Metabolic Burden and Disease and Mortality Risk Associated with Impaired Fasting Glucose in Elderly Adults

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OBJECTIVES: To examine whether impaired fasting glucose (IFG) represents an intermediary condition between normal fasting glucose and diabetes mellitus and, specifically, whether elderly adults with IFG have higher disease burden, cardiovascular risk, and systemic inflammation and higher 2-year mortality and incident disease.

DESIGN: Prospective observational study.

SETTING: Population-derived cohort.

PARTICIPANTS: Individuals with a mean age of 78.6 ± 4.7 (N = 945).

MEASUREMENTS: Disease was ascertained using a standardized questionnaire at baseline and 2 years. Fasting metabolic, inflammatory, and oxidative metabolism markers were measured. Disease prevalence, cardiovascular risk, and biochemical markers were compared to determine disease burden and metabolic disturbances in IFG. Adjusted odds ratios (ORs) for 2-year all-cause mortality and incident disease were determined.

RESULTS: IFG prevalence was 41%. Individuals with IFG had higher baseline rates of heart disease than those with normal fasting glucose (NFG), similar to that in individuals with diabetes mellitus. IFG was characterized by higher inflammatory markers and oxidative metabolism end products and was an intermediary between NFG and diabetes mellitus for triglycerides and malondialdehyde. Discriminant analysis showed that IFG was independently associated with stroke and higher triglycerides and oxidative stress. Two-year all-cause mortality was 3.9%. The 2-year adjusted ORs for all-cause mortality, incident cardiac disease, stroke, and cancer were similar between IFG and NFG, using both American Diabetes Association and World Health Organization IFG criteria. IFG did not predict secondary cardiac events, stroke, or cancer.

CONCLUSION: IFG was an intermediary condition for heart disease, inflammation, and oxidative stress in elderly adults but not for 2-year incident disease or all-cause mortality. Longer-term prospective studies are needed to clarify whether IFG in elderly adults portends greater morbidity and mortality. **J Am Geriatr Soc 63:1435–1442, 2015.**

Key words: geriatric; diabetes mellitus; impaired fasting glucose; glucose; inflammation; cardiovascular disease; hypertension; cholesterol; cancer; obesity

Type 2 diabetes mellitus is associated with an excess burden of disease and mortality due to macrovascular and microvascular complications[1,2] and higher cancer rates.[3] Identification of the prediabetic state of impaired fasting glucose (IFG) is fundamental to preventing progression to diabetes mellitus.[4,5] The effect of IFG on health and mortality in elderly adults is unclear, particularly whether IFG heralds poorer health outcomes.

International IFG definitions have changed over time. The World Health Organization (WHO) defines IFG as 6.1 to 6.9 mmol/L, as did the American Diabetes Association (ADA) until 2003, when the cutoffs broadened to 5.6 to 6.9 mmol/L.[6] Definition differences affect prevalence but also, potentially, disease associations.

Cross-sectional studies report greater cardiovascular disease prevalence using the WHO definition.[7] Prospective studies show conflicting results; both definitions are associated with increased 4-year coronary disease incidence in middle-aged women but not men.[8] Three-year mortality after acute myocardial infarction requiring invasive intervention was similar between IFG and normal glucose.[9]

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Most studies applying the wider definition have reported no association between IFG and incident cardiovascular disease, all-cause mortality, or cardiovascular mortality.[10–12] One exception found greater 3-year cardiovascular mortality in individuals with impaired glucose tolerance or IFG admitted to coronary units for diagnosed coronary artery disease,[13] but all-cause mortality did not differ.[13] All of these studies were in middle-aged individuals.

Few studies have reported the effect of IFG in elderly adults, in whom IFG prevalence ranges from 35% to 50%[14,15] and in whom interventions or medications may increase the complexity of geriatric regimens.

It was hypothesized that IFG in elderly adults would be found to be an intermediate state between NFG and diabetes mellitus and specifically that IFG in elderly adults would be associated with greater disease burden and metabolic derangements and higher rates of mortality and incident disease at 2 years.

RESEARCH DESIGN AND METHODS

Participants were drawn from the Sydney Memory and Aging Study, a population-based cohort of 1,037 community-dwelling mainly Caucasian adults aged 70 to 90 without dementia recruited from the compulsory electoral roll.[15,16] Exclusion criteria for study entry were insufficient English, advanced cancer, major neurological or psychiatric disorder, and dementia. The University of New South Wales research and ethics committee approved the study protocol. Participants provided written informed consent.

At baseline and 2 years, all participants visited a research center and completed a comprehensive, standardized medical history questionnaire under the supervision of trained nurses, who also made physical measures and collected fasting blood samples.[15]

Participants without fasting blood samples (n = 89) or with type 1 diabetes mellitus (n = 3) were excluded from analyses.

Glucose Status Classification

Type 2 diabetes mellitus was ascertained according to a previous diagnosis or a fasting glucose level of 7.0 mmol/L or greater (≥126 mg/dL).[6] In participants without diabetes mellitus, IFG was determined using ADA (IFG 5.6–6.9 mmol/L (100–125 mg/dL))[6] and WHO (IFG 6.0–6.1 mmol/L (110–125 mg/dL))[17] criteria.

Procedures and Laboratory Analyses

Weight and height were measured barefoot in light clothing, and body mass index (BMI; kg/m^2) was calculated. Rested seated blood pressure was measured. Hypertension was ascertained according to history, use of antihypertensive medications, or blood pressure readings of greater than 140 mmHg systolic or greater than 90 mmHg diastolic.

Venous blood was collected after an overnight 10-hour fast. Assays were glucose according to the oxygen rate method using an oxygen electrode and glucose oxidase solution (Beckman Coulter, Fullerton, CA); insulin according to radioimmunoassay (Linco, St. Charles, MO); insulin resistance estimated using the homeostasis model assessment (HOMA-IR);[18] total cholesterol, high-density lipoprotein cholesterol, triglycerides, and plasma urate using a timed-endpoint method (Beckman Coulter); low-density lipoprotein cholesterol according to the Friedewald equation; homocysteine, malondialdehyde, vitamin A, vitamin E, and beta-carotene according to reverse-phase high-performance liquid chromatography (BioRad Munich, Germany);[10,12,19] high-sensitivity C-reactive protein (CRP) according to near-infrared particle immunoassay rate (PAI)-1 (Beckman Coulter); interleukin (IL)-1ß, -6, -8, -10, and -12p70 and tumor necrosis factor alpha according to cytometric bead array (BD Biosciences, San Diego, CA);[16,19] vascular cell adhesion molecule-1, plasminogen activator inhibitor-1, and serum amyloid A according to sandwich enzyme-linked immunosorbent assay (Bender Medsystems GmbH, Vienna, Austria; United States Biological, Marblehead, MA).

Statistical Analyses

Nonnormally distributed variables were transformed (logarithmic: insulin, HOMA-IR, triglycerides, CRP, IL-8, IL-10, IL-12p70, SAA, PAI-1, vitamin B12, homocysteine, creatinine; normalized rank-order scores: soluble VCAM, malondialdehyde, IL-1ß, IL-6, tumor necrosis factor alpha).

Cross-Sectional Statistical Analyses

Demographic data were compared using the chi-square test. Disease frequencies were compared using binary logistic regression analysis, with age and sex as covariates, and odds ratios (ORs) were derived. Metabolic and inflammatory variables were compared using analysis of covariance, with age and sex included as covariates.

To examine the relationships between IFG and disease and metabolic variables, a binary logistic analysis was performed to investigate which variables discriminated between IFG and NFG, avoiding the use of multiple analyses (and hence loss of power through correction for type 1 error). A binary logistic regression analysis was performed with IFG and NFG as binary dependent variables and the variables found as potential statistical predictors. Because of the number of disease and metabolic variables, only those, when examined singly, with $P < .10$ were included in the multivariable logistic regression model.

Prospective Statistical Analyses

Binary logistic regression analysis was used to determine risk of 2-year mortality and incident disease in IFG, with NFG as the reference group. Analyses were repeated using the WHO classification and for diabetes mellitus (with NFG as the reference group). Age, sex, BMI, hypertension, and smoking were included as covariates. Analyses were performed using PASW Statistics (SPSS, Inc., Chicago, IL).

RESULTS

Nine hundred forty-five participants were included in the analyses. Diabetes mellitus prevalence was 16.6%, and

Table 1. Sydney Memory and Ageing Study: Baseline Sociodemographic Characteristics Categorized According to Glucose Status (American Diabetes Association Definition)

Characteristic	Normal Fasting Glucose, n = 403[a]	Impaired Fasting Glucose, n = 385[b]	Diabetes Mellitus, n = 157[c]	*P*-Value Overall
Age, mean ± SD	78.2 ± 4.9	78.7 ± 4.5	79.3 ± 4.9	NS
Aged >80, %	34	39	37	NS
Male, %	37	49[§]	62[#§]	<.001
Weight, kg, mean ± SD	69.0 ± 13.7	73.8 ± 14.6[§]	79.8 ± 1.1[#§]	<.001
Body mass index, kg/m^2, mean ± SD	26.1 ± 4.5	27.4 ± 4.8[§]	29.1 ± 5.0[#§]	<.001
Systolic blood pressure, mmHg, mean ± sd	143 ± 20	146 ± 20	145 ± 20	NS
Diastolic blood pressure, mmHg, mean ± SD	82 ± 11	83 ± 11	80 ± 11[#§]	.008
Alcohol intake ≥20 g/d, %	49	54	49%	NS
Ever smoked, %	51	54	64[#§]	.01
Lipid-lowering medications, %	42	55[§]	70[#§]	<.001
Highest education, %				
Primary	2	3	2	NS
High school	65	64	63	NS
Tertiary	33	33	36	NS
Living situation, %				
In community alone	50	45	37[§]	<.01
In community with other	48	54	59	NS
Hostel or retirement home	2	1.8	3	NS
Disability measures, %				
Walker	1.1	0.3	4[#]	<.01
Cane	7	8	13	NS
Motorized wheelchair	0.5	0	1	NS

[a]No past diagnosis of diabetes mellitus and fasting glucose level <5.6 mmol/L (<100mg/dL).
[b]No past diagnosis of diabetes mellitus and fasting glucose level 5.6–6.9 mmol/L (100mg – 125mg/dL).
[c]Diagnosed Type 2 diabetes mellitus or fasting glucose level ≥7.0 mmol/L (≥ 126mg/dL).
Comparisons across the three groups using analysis of variance for continuous variables and chi-square for categorical variables: *p*-value overall presented. $P < 0.05$: [#]compared IFG participants; §compared to NFG participants.
SD = standard deviation.

Table 2. Sydney Memory and Ageing Study: Burden of Disease According to Glucose Status

Disease	NFG, n = 403	IFG, n = 385	Diabetes Mellitus, n = 157	IFG Versus NFG	Diabetes Mellitus Versus IFG	Diabetes Mellitus Versus NFG
				Odds Ratio (*P*-Value)		
Hypertension	222 (55.5)	231 (59.8)	117 (74.5)	1.23 (.17)	2.21 (<.001)	2.66 (<.001)
Hyperlipidemia	228 (56.9)	239 (62.1)	106 (67.5)	1.30 (.08)	1.36 (.13)	1.73 (.007)
Cardiac disease	103 (25.8)	139 (36.0)	72 (45.9)	1.40 (.04)	1.35 (.13)	1.90 (.02)
Acute myocardial infarction	36 (9.0)	42 (11.0)	31 (19.7)	0.97 (.90)	1.76 (.03)	1.72 (.048)
Angina pectoris	34 (8.6)	45 (11.8)	37 (23.6)	1.25 (.35)	2.09 (.003)	2.60 (<.001)
Atrial fibrillation	24 (6.0)	26 (6.8)	13 (8.3)	1.07 (.83)	1.27 (.50)	1.27 (.52)
Cardiac arrhythmia	23 (5.4)	33 (8.6)	12 (7.6)	1.43 (.21)	0.84 (.62)	1.16 (.69)
Claudication	79 (19.9)	89 (23.4)	35 (22.3)	1.17 (.37)	0.91 (.69)	1.08 (.74)
Stroke	17 (4.3)	9 (2.3)	9 (5.7)	0.46 (.07)	2.26 (.09)	1.07 (.88)
Transient ischemic attack	24 (6.1)	18 (4.8)	17 (10.8)	0.80 (.49)	2.44 (.01)	2.03 (.04)
Any cancer	145 (36.2)	167 (43.3)	57 (36.3)	1.26 (.12)	0.70 (.07)	0.89 (.56)
Lung cancer	1 (0.2)	3 (0.8)	1 (0.6)	0.41 (.44)	1.51 (.72)	0.59 (.71)
Breast cancer	17 (4.2)	18 (4.7)	4 (2.5)	0.68 (.28)	1.40 (.55)	0.95 (.93)
Prostate cancer	8 (2.0)	9 (2.3)	3 (1.9)	0.99 (.97)	1.13 (.75)	1.12 (.78)
Colon cancer	3 (0.7)	5 (1.3)	3 (1.9)	0.83 (.70)	1.16 (.83)	1.00 (.99)
Depression	69 (17.5)	53 (14.4)	26 (16.5)	0.85 (.42)	1.35 (.26)	1.09 (.74)
Renal disease	1 (1.7)	6 (1.6)	9 (5.7)	0.69 (.51)	3.19 (.03)	2.18 (.14)

Normal fasting glucose (NFG): no past diagnosis of diabetes mellitus and fasting glucose level <5.6 mmol/L (<100mg/dL).
Impaired fasting glucose (IFG): no past diagnosis of diabetes mellitus and fasting glucose level 5.6–6.9 mmol/L (100mg – 125mg/dL).
Diabetes mellitus: diagnosed diabetes mellitus or fasting glucose level ≥7.0 mmol/L (≥ 126mg/dL).
Odds ratios were derived using binary logistic regression analysis, with age and sex as covariates.

Table 3. Sydney Memory and Ageing Study: Baseline Metabolic Data Categorized According to Glucose Status (American Diabetes Association Definition)

Biochemistry	NFG, n = 403	IFG, n = 385	Diabetes Mellitus, n = 157	IFG Versus NFG	Diabetes Mellitus Versus IFG	Diabetes Mellitus Versus NFG
	Mean ± Standard Deviation					
Glucose, mg/dL	92 ± 7	108 ± 5	139 ± 34	<.001	<.001	<.001
Insulin, uU/mL	13.5 ± 4.8	16.0 ± 6.6	20.5 ± 12.7	<.001	<.001	<.001
HOMA-IR	3.1 ± 1.1	4.3 ± 1.8	7.2 ± 5.3	<.001	<.001	<.001
Creatinine, mg/dL	1.0 ± 0.3	1.0 ± 0.3	1.1 ± 0.6	.97	.19	.17
Total cholesterol, mg/dL	189 ± 39	182 ± 35	162 ± 35	.36	<.001	<.001
HDL cholesterol, mg/dL	59 ± 19	55 ± 15	47 ± 12	.16	<.001	<.001
LDL cholesterol, mg/dL	112 ± 35	108 ± 31	89 ± 31	.39	<.001	<.001
Triglycerides, mg/dL	88 ± 44	98 ± 44	124 ± 0.8	.04	<.001	<.001
CRP, mg/L	2.8 ± 4.7	3.2 ± 5.7	3.4 ± 6.8	.10	.41	.06
Urate, mg/dL	5.4 ± 1.2	5.9 ± 1.3	6.1 ± 2.0	.002	.32	.001
Malondialdehyde, μmol/L	12.8 ± 2.5	13.4 ± 1.9	16.2 ± 5.8	<.001	<.001	<.001
Homocysteine, mg/L	1.5 ± 0.5	1.5 ± 0.5	1.7 ± 0.6	.91	.02	.03
Vitamin B12, pg/mL	298 ± 449	291 ± 484	248 ± 140	.72	.61	.45
Vitamin E, mg/dL	1.6 ± 0.5	1.4 ± 0.5	1.5 ± 0.6	.009	.75	.12
Vitamin A, μg/dL	86 ± 23	89 ± 23	92 ± 26	.06	.049	.08
Carotene, μg/dL	48 ± 37	37 ± 27	27 ± 27	.04	.06	.06
PAI-1, ng/mL	79.8 ± 29.9	83.7 ± 29.1	80.1 ± 30.0	.02	.24	.61
sVCAM-1, ng/mL	1,070 ± 862	1,088 ± 614	1,181 ± 551	.98	.04	.006
Serum amyloid A, μg/mL	48.5 ± 124.6	67.2 ± 245.7	58.4 ± 4.4	.13	.014	.001
TNF-α, pg/mL	3.2 ± 17.6	2.5 ± 3.1	2.4 ± 2.2	.35	.91	.27
IL-1β, pg/mL	3.4 ± 9.0	3.1 ± 3.4	3.1 ± 2.4	.31	.48	.13
IL-6, pg/mL	6.6 ± 10.5	6.3 ± 6.1	7.2 ± 6.5	.69	.15	.07
IL-8, pg/mL	18.6 ± 9.4	21.8 ± 17.3	19.8 ± 10.5	.02	.53	.10
IL-10, pg/mL	2.6 ± 2.3	2.6 ± 1.8	2.8 ± 1.4	.83	.82	.62
IL-12p70, pg/mL	3.0 ± 2.4	3.1 ± 2.6	3.4 ± 2.6	.06	.64	.02

Normal fasting glucose (NFG): no past diagnosis of diabetes mellitus and fasting glucose level <5.6 mmol/L (<100mg/dL).

Impaired fasting glucose (IFG): no past diagnosis of diabetes mellitus and fasting glucose level 5.6–6.9 mmol/L (100mg – 125mg/dL).

Diabetes mellitus: diagnosed diabetes mellitus or fasting glucose level ≥7.0 mmol/L (≥ 126mg/dL).

Comparisons were by analysis of covariance, with age and sex included as covariates, except for inflammatory markers, for which age, sex and lipid-lowering medications were included as covariates.

Data normalization: logarithmic transformation (insulin, insulin resistance estimated using the homeostasis model assessment (HOMA-IR), vitamin B12, high-density lipoprotein (HDL) cholesterol, C-reactive protein (CRP), urate, homocysteine, particle immunoassay rate (PAI-1), serum amyloid A, interleukin (IL)-8) or normalized rank-order scores (glucose, malondialdehyde, serum vascular cell adhesion molecule (sVCAM), tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, -6, -8, -10, -12p70).

SI unit conversion factors: multiply glucose mg/dL by 0.0555 for mmol/L; total, HDL, and low-density lipoprotein (LDL) cholesterol mg/dL by 0.0259 for mmol/L; triglycerides mg/dL by 0.0113 for mmol/L; creatinine mg/dL by 88.4 for mcmol/L; urate mg/dL 59.48 for mmol/L; homocysteine by 7.397 for μmol/L; vitamin B12 pg/mL by 0.738 for pmol/L; carotene μg/dL by 0.0186 for μmol/L; vitamin A μg/dL by 0.0349 for μmol/L; and vitamin E mg/dL by 23.22 for μmol/L.

IFG prevalence was 40.7% according to ADA criteria and 18% according to WHO criteria. Demographic details using ADA criteria are shown in Table 1. Mean age was 78.6 ± 4.7, with age similar for the different glucose categories. Sex distribution was similar between IFG and NFG, with a male preponderance in those with diabetes mellitus. Smoking rates were similar; lipid-lowering medication use was similar between NFG and IFG and higher in those with diabetes mellitus.

Baseline Disease Prevalence and Metabolic and Inflammatory Associations in IFG

IFG was associated with a higher cardiac disease rate than NFG and similar to that in individuals with diabetes mellitus (Table 2). Rates of other vascular diseases were similar between IFG and NFG and lower than in individuals with diabetes mellitus.

Baseline biochemical measures are shown in Table 3. IFG was associated with significantly higher triglyceride, insulin, urate, malondialdehyde, PAI-1, and IL-8 levels and lower vitamin E and ß-carotene levels than NFG. There was evidence of IFG being an intermediary between NFG and diabetes mellitus for triglycerides and malondialdehyde only.

Binary logistic regression analysis determined those variables that, in combination, best discriminated between IFG and NFG. Age, sex, stroke, cardiac disease, triglycerides, malondialdehyde, urate, IL-8, and PAI-1 were included in this multivariable model. Stroke (B = 1.24, OR = 3.54, $P = .04$), triglycerides (B = 0.78, OR = 2.17, $P = .002$), malondialdehyde (B = 0.49, OR = 1.64, $P < .001$), and vitamin E (B = –0.34, OR = 0.96, $P = .01$) were statistically significantly independently associated with IFG. The regression coefficients (B) are the weights in the linear combination of the above variables that, in combination, discriminated between IFG and NFG.

Table 4. Two-Year Mortality and Incident Disease in the Sydney and Memory Study in Participants with Impaired Fasting Glucose (IFG) and Type 2 Diabetes Mellitus

Mortality and Disease	NFG[a]	IFG	Diabetes Mellitus	IFG Versus NFG	DM Versus NFG
	n (%)			Odds Ratio (95% Confidence Interval)[a] *P*-Value	
Mortality	15 (3.7)	13 (3.4)	9 (5.7)	1.12 (0.53–2.43) .71	1.29 (0.51–3.24) .59
Past heart disease, n = 209	5 (5.3)	8 (6.3)		1.49 (0.43–4.73) .56	
Past cancer, n = 274	5 (3.8)	8 (5.0)		1.57 (0.42–5.86) .50	
Dropped out	33 (8.2)	23 (6.0)	14 (8.9)	0.98 (0.93–1.04) .49	1.09 (0.52–2.27) .37
Incident disease					
Heart disease	50 (14.1)	57 16.7)	27 20.5)	0.96 (0.62–1.48) .85	1.10 (0.62–1.94) .74
No baseline disease, n = 483	16 (6.3)	12 (5.3)		0.67 (0.29–1.53) .34	
Preexisting disease, n = 209	33 (37)	46 (39)		1.11 (0.61–2.00) .73	
Acute myocardial infarction	5 (1.4)	5 (1.5)	3 (2.3)	1.08 (0.30–3.94) .91	1.29 (0.28–5.93) .74
Angina pectoris	19 (5.4)	15 (4.4)	9 (6.8)	0.65 (0.31–1.36) .25	1.01 (0.42–2.45) .98
No baseline disease, n = 597	8 (2.3)	6 (1.8)		0.55 (0.17–1.74) .31	
Preexisting disease, n = 69	11 (3.2)	7 (2.1)		0.42 (0.12–1.45) .17	
Cerebrovascular accident or transient ischemic attack	8 (2.3)	12 (3.5)	7 (5.3)	1.49 (0.59–3.74) .39	2.71 (0.83–8.92) .09
All cancers	47 (13.2)	46 13.2)	18 (13.8)	0.96 (0.61–1.52) .87	1.00 (0.52–1.91) .99
No baseline cancer, n = 417	17 (7.6)	16 (8.3)		1.23 (0.58–2.62) .59	
Past cancer, n = 274	30 (24.4)	30 (19.9)		0.72 (0.39–1.31) .28	
Breast cancer, n = 436 women	4 (1.8)	1 (0.6)	0	0.55 (0.05–5.57) .61	
Prostate cancer, n = 384 men	4 (2.1)	10 (6.0)	3 (3.6)	2.16 (0.65–7.18) .20	1.88 (0.33–10.8) .48

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Diabetes mellitus: diagnosed diabetes mellitus or fasting glucose level ≥7.0 mmol/L (≥ 126mg/dL).
[a]Derived using binary logistic regression analysis including age, sex, body mass index, smoking, and hypertension as covariates.

Two-Year All-Cause Mortality and IFG

Table 4 shows raw mortality data and adjusted odds risk ratios at 2 years. At 2 years, 838 (88%) participants had attended follow-up, 37 (3.9%) had died, and 70 (7.4%) had dropped out; dropout rates were similar between the groups. At follow-up, glucose status representation was 16% (n = 134) diabetes mellitus, 41.5% (n = 349) IFG according to ADA criteria, and 18.5% (n = 155) IFG according to WHO criteria.

All comparisons of incident risk in IFG were made against NFG. Applying ADA IFG criteria, all-cause mortality in IFG was similar to NFG. Adding past heart disease and cancer to the model did not alter results (OR = 1.14, 95% confidence interval (CI) = 0.51–2.82, *P* = .54).

Whether prior heart disease or cancer was associated with greater 2-year all-cause mortality in individuals with IFG was examined and found not to be greater in those with baseline heart disease or baseline cancer.

Applying the WHO criteria, mortality was 3.1% (n = 23) for NFG and 2.9% (n = 5) for IFG, with dropout rates of 7.6% (n = 47) for NFG and 5.9% (n = 10) for IFG. Risk of 2-year all-cause mortality in individuals with IFG was not greater than in those with NFG (1.29, 95% CI = 0.45–3.46, *P* = .66).

Two-Year Incident Cardiovascular Disease and Stroke and IFG

Table 4 shows raw data and adjusted odds ratios for incident cardiovascular disease and stroke at 2 years. There were 107 incident heart disease events. According to the ADA criteria, incident heart disease risk in individuals with IFG was not greater than in those with NFG. Subgroup analyses examined whether IFG was associated with greater risk of incident heart disease in participants with and without preexisting heart disease. In participants without baseline heart disease, IFG was not associated with greater risk of a primary heart disease event. Similarly, in participants with preexisting heart disease, IFG was not associated with any greater risk of a subsequent heart disease event.

Incident 2-year risk of acute myocardial infarction or angina pectoris was not greater in individuals with IFG. There were insufficient cases to allow subgroup analyses for acute myocardial infarction. Subgroup analyses examined whether IFG was associated with greater risk of incident angina pectoris episodes in participants with and without prior angina pectoris. IFG was not associated with any greater risk of a primary or subsequent angina pectoris event in those with or without baseline angina pectoris.

In participants with NFG or IFG, there had been six incident cerebrovascular accidents (CVAs) and 21 transient ischemic attacks (TIA) at 2 years that were pooled into a combined CVA/TIA variable. The risk of an incident CVA/TIA was not greater in individuals with IFG.

Incident disease analyses in individuals with IFG were repeated applying the WHO IFG criteria, with results similar to those found using the ADA criteria (data not shown).

Two-Year Incident Cancer and IFG

Table 4 shows raw data and adjusted odds ratios for incident cancer at 2 years. Using ADA criteria, incident cancer at 2 years occurred in 13.5% (n = 47) of individuals with

NFG and 13.3% (n = 46) of those with IFG. IFG was not associated with greater risk of incident cancer. Subgroup analyses examined whether IFG was associated with greater 2-year cancer risk in participants with a past cancer diagnosis than in those without. IFG was not associated with greater risk of a primary or subsequent cancer diagnosis.

Sex-specific analyses were used to examine whether there were any associations between IFG and high risk of breast or prostate cancer. No greater risk was found in participants with IFG than in those with NFG.

Applying the WHO IFG criteria, the 2-year adjusted OR for all incident cancer in participants with IFG was similar to that in participants with NFG (0.83, 95% CI = 0.47–1.45, $P = .51$).

Diabetes Mellitus, Mortality, and Incident Disease

Data on mortality and incident disease in participants with diabetes mellitus at baseline are shown in Table 4. Participants with diabetes mellitus had higher 2-year all-cause mortality than those with NFG, although the all-cause mortality OR was not significantly greater after adjusting for covariates.

Diabetes mellitus was associated with higher overall rates of incident heart disease, CVA/TIA, and prostate cancer, but again the adjusted ORs were not greater. A nonsignificant trend was observed for a higher OR for diabetes mellitus and the combined CVA/TIA endpoint ($P = .09$).

DISCUSSION

This study examined whether IFG in an elderly community-dwelling cohort represented an intermediate state between NFG and diabetes mellitus. There was evidence that IFG was associated with a higher rate of cardiac disease at baseline but not any greater risk of mortality or incident vascular disease or cancer at 2 years. Furthermore, IFG was not associated with greater risk of a secondary vascular or cancer event. The results were consistent using the ADA and WHO definitions.

This study also found that IFG was characterized by higher levels of inflammation, oxidative metabolism, and thrombosis biomarkers, with lower circulating levels of the antioxidant vitamin E. Logistic regression analyses found that higher malondialdehyde and lower vitamin E levels mostly strongly discriminated the state of IFG from that of NFG. These results suggest that compensatory metabolic alterations exist in IFG.

This study adds to the literature on IFG prevalence, disease associations, and outcomes in elderly adults. IFG is common in elderly adults; understanding its relevance and effect is important in clinical decision-making, particularly because complex treatment regimens already exist. This short-term study found no strong evidence to support the extrapolation of the clinical relevance of IFG and disease outcomes from middle-aged to elderly adults.

The published evidence of detrimental health outcomes in individuals with IFG is restricted to studies of predominantly cardiovascular outcomes in middle-aged cohorts.[7,8,13,20,21] In the elderly cohort examined in the current study, although IFG was associated with higher baseline prevalence of heart disease, heart disease was not among the variables that best differentiated IFG from NFG. Furthermore, the 2-year incident cardiovascular disease risk was not greater in individuals with IFG than in those with NFG, concurring with one prior study in elderly adults.[22]

Type 2 diabetes mellitus is associated with greater risk of some cancers.[3] Few studies have reported associations between IFG and cancer risk. In this elderly cohort, no cross-sectional or longitudinal associations were found between IFG and cancer. The short follow-up or survivor or selection bias may explain this, because active or progressive malignancy was a study exclusion criterion. IFG was not associated with greater subsequent cancer risk in cancer survivors.

Why might IFG affect the health of middle-aged individuals differently from that of elderly adults? The metabolic disturbances associated with IFG in midlife may have a different or more-rapid trajectory. IFG may also evolve differently between the ages, perhaps with distinct mechanisms of beta-cell dysfunction. In midlife, IFG may develop as a consequence of earlier onset or prolonged obesity with greater nutrient overload exposure or genetic beta-cell susceptibility. Obesity-induced insulin resistance or hyperinsulinism or early onset of hyperglycemia (a duration-exposure effect) may thus drive the associations between midlife hyperglycemia and disease By contrast, these factors may influence IFG in elderly adults less and represent age-related beta-cell decline, as described previously.[23] Mild and late-onset dysglycemia may also indicate less lifetime exposure to the adverse metabolic milieu of obesity and systemic inflammation, with potentially less contribution to disease pathogenesis.

This study also identified lower serum levels of carotene and vitamin E in individuals with IFG, consistent with systemic antioxidant depletion, probably because of greater turnover in oxidative metabolism pathways, as indicated by higher urate and malondialdehyde levels. It is possible that these perturbations reflect metabolic stress as a consequence of excess fuel burden in aging cells.

Strengths of this study include extensive historical, clinical, and biochemical evaluation of a large, community-dwelling, elderly cohort. There was comprehensive assessment of inflammatory and other biomarkers. Further strengths were the low dropout rate and the 2-year evaluation for all-cause mortality data and incident disease. A number of covariates were evaluated, including education, smoking, and measures of functional independence.

Study limitations include possible selection bias with survivor effects, because progressive malignancy was an exclusion criterion. A diabetes mellitus survivor effect is likely and explains why the expected higher mortality in diabetes mellitus was absent, despite diabetes mellitus prevalence being in agreement with age-specific national reports.[24] It is possible that only healthier people with diabetes mellitus were included in the study, given study eligibility criteria that actively excluded individuals with dementia or those in assisted accommodation. Furthermore, a significant proportion of people with diabetes mellitus and poorer health may have already died as a consequence of diabetes mellitus–related morbidities. The 2-

year observation period was short, despite the advanced age of many participants. Longer-duration follow-up of the cohort is proceeding. Exclusion of progressive malignancy may have reduced the sensitivity of incident cancer analyses.

Fasting glucose, diabetes mellitus history, and antidiabetic medication use were used to ascertain glucose status. Oral glucose tolerance testing was not performed and glycosylated hemoglobin levels were not measured. This may have misclassified some participants with unrecognized diabetes mellitus as having NFG or IFG. The study could not examine for adverse health associations with impaired glucose tolerance or high postprandial glucose. In diabetes mellitus, postprandial glucose excursions are associated with inflammation, oxidative metabolism, endothelial dysfunction,[25] and a prothrombotic state.[26] Despite this limitation, the current study found that IFG was also characterized by high markers of inflammation and oxidative metabolism, as well as a prothrombotic tendency.

The potential for dose-exposure effects could not be determined. As more longitudinal data are collected in this cohort, such analyses will become possible. The cohort was predominantly Caucasian, which prevents data extrapolation to other groups.

In conclusion, although individuals with IFG in this elderly cohort were characterized by low-grade systemic inflammation and oxidative stress, they did not have greater 2-year mortality or 2-year incidence of major cardiovascular disease or cancer. Longer-term prospective data are required to determine whether IFG detection identifies elderly adults at risk of incident disease or if the accompanying metabolic and inflammatory alterations are a signal of future adverse health outcomes.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Samaras receives royalties from a book about diabetes mellitus for health professionals (*Fast Facts Diabetes*, Health Press Limited, Abingdon, Oxfordshire, UK). Baune is a member of advisory boards or has given presentations for AstraZeneca, Lundbeck, Pfizer, Servier, and Wyeth. Brodaty has received honoraria, has been a sponsored speaker, is on an advisory board, has been or is an investigator with regards to dementia and Alzheimer's disease for Pfizer, Novartis, Janssen, Lundbeck, Lilly, Sanofi, Servier, Merck, Baxter, and Wyeth. Sachdev has received honoraria for seminar presentations on neurocognitive disorders.

Author Contributions: All authors were involved in the design of the study and contributed to drafts of this manuscript. Samaras: study concept, data analysis and interpretation, writing the report. Crawford Lutgers: statistical analyses, writing and revising the report. Samaras, Baune, Lux: laboratory assays. Campbell, Baune, Lux, Brodaty, Trollor, Sachdev: critical evaluation of analytical output, revising the report. Katherine Samaras, Helen L. Lutgers, John Crawford, Henry Brodaty, Julian N. Trollor, and Perminder Sachdev had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

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