as present if graded as either definite or probable.

2.4. Ascertainment of incident diabetes mellitus and IFG

Methods of ascertainment and diagnosis of diabetes mellitus have been previously described [18]. Participants underwent a 12-h overnight fast and had morning blood collection. Diabetes mellitus was defined as fasting plasma glucose value of ≥126 mg/dl (7.0 mmol/L) or use of insulin or oral hypoglycaemic medication. IFG was defined as fasting plasma glucose level of 110–125 mg/dL (6.0–6.9 mmol/L). All other participants were defined as having normal glucose metabolism.

Incident diabetes was defined in persons free of diabetes at the first and second examinations who subsequently developed diabetes by the third or fourth examination. Incident IFG was defined in persons with normal fasting glucose at the first and second examinations who subsequently developed IFG by the third or fourth examination.

2.5. Assessment of other risk factors

All participants underwent an extensive interview, physical examination and laboratory investigation at each follow-up examination. Information on past medical history, medication use, cigarette smoking status, alcohol consumption, physical activity and family history were self-reported [18]. A positive family history of diabetes was defined by

participant report of diabetes in either biological parent. Physical activity was surveyed in detail and for this report the MESA-computed value for total intentional exercise was analysed. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or current use of antihypertensive medications. Height and weight were measured with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. Fasting (>12 h) blood samples were drawn from participants and analysed for serum glucose and insulin levels, Hb_{A1C}, plasma total and HDL-cholesterol and triglycerides. LDL-cholesterol was calculated using the Friedewald equation [24]. A urine sample was collected and analysed for albumin and creatinine.

2.6. Power calculation

When the sample size in each group is 1621, with a total number of events required, *E*, of 3139, a 0.050 level two-sided log-rank test for equality of survival curves will have 80% power to detect the difference between groups by CRVE. The proportion of incident diabetes in people with higher CRVE is 0.025 and the proportion of incident diabetes in people with lower is 0.035 (a constant hazard ratio of 1.05); this assumes no dropouts before time *t*.

2.7. Statistical analysis

Descriptive statistics were computed for all variables. Retinal arteriolar and venular calibre values (CRAE/CRVE) were categorized into tertiles, with the first tertile representing the narrowest calibre and the third tertile the widest. Retinopathy signs, categorized as presence of microaneurysms, haemorrhage, hard exudates, or any retinopathy, were analysed as binary categorical variables (present vs. absent).

The relationship between baseline retinal vascular calibre/retinopathy and incident diabetes/IFG was examined using Kaplan–Meier survival estimates and Cox's proportional hazards regression model after adjusting for potential confounders. We constructed 3 models: Model 1 initially adjusted for age, gender, race, study centre and CRVE in models of CRAE and vice versa [25]. Models for arteriolar diameter were adjusted for venular diameter (and vice versa) because this allows for controlling the potential confounding effects of fellow vessels on the outcomes of interest. This is detailed in a study by Liew et al. [25] and is an approach used in previous publications such as in MESA [26,27]. Stepwise Cox regression was used to find the best-fitting survival model from all available covariates. Model 2 included additional adjustments for SBP, family history of diabetes, BMI, Hb_{A1C}, fasting insulin concentration, antihypertensive treatment and urinary albumin excretion (UAE), which were significant in the stepwise Cox regression model; and Model 3 was adjusted for all the variables in Model 2 plus presence of any retinopathy. The latter additional covariate was selected to demonstrate that the relationship between CRAE/CRVE and incident diabetes is independent of baseline retinopathy. All pertinent variables were examined for correlations and multicollinearity using Pearson product-moment correlation. We used the Schoenfeld residual tests to evaluate the proportional hazard assumption and checked interactions between variables. Tests for interaction between identified risk factors were carried out. No interaction between such variables was found. A *p*-value of 0.05 was used for significance testing. We also performed supplementary analysis of retinal vascular calibre with incident diabetes by ethnic subgroups. All statistical analyses were performed using Stata software, version 11.0 (Stata Corp., College Station, TX).

3. Results

Among participants with baseline retinal vascular calibre, retinopathy data and known diabetes status who attended at least one follow-up examination, 4955 participants were free of diabetes and 3756 of both diabetes and IFG at baseline. The proportion of participants with ungradable photographs did not differ between the incident diabetes and incident IFG groups. Table 1 compares the baseline characteristics of participants that developed incident diabetes with those that did not. In general, participants that developed incident diabetes were more likely to be overweight and hypertensive; have a positive family history of diabetes; have baseline IFG and higher fasting serum glucose and insulin levels; and have poorer lipid profiles and physical activity scores (Table 1.1).

Over a median follow-up of 3 years (range: 2 months–4.5 years), 243 people developed diabetes and 565 developed IFG. The incidence rates of diabetes and IFG were 1.60 and 5.25 per 100 person years respectively. Table 2 shows that incident diabetes was associated with CRAE but not CRVE. The incidence rate of diabetes increased from 1.26% to 1.41% and 2.19% with each increasing tertile of CRAE. After adjusting for age, gender, race, study centre, SBP, family history of diabetes, BMI, Hb_{A1C} and other risk factors, persons with the highest compared to the lowest CRAE tertile were 60% more likely to develop incident diabetes [HR 1.60; 95% CI: 1.12–2.29]. This association remained similar with additional adjustment for retinopathy.

Subgroup analysis by ethnic/racial subgroups showed higher odds of incident diabetes with wider CRAE in all 4 groups; however, the association was statistically significant only among the Caucasians (Table 3). Caucasians with the highest compared to the lowest tertile of CRAE were almost three times [HR: 2.78; 95% CI: 1.37–5.62] more likely to develop incident diabetes. Retinal vascular calibre was not associated with risk of incident IFG (data not shown).

Retinopathy signs such as retinal haemorrhage [HR: 0.61; 95% CI: 0.27–1.37], microaneurysms [HR: 0.97; 95% CI: 0.53–1.79], hard exudates [HR: 0.77; 95% CI: 0.20–2.95] and “any retinopathy signs” [HR: 0.82; 95% CI: 0.56–1.20] were not related to incident diabetes (data not shown). There were also no associations between focal retinopathy signs and incident IFG (data not shown).

4. Discussion

In this large prospective multi-ethnic cohort study of persons free of diabetes, we found that persons with wider retinal arterioles were more likely to develop incident diabetes than those with narrower arterioles, independent of age, gender, race, study centre, SBP, Hb_{A1C}, fasting insulin levels, family history of diabetes, and other risk factors. We found no association between retinal venular calibre and retinopathy with incident diabetes or IFG.

Our finding that wider retinal arteriolar calibre is associated with subsequent development of diabetes has not been previously reported (Table 4). Cross-sectional data in different population-based studies support our findings and suggest that persons with diabetes have wider retinal arterioles [5–8]. However, prospective data have been more conflicting. In the Atherosclerosis Risk In Communities (ARIC) and Beaver Dam Eye Study (BDES) [9,10], after adjusting for baseline risk factors, persons with narrower, and not wider, retinal arterioles at baseline were more likely to subsequently develop diabetes over a median of 3.5 years (OR: 1.71; 95% CI: 1.13–2.57) and 10 years (OR: 1.53; 95% CI: 1.03–2.27), respectively. Recent data from the Australian Diabetes, Obesity and Lifestyle (AusDiab) study also found a similar relationship between narrower retinal arterioles and 5-year incidence of diabetes (OR: 2.21; 95% CI: 1.02–4.80) [11]. In comparison, the Rotterdam

Study and Blue Mountains Eye Study (BMES) found no association between retinal arteriolar calibre and incident diabetes; however, reported that wider venules were related to incident IFG [12,13].

Several reasons could account for the discrepancies between studies. First, the findings of MESA may not be directly comparable to those from the above predominantly white populations. The effect of ethnic variation and its associated differences in risk factors could have attenuated some associations or strengthened others. In support of this, we found a stronger relationship among the Caucasians than in other racial/ethnic groups. However, these racial/ethnic variations should be interpreted cautiously because after stratifying by ethnic groups, sample sizes in the Chinese, African-Americans and Hispanics were underpowered to detect significant associations. Second, our median follow-up duration of 3 years was shorter than some prospective studies with 10-year observation periods. We speculate that there may be a sequential dynamic evolution in microvasculature change that occurs during the natural history of diabetes development [4]. Arteriolar narrowing could be the earliest microvascular change that predicts long-term diabetes risk, as shown in studies with longer follow-up [9–11]. Wider retinal arterioles could therefore reflect later and more advanced stages of diabetes development as suggested by our study and other cross-sectional analyses [5–8]. Further research is needed to investigate whether it is the absolute value of CRAE/CRVE or the progression of changes in these variables that is important in determining the association with incident diabetes. Finally, reverse causation accounting for these findings cannot be completely excluded due to the short follow-up duration. This is supported somewhat by the fact that at baseline when the retinal vessels were examined, those who developed diabetes already had elevated glucose, insulin, HbA1c, and HOMA_IR, and 66% had impaired fasting glucose.

The specific mechanisms linking wider arterioles and diabetes are not known. Wider arterioles possibly reflect a combination of tissue hypoxia, hyperperfusion and impaired vascular autoregulation [28]. As a response to hypoxia, retinal arterioles dilate to increase retinal tissue perfusion, which leads to hyperperfusion, impaired vasoregulation, and further and persistent widening of the arterioles [4]. Longitudinal studies of retinal vascular measurements over time are needed to clarify these relationships and to improve our understanding of the pre-diabetic microvascular changes that occur.

We report no association between retinopathy signs and incident diabetes, a finding that is consistent with data from the ARIC, BDES and BMES [15–17] (Table 4). The AusDiab study is the only study so far to report a two-fold higher risk of incident diabetes in nondiabetic individuals with retinopathy signs at baseline [14]. In the ARIC study, among persons with a family history of diabetes, the presence of retinopathy signs was associated with a two-fold increase in diabetes risk [15]. Our cohort did not show such an association (data not shown), which may be related to the small sample size with a family history of diabetes (n = 663 vs. 1727).

The strengths of our study include its large sample size, the recruitment of participants from a population-based cohort with comprehensive data on risk factors, the multi-ethnic composition which enabled exploration of possible ethnic differences, and the quantitative and masked assessment of retinal vascular calibre and retinopathy signs. Potential limitations include its relatively short follow-up duration and the absence of a more accurate method such as an oral glucose tolerance test to diagnose diabetes. The imprecision of a single fasting glucose could have led to misclassification of diabetes status; however, this error is likely to be random and would only tend to bias any associations towards the null.

In conclusion, our population-based study demonstrates a prospective association between wider retinal arteriolar calibre and incident diabetes in middle-aged persons, independent of known risk factors. These findings suggest that arteriolar processes occur early in the course of diabetes development and may play a role and contribute to its pathogenesis. Ethnic differences in association may reflect differential susceptibility to diabetes from microvascular pathways, an area of research that should be further explored.

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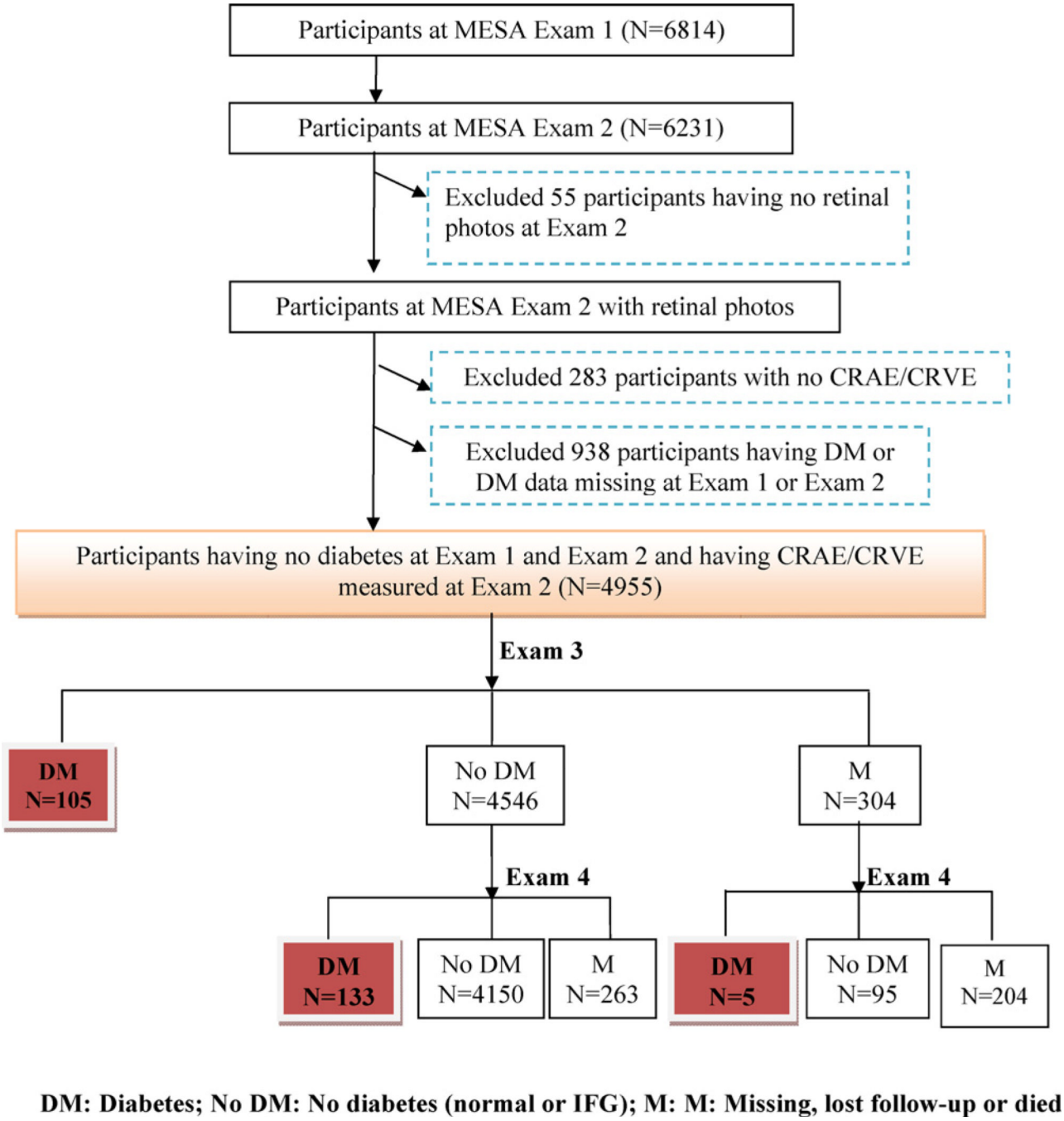

Fig. 1.
Participants included/excluded at each MESA follow-up examination in the incident diabetes prediction model.

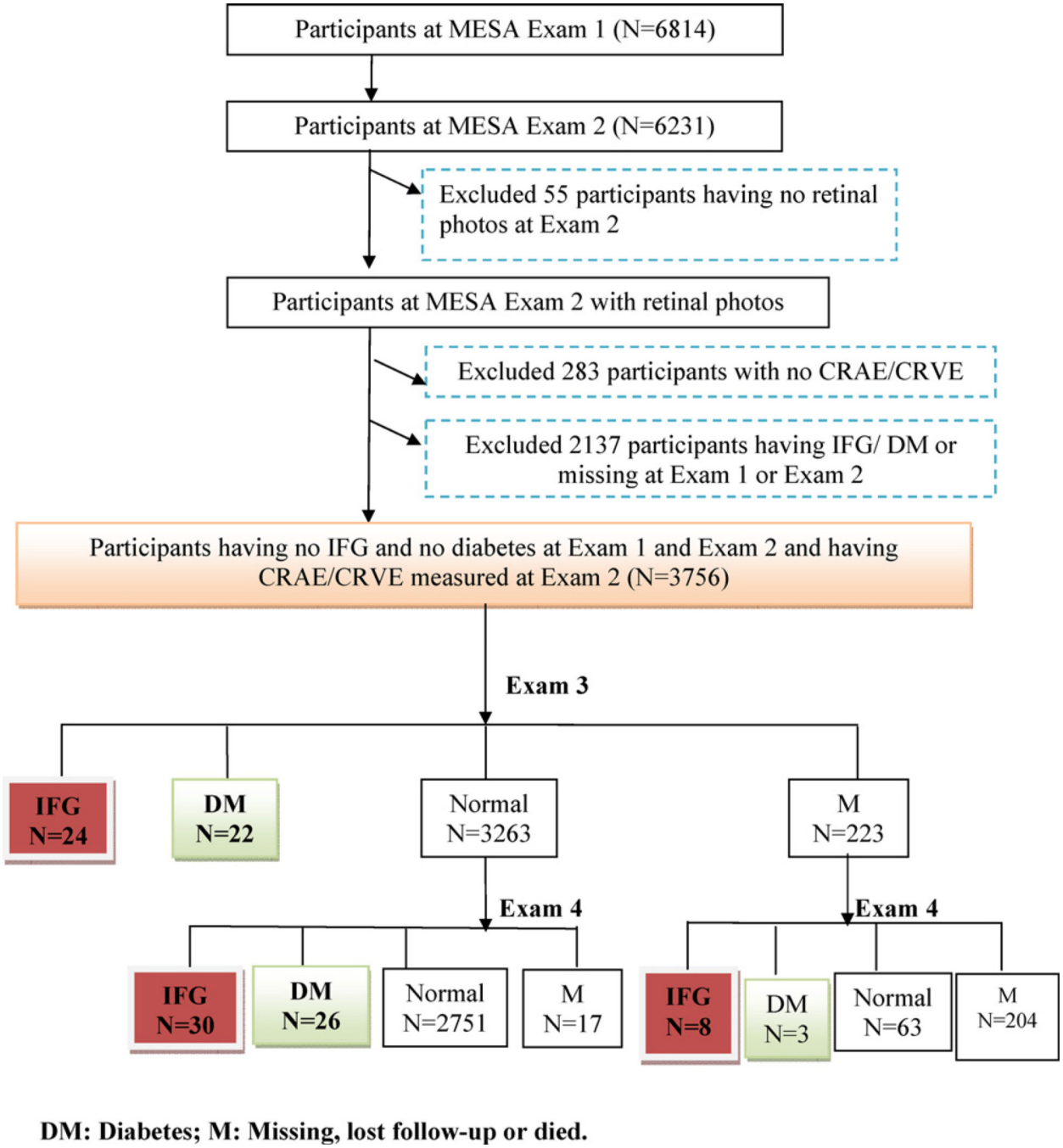

Fig. 2.
Participants included/excluded at each MESA follow-up examination in the incident IFG prediction model.

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Table 1

Participant characteristics at baseline (Exam 2), comparing those who did and did not develop diabetes at the end of Exam 4 (*N* = 4955).

	Participants who did not develop diabetes (*N* = 4712)		**Participants who developed diabetes (*N* = 243)**		***p* value**
	n	**%**	***n***	**%**	
Gender, Men	2221	47.1	112	46.1	0.75
Race					
White Caucasian	2059	43.7	67	27.6	<0.001
African American	1167	24.7	81	33.3	
Hispanics	936	19.9	67	27.6	
Chinese American	550	11.7	28	11.5	
Hypertension, present	1891	40.5	128	54.2	<0.001
Antihypertensive treatment	1616	35.9	121	52.2	<0.001
Lipid-lowering medication	881	19.6	54	23.3	0.16
Fasting glucose status at Exam 2					
Normal	3907	82.9	82	33.7	<0.001
IFG	805	17.1	161	66.3	
Family history of diabetes	606	12.9	57	23.6	<0.001
Smoking status					
Never smoked	2331	49.7	119	49.2	0.96
Ex smoker	1804	38.5	93	38.4	
Current	554	11.8	30	12.4	
	Median	p25, p75	Median	p25, p75	
Age, years	62	54, 70	61	54, 69	0.27
Systolic blood pressure, mmHg	119	108, 136	124	114, 138	0.0002
Diastolic blood pressure, mmHg	71	64, 77	72	66, 78	0.023
Waist circumference (cm)	95.4	86.5, 104.2	103.0	94.3, 115.2	<0.001
Waist hip ratio (unit)	0.93	0.87, 0.98	0.96	0.91, 0.99	<0.001
Fasting plasma glucose, mg/dL	90	85, 97	107	95, 115	<0.001
Serum insulin (μmol/L)	4.9	3.4, 7.6	8.0	5.6, 12.3	<0.001
Haemoglobin A1c (%)	5.4	5.2, 5.7	5.9	5.5, 6.3	<0.001

	Participants who did not develop diabetes (*N* = 4712)		Participants who developed diabetes (*N* = 243)		*p* value
	n	**%**	***n***	**%**	
Total cholesterol, mg/dL	191	169, 215	187	166, 212	0.14
HDL cholesterol, mg/dL	50	42, 61	45	40, 53	<0.001
Triglycerides, mg/dL	108	77, 155	123	90, 174	<0.001
Physical activity (total intentional exercise (Q9–15) MET-min/wk)	825	105, 1920	630	0, 1575	0.04
HOMA_IR	1.05	0.70, 1.69	1.98	1.34, 3.05	<0.001
Urinary creatinine (mg/dl)	113	67, 164	124	73, 181	0.014
Urinary albumin excretion	0.60	0.30, 1.10	0.80	0.40, 1.80	<0.001
Urinary albumin creatinine ratio (mg/g)	113	67, 164	124	73, 181	0.014
Retinal arteriolar calibre (CRAE)	144.1	134.9, 152.8	146.3	137.4, 155.2	0.009
Retinal venular calibre (CRVE)	212.7	198.6, 227.1	219.0	207.2, 232.5	<0.001

Data shown as medians or proportions at 25th and 75th percentiles (p25 and p75).

Table 1.1

Participant characteristics at baseline (Exam 2), comparing those who did and did not develop IFG at the end of Exam 4 (N = 3756).[a]

	Participants who did not develop IFG (N = 3140)		Participants who developed IFG (N = 565)		p value
	n	**%**	***n***	**%**	
Gender, Men	1374	43.8	284	50.3	0.004
Race					
White Caucasian	1459	46.5	223	39.5	<0.001
African American	751	23.9	137	24.3	
Hispanics	566	18.0	152	26.9	
Chinese American	364	11.6	53	9.4	
Hypertension, present	1115	35.8	255	45.6	<0.001
Antihypertensive treatment	937	31.2	219	40.3	<0.001
Lipid-lowering medication	514	17.1	129	2378	<0.001
Family history of diabetes	402	13.1	81	14.3	0.31
Smoking status					
Never smoked	1605	51.3	272	48.2	0.29
Ex smoker	1151	36.8	227	40.3	
Current	371	11.9	65	11.5	
	Median	p25, p75	Median	p25, p75	
Age, years	61.0	53.0, 70.0	62.0	55.0, 70.0	0.16
Systolic blood pressure, mmHg	117.5	107.0, 134.5	122.0	111.5, 136.5	<0.001
Diastolic blood pressure, mmHg	69.5	63.0, 76.0	71.2	64.7, 78.0	0.003
BMI (cm)	26.4	23.7, 29.7	28.2	25.6, 31.6	<0.001
Fasting plasma glucose, mg/dL	87.0	84.0, 92.0	93.0	89.0, 96.0	<0.001
Serum insulin (μmol/L)	4.6	3.2, 7.0	4.4	3.2, 6.9	<0.001
Haemoglobin A1c (%)	5.3	5.1, 5.6	5.5	5.3, 5.7	<0.001
Total cholesterol, mg/dL	192.0	170.0, 216.0	190.0	168.0, 214.0	0.09
HDL cholesterol, mg/dL	52.0	43.0, 63.0	49.0	42.0, 59.0	0.001
Triglycerides, mg/dL	104.0	75.0, 147.0	111.0	80.5, 159.0	0.006
Physical activity (total intentional exercise (Q9–15) MET-min/wk)	840.0	157.5, 1927.5	735.0	67.5, 1972.5	0.16

	Participants who did not develop IFG (*N* = 3140)		Participants who developed IFG (*N* = 565)		*p* value
	n	**%**	***n***	**%**	
HOMA_IR	0.90	0.62, 1.39	1.24	0.84, 1.85	<0.001
Urinary albumin	0.50	0.30, 1.0	0.6	0.3, 1.2	0.002
Urinary albumin creatinine ratio (mg/g)	4.6	3.1, 8.2	4.7	3.1, 8.3	0.15
Retinal arteriolar calibre (CRAE)	144.4	135.2, 153.1	143.7	134.0, 152.8	0.53
Retinal venular calibre (CRVE)	212.1	198.3, 225.5	212.2	199.7, 227.3	0.14

Data shown as medians or proportions at 25th and 75th percentiles (p25 and p75).

[a] 51 participants with unknown IFG status.

Table 2

Cox proportional hazard model of the association between retinal vascular calibre and incident diabetes.

	Person time (years)	Incident DM cases	Incident DM rate (%)	Model 1[a]: Adjusted HR		Model 2[b]: Adjusted HR		Model 3[c]: Adjusted HR	
				HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Retinal arteriolar calibre									
Tertile 1, ≤139 μm	5165	65	1.26	1		1		1	
Tertile 2, 139–150 μm	5104	72	1.41	0.97 (0.69, 1.37)	0.88	1.03 (0.72, 1.46)	0.84	1.03 (0.72, 1.46)	0.85
Tertile 3, ≥150 μm	4845	106	2.19	1.34 (0.96, 1.87)	0.08	1.60 (1.12, 2.29)	0.010	1.60 (1.12, 2.29)	0.011
Retinal venular calibre									
Tertile 1, ≤205 μm	5259	56	1.06	1		1		1	
Tertile 2, 205–223 μm	4054	79	1.55	1.22 (0.85, 1.76)	0.27	1.02 (0.71, 1.48)	0.90	1.02 (0.71, 1.48)	0.91
Tertile 3, ≥223 μm	4771	108	2.26	1.57 (1.09, 2.27)	0.016	1.0 (0.68, 1.46)	0.97	1.00 (0.68, 1.48)	0.91

[a] Model 1: Adjusted for age, gender, race, study centre and venular calibre (in models of arteriolar calibre) or arteriolar calibre (in models of venular calibre).

[b] Model 2: Adjusted for variables in Model 1 plus SBP, family history of diabetes, BMI, Hb_{A1C}, fasting insulin concentration, antihypertensive treatment, and urinary albumin excretion.

[c] Model 3: Adjusted for variables in Model 2 plus presence of any retinopathy.

Table 3

Cox proportional hazard model of the association between retinal vascular calibre and incident diabetes by ethnicity.[a]

	White Caucasians (*n* = 2126, incident DM: 1.02%)		Chinese Americans (*n* = 578, incident DM: 1.57%)		African-Americans (*n* = 1248, incident DM: 2.15%)		Hispanics (*n* = 1003, incident DM: 2.21%)	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Retinal arteriolar calibre								
Tertile 1, ≤139 μm	1		1		1		1	
Tertile 2, 139–150 μm	1.22 (0.60, 2.46)	0.59	1.06 (0.38, 3.00)	0.91	0.88 (0.48, 1.62)	0.70	0.87 (0.46, 1.66)	0.71
Tertile 3, ≥150 μm	2.78 (1.37, 5.62)	0.005	1.71 (0.49, 5.93)	0.40	1.26 (0.70, 2.28)	0.45	1.20 (0.64,2.24)	0.57
Retinal venular calibre								
Tertile 1, ≤205 μm	1		1		1		1	
Tertile 2, 205–223 μm	0.98 (0.52, 1.83)	0.91	0.65 (0.16, 2.65)	0.55	1.03 (0.48 2.23)	0.94	1.10 (0.59, 2.04)	0.75
Tertile 3, ≥223 μm	1.10 (0.55, 2.21)	0.78	1.83 (0.53, 6.29)	0.34	1.14 (0.54 2.44)	0.75	0.67 (0.34, 1.33)	0.26

[a] Adjusted for age, gender, venular calibre (in models of arteriolar calibre) or arteriolar calibre (in models of venular calibre), SBP, family history of diabetes, BMI, Hb_{A1C}, fasting insulin concentration, antihypertensive treatment, urinary albumin excretion and retinopathy.

Table 4

Summary of prospective studies examining the association between retinal vascular calibre and retinopathy signs with incident diabetes/IFG, and cross-sectional studies examining the association between retinal vascular calibre and diabetes.

	Study	Year	Sample size (*n*)	Ethnicity	Age (yrs)	Follow-up duration (yrs)	Measure of retinal calibre	Association	Odds ratio (95% CI)
Retinal vascular calibre and incident diabetes/IFG									
1.	ARIC [23]	2002	7993	Whites Blacks	49–73	0.7–5.5 Median: 3.5	Lowest AVR quartile	Higher risk of incident diabetes	1.71(1.13–2.57)
2.	BDES [25]	2005	3251	Whites	43–86	10	Lowest AVR quartile	Higher risk of incident diabetes	1.53 (1.03–2.27)
3.	Rotterdam [7]	2006	2307	Whites	≥55	5.2–9.5 Mean: 6.4	Per SD increase in CRVE	Higher risk of incident IFG	1.15 (0.99–1.34)
4.	Ausdiab [15]	2008	803	Whites	≥25	5	Lowest CRAE tertile	Higher risk of incident diabetes	2.21 (1.02–4.80)
5.	BMES [11]	2008	2123	Whites	≥49	10	Per SD increase in CRVE	Higher risk of incident IFG in persons <70 years	1.53 (1.11–2.12)
Retinopathy signs and incident diabetes									
1.	ARIC [25]	2006	7992	Whites Blacks	49–73	Median: 3.5	Any retinopathy	No association in total cohort	1.10 (0.7–1.9)
								Higher risk in those with diabetes family history	2.30 (1.0–5.3)
2.	BDES [12]	2006	3402	Whites	43–86	15	Any retinopathy	No association in total cohort	1.35 (0.90–2.03)
								Higher risk of incident diabetes in persons ≤65 years	1.80 (1.12–2.89)
3.	BMES [14]	2006	3653	Whites	≥49	5	Any retinopathy	No association with incident diabetes	NR
4.	Ausdiab [19]	2008	1192	Whites	≥25	5	Any retinopathy	Higher risk incident diabetes	2.66 (1.14–6.21)
Cross-sectional association of retinal vascular calibre and diabetes									
1.	Ausdiab [20]	2007	1998	Whites	≥25	–	Per SD increase in CRAE	Higher odds of diabetes compared to persons with NGT	1.34 (1.07–1.67)
2.	BMES [10]	2007	3654	Whites	≥49	–	Mean CRAE	Wider in diabetics than in nondiabetics	$p < 0.01$
3.	MESA [16]	2008	5976	Multi-ethnic[a]	45–84	–	Mean CRAE Mean CRVE	Wider in persons with diabetes compared to persons with NGT and IFG	$p = 0.0008$ for increasing trend
								Wider in persons with diabetes compared to persons with NGT and IFG	$p = 0.02$ for increasing trend
4.	SP2 [9]	2009	3404	Multi-ethnic Asians[b]	24–95	–	Mean CRAE Mean CRVE	Wider in persons with diabetes compared to persons with NGT and IFG	$p = 0.01$ for increasing trend

Retinal vascular calibre and incident diabetes/IFG								
Study	**Year**	**Sample size (*n*)**	**Ethnicity**	**Age (yrs)**	**Follow-up duration (yrs)**	**Measure of retinal calibre**	**Association**	**Odds ratio (95% CI)**
							Each mmol increase in FPG associated with a 0.51 μm increase in CRVE	$p = 0.006$ for increasing trend

CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; AVR, arteriole-to-venule ratio; NR, not reported; NGT, normal glucose tolerance; IFG, impaired fasting glucose; FPG, fasting plasma glucose; SP2, Singapore Prospective Study Program and Singapore Cardiovascular Cohort Study 2.

[a] White Caucasians, African-Americans, Chinese-Americans and Hispanics.

[b] Chinese, Malays and Indians.