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Age, Gene/Environment Susceptibility–Reykjavik Study: Multidisciplinary Applied Phenomics

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In anticipation of the sequencing of the human genome and description of the human proteome, the Age, Gene/Environment Susceptibility–Reykjavik Study (AGES–Reykjavik) was initiated in 2002. AGES–Reykjavik was designed to examine risk factors, including genetic susceptibility and gene/environment interaction, in relation to disease and disability in old age. The study is multidisciplinary, providing detailed phenotypes related to the cardiovascular, neurocognitive (including sensory), and musculoskeletal systems, and to body composition and metabolic regulation. Relevant quantitative traits, subclinical indicators of disease, and medical diagnoses are identified by using biomarkers, imaging, and other physiologic indicators. The AGES–Reykjavik sample is drawn from an established population-based cohort, the Reykjavik Study. This cohort of men and women born between 1907 and 1935 has been followed in Iceland since 1967 by the Icelandic Heart Association. The AGES–Reykjavik cohort, with cardiovascular risk factor assessments earlier in life and detailed late-life phenotypes of quantitative traits, will create a comprehensive study of aging nested in a relatively genetically homogeneous older population. This approach should facilitate identification of genetic factors that contribute to healthy aging as well as the chronic conditions common in old age.

aging; body composition; cardiovascular diseases; cognition; genetics, population; osteoporosis; phenotype

Abbreviation: AGES–Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik Study.

Aging is a complex process that reflects a person's social and biologic history. Aging may be accompanied by multiple pathologic conditions that increase the occurrence of disease, reduce cognitive and physical function, and impair quality of life. To better understand the determinants of aging, identify potential therapeutic interventions, and design

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effective prevention programs, a multidisciplinary approach to study well-defined older populations is needed. This approach also lends itself well to the study of genetics since the effects of genes often extend well beyond the single organ system to which a gene was thought to contribute. The rationale for establishing comprehensively evaluated phenotypes across organ systems was described by Freimer and Sabatti in what they term the ''The Human Phenome Project'' (1). The Age, Gene/Environment Susceptibility–Reykjavik Study (AGES–Reykjavik) was conceived and designed to provide an approach to study, among other risk factors, the genetic contribution to conditions of old age. This paper describes the rationale and design of AGES–Reykjavik and the measurements included in the study, and it provides select descriptive data on the first 2,300 participants.

MATERIALS AND METHODS

Study rationale

AGES–Reykjavik is based on three general hypotheses: first, that genetic variation contributes to disease occurring in old age; second, that selected diseases common in old age share genetic, behavioral, and environmental risk factors; and third, that better classification of phenotypes based on multiple streams of data, including midlife history and subclinical disease, will further the exploration of how these risk factors are associated with complex traits and diseases manifest late in life.

AGES–Reykjavik is an epidemiologic study focusing on four biologic systems: vascular, neurocognitive (including sensory), musculoskeletal, and body composition/metabolism. These four systems were chosen because similar risk factors contribute to physiologic changes and disease in these systems. For instance, inflammation is associated with atherosclerosis (2, 3), diabetes (4), obesity (5), smoking-related illnesses (6), dementia (7), osteoporosis (8), and macular degeneration (9).

AGES–Reykjavik originates from the Reykjavik Study, a cohort established in 1967 to prospectively study cardiovascular disease in Iceland. Combining midlife data from the Reykjavik Study and old-age data from AGES–Reykjavik allows a life course approach to better characterize phenotypes. This combination of data can be used to identify patterns of risk factors and evaluate whether these patterns have remained stable or changed with age. For instance, previous studies demonstrate convincingly that risk factors such as blood pressure, weight, and cholesterol measured in late life are influenced by prevalent old-age morbidities and no longer reflect the exposures that initiated these pathologies (10, 11). Furthermore, midlife data are unbiased with regard to health history and are more accurate than retrospective recall.

Apart from improved phenotypic description, the availability of the midlife data allows for a complete assessment of nonresponse, particularly how death and refusals might contribute to bias. This assessment will be enhanced by additional information from hospital records, a national mortality index with authentication of all death certificates, a Minimum Data Set for Nursing Home patients (12) and Minimum Data Set for Home-Care patients (13, 14), and archival information from birth records, all available for linkage with the cohort.

To define quantitative traits as well as subclinical and clinical disease, AGES–Reykjavik includes extensive state-of-the-art imaging techniques, biochemical measurements, and diagnostic evaluations. These measures should provide insights into preclinical disease states, identify patterns of concomitant traits, and increase our ability to understand prognostic indicators underlying pathophysiologic changes. Imaging techniques yield standardized information on morphometry of organs and tissues in vivo. Use of imaging in epidemiologic studies has been an effective way to understand subclinical disease, particularly in the fields of osteoporosis (15), atherosclerosis (16), brain structure (17), and body composition (18). Because the imaging protocols used in AGES–Reykjavik are similar to protocols in other studies (19, 20), data can directly be compared with these studies. This multimeasurement strategy of phenotypic definition offers important advantages, and it has been successfully used elsewhere (21).

Some characteristics of Iceland and the Icelandic population should enhance the power to examine genetic and gene-environment interactions that modulate expression of genes in old age. The Icelandic population is relatively genetically homogeneous (22), which reduces the problem of population stratification. Thus, a greater proportion of persons at the phenotypic extremes may share the same genetic susceptibility. Genealogic databases in Iceland allow identification of relationships in the cohort. The relative isolation and hardship due to deadly infectious epidemics, few major roads, and foreign rule, coupled with volcanic soil and a cold-climate, lead to restricted diet and high physical activity levels, until the mid-20th century. Nonetheless, Iceland has had high literacy rates and, across the last century, relatively low neonatal mortality. Lastly, Iceland is freer of air and water pollution than many other countries because most electrical energy is generated by a geothermal process (23), minimizing several environmental factors affecting health.

Study design: the Reykjavik Study and AGES–Reykjavik protocols

The Reykjavik Study originally comprised a random sample of 30,795 men and women born in 1907–1935 and living in Reykjavik in 1967 (24–33). The study sample was divided into six groups (B, C, A, D, E, and F) by birth year and birth date within month (table 1). Each group was invited to participate in specific stages of the study. The B group was designated for longitudinal follow-up and was examined in all stages. The F group was designated a control group and was not included in examinations until 1991. Men and women were examined in separate years for more efficient clinic operation. Table 1 shows the number from each group sampled at each stage and the number examined in each stage. Since a standard examination was performed in each stage (refer to tables 2 and 3 for measures), longitudinal and cross-sectional data could be used to study secular and individual changes over the 30-year follow-up

TABLE 1. Cohort recruitment and examination schedule for participants in the Reykjavik Study (1967–1996)* and AGES–Reykjavik† (2002–2006) through February 2004

	Dates of examination	Gender	No. of participants in each subcohort						No. of participants examined in each stage
			B	C	A	D	E	F	
Total Reykjavik Study sample ($n = 30,795$)		Men	2,954	2,743	2,756	2,283	2,106	2,081	
		Women	3,101	2,990	2,936	2,429	2,191	2,225	
Stage of the Reykjavik Study									
I	1967–1968	Men	2,203						2,203
	1968–1969	Women	2,371						2,371
II	1970–1971	Men	2,072	1,985					4,057
	1971–1972	Women	2,049	2,134					4,183
III	1974–1976	Men	1,916	1,785	1,859				5,560
	1977–1979	Women	1,014	955	1,931				3,900
IV	1979–1981	Men	1,801			1,443			3,244
	1981–1984	Women	1,968			1,619			3,587
V	1985–1987	Men	1,477				1,115		2,592
	1987–1991	Women	1,765				1,266		3,028
VI	1991–1994	Men	664					169	833
	1994–1996	Women	943					267	1,210
AGES–Reykjavik‡	2002–2004	Men	344	320	305	2	5	0	976
	2002–2004	Women	467	414	426	7	10	0	1,324

* The Reykjavik Study cohort was randomized into six groups or subcohorts (B, C, A, D, E, and F) based on birth dates within month. The Reykjavik Study examinations were conducted in six stages (as listed in the first column), during which different subcohort groups were invited to participate. The total number of invited persons is shown in the first two rows for each subcohort. The data that follow refer to the number of participants examined at each stage and from each subcohort. The B group was designated for longitudinal follow-up and was examined at each stage. Men and women were examined separately at each stage to optimize examination clinic logistics.

† AGES–Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik Study.

‡ The values represent the number of persons from each of the Reykjavik Study subcohorts recruited among the first 2,300 participants to enter AGES–Reykjavik. When AGES–Reykjavik began, 4,800 men and 6.749 women from the Reykjavik Study were alive (as of March 2002).

period. The stage VI examination (1991–1996) focused on persons aged 70 years or older from the F and B groups. It included the core examination components, plus measures of cognitive and physical function, social support, and other topics particularly relevant to aging. Surveillance for vital events and cardiovascular disease events has been continual in the cohort since 1967. Some of the major published research findings from the Reykjavik Study are summarized in table 4.

AGES–Reykjavik examinations began in 2002. At that time, 11,549 previously examined Reykjavik Study cohort members were still alive. From these persons, recruitment order was randomly assigned within the six Reykjavik Study groups. First, the A, B, and C groups were sampled, since the largest amount of past examination data was available for these persons. Then the rest of the formerly examined participants (D and E groups) were sampled. AGES–Reykjavik was not sampled within gender to preserve the fact that the Reykjavik Study was initiated with a random sample of the population of Reykjavik in these birth cohorts. The AGES–Reykjavik examinations concluded in February 2006, with a total sample size of 5,764 survivors of the Reykjavik Study cohort (42 percent are male). The single-wave AGES–Reykjavik examination was completed in three clinic visits, with a participant's full examination finished within a 4- to 6-week time window.

Phenotypic data in AGES–Reykjavik are collected by using standardized protocols (table 3). The first clinic visit includes a blood draw, blood pressure measurement, electrocardiography, anthropometry, and measures of different domains of physical and cognitive function. The questionnaire, based on the original Reykjavik Study questions, includes health history, lifestyle practices, a medication survey, and a food history including early-life diet and social aspects of daily life (table 2). Serum, plasma, salivary swabs, and urine are obtained for metabolic, hormonal, and inflammatory markers. White blood cells for DNA are obtained, processed, and stored. Chemical measurements are carried out in the laboratory of the Icelandic Heart Association with independent external standards. Additional white blood cells have been saved for transformation for more than half the cohort.

The second examination day includes imaging protocols using magnetic resonance imaging, computed tomography, and ultrasound instrumentation (table 3). The third examination includes vision screening, assessment of intraocular pressure, digital retinal photographs through dilated pupils, a hearing test, a dementia assessment (if indicated), and

TABLE 2. The Reykjavik Study and AGES-Reykjavik* questionnaire components

Component	Reykjavik Study (1967–1991)	Reykjavik Study for participants aged >70 years (1991–1996)	AGES–Reykjavik (2002–2006)	AGES–Reykjavik follow-up (2007–2011)
Proxy contact information			X	X
General health status and hospitalizations	X	X	X	X
Medical history				
Heart and arteries: general diagnosis, surgical procedures, chest pain history	X	X	X	X
Diabetes: general diagnosis, medications, diet	X	X	X	X
Lung disease	X	X	X	X
Hypertension: general diagnosis, medications	X	X	X	X
High cholesterol			X	X
Falls and broken bones		X	X	X
Arthritis: type, location, related impairment	X	X	X	X
Migraines: symptoms	X	X	X	
Stroke or transient ischemic attack: general diagnosis, symptoms		X	X	X
Parkinsonism symptoms		X	X	
Restless leg syndrome symptoms			X	
Other diseases	X	X	X	
Cancer	X	X	X	X
Hearing problems and ear diseases: occupational exposure, degree of impairment		X	X	
Vision problems: cataracts, glaucoma, macular degeneration		X	X	
Dentition: periodontal disease, dentures			X	
Prostate disease (men)		X	X	X
Reproductive history (women): pregnancies, menopause, medications		X	X	
Weight history			X	X
Sleeping habits		X	X	
Urinary incontinence		X	X	
Anxiety		X	X	
Geriatric Depression Scale		X	X	X
Depression history and medications		X	X	X
Subjective memory problems		X	X	X
Social activity and contacts		X	X	X
Coping and perceived stress		X		
Cognitively stimulating leisure activities		X	X	X
Functional limitations: stairs, 500-m walk, activities of daily living, instrumental activities of daily living, use of assistive devices		X	X	X
Family medical history	X	X	X	
Education and language studied	X	X	X	
Occupational history	X	X	X	
Wealth indicators	X	X		
Residence location in youth and midlife	X	X	X	
Diet history: youth, midlife, current (old age)			X	
Smoking and tobacco use history	X	X	X	
Alcohol consumption		X	X	
Physical activity: winter, summer, youth, midlife	X	X	X	X

* AGES–Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik Study.

TABLE 3. The Reykjavik Study and AGES-Reykjavik* examination components†

Measurement	Reykjavik Study (1967–1991)	Reykjavik Study for participants aged >70 years (1991–1996)	AGES–Reykjavik (2002–2006)	AGES–Reykjavik follow-up (2007–2011)
Vascular				
Pulse, blood pressure	X	X	X	X
Electrocardiogram: heart rate, rhythm, ischemia, silent myocardial infarction (exercise test of subgroup in the Reykjavik Study)	X	X	X	X
Heart rate variability (measured during cognitive and physical function assessment for stress response)			$n = 1,023$	
Ultrasonography of carotid artery: intimal-medial thickness, plaque count, carotid distensibility			X	
Computed tomography of vascular calcium: coronary calcium, calcium volumes for aortic arch and descending aorta			X	X
Digitized retinal photograph: arterial damage, drusen, retinal exudates			X	
Echocardiography: left ventricular thickness, wall motion, valve structure/function			$n = 900$	
Arterial tonometry: pulse wave velocity			$n = 900$	X
Cardiac MRI* with gadolinium enhancement: MRI-defined MI,* cardiac output, wall motion			$n = 1,000$	
Lipids (laboratory): total, HDL*, and LDL* cholesterol; triglycerides	X	X	X	X
Renal function (laboratory): creatinine, microalbuminuria	X	X	X	X
Neurocognitive				
Neuropsychological testing: memory, speed of processing, working memory		X	X	X
Mood: depression symptoms, anxiety		X	X	X
History of depression: depression diagnosis			X	X
MRI of the brain: atrophy/ventricular size, infarct size and location, white matter lesion load and location, voxel-based morphometry			X	X
Dementia evaluation: dementia diagnosis and subtype adjudication by clinical consensus			X	X
Visual acuity and functional vision			X	
Audiometry evaluation			X	
Musculoskeletal				
Computed tomography of L1/L2 (1-mm slices): integral and trabecular bone quality, structural properties			X	X
Computed tomography of hip (1-mm slices): integral, cortical, and trabecular bone quality of total and regional femur, structural properties			X	X
Hand photographs for osteoarthritis assessment: phalangeal abnormalities			X	

Table continues

the exit interview with a physician or nurse. The clinic, laboratory, and imaging suite are all housed in the same building. For those unable or unwilling to come to the clinic, a home examination has been available but was used sparingly.

Dementia case ascertainment is a three-step process. The Mini-Mental State Examination (34) and the Digit Symbol Substitution Test (35) are administered to all participants. Persons who are screen positive based on a combination of these tests are administered a second, more diagnostic test battery, and a subset of them are selected for a neurologic examination. Proxies for this latter group are interviewed about medical history and social, cognitive, and daily functioning relevant

TABLE 3. Continued

Measurement	Reykjavik Study (1967–1991)	Reykjavik Study for participants aged >70 years (1991–1996)	AGES–Reykjavik (2002–2006)	AGES–Reykjavik follow-up (2007–2011)
Obesity/sarcopenia and metabolism				
Anthropometric measurements: height, weight, waist circumference	X	X	X	X
Bioelectrical impedance: total body fat and nonfat lean			X	X
Isometric dynamometry: quadriceps strength, hand grip strength			X	X
Computed tomography of L4/L5: sagittal diameter; waist and thigh circumference; visceral, subcutaneous, intermuscular, intramuscular fat areas; total and selected muscle areas			X	X
Computed tomography of thigh: subcutaneous, intermuscular, intramuscular fat areas; total and selected muscle areas			X	X
Integrative function				
Health questionnaire: behavioral risk factors, social support/network, medical history (refer to detailed information in table 2)	X	X	X	X
Motor and proprioceptive function: balance platform, performance measures (TUG,* 6-m walk)		X	X	X
EuroQol EQ-5D questionnaire of health outcomes (42)			X	X
Inflammation (laboratory): C-reactive protein, sedimentation rate	X	X	X	X
Stress response (laboratory): evening and morning salivary cortisol			X	
Glucose regulation (laboratory): fasting insulin, fasting glucose, hemoglobin A1C	X	X	X	X
Pulmonary function: spirometry	X	X	$n = 3{,}000$	
Medications inventory: prescriptions, over-the-counter		X	X	X
Image archive: MRI, computed tomography, ultrasound, retinal photographs			X	X
Biorespository: serum, plasma, urine, cells	X	X	X	X

* AGES–Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik Study; MRI, magnetic resonance imaging; MI, myocardial infarction; HDL, high density lipoprotein; LDL, low density lipoprotein; TUG, timed up and go test.

† The *n* entries refer to the number of participants for whom that measurement was obtained.

to the diagnosis. A consensus diagnosis based on international guidelines is made by a panel that includes a geriatrician, neurologist, neuropsychologist, and neuroradiologist. Screening for depression is done at the first clinic visit, with follow-up testing for screen positives with the Mini-International Neuropsychiatric Interview, which gives more detailed diagnostic information about psychiatric morbidity (36).

The image acquisition and reading protocols were designed in conjunction with expert consultants. Image acquisition is performed by a team of radiographers trained and certified in each of the protocols. This group, augmented by trained lay readers, also analyzes all images except the retinal photographs, which are read by an independent reading center. Scans are first reviewed by a radiologist for major clinical abnormalities. Image analysis is generally semiautomated. All information, including images, are deidentified prior to transfer into the permanent study database.

Phenotypic data will be combined with supplemental data on clinical outcomes. Sources of supplemental data include registries of vital status, cardiovascular disease and procedures, and fractures; hospital records with *International Classification of Diseases*, Ninth Revision, and *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision codes; the Minimum Data Set for Nursing Home patients (12); and the Minimum Data Set for Home-Care patients (13, 14). Registries are based on medical record data using predetermined algorithmic criteria.

Standardized quality control protocols have been established for the clinical and laboratory measures, image acquisition, and image analysis. For all image modalities, a 5–10 percent random sample is reread by consulting experts. In addition, a standard set of scans for each core measure is reread over the year by the image analysis team to monitor drift in the readings. For the laboratory, all analyses are

TABLE 4. Selected findings from the Reykjavik Study

First author, year (reference no.)	Summary of findings
Sigurdsson, 1995 (24); Jónsdóttir, 1998 (25)	Unrecognized MI*
	Risk factors and prognosis were similar for recognized and unrecognized MI.
	Risk of recurrent MI following an unrecognized MI was similar for men and women.
	Unrecognized MI is as common in women as in men.
Andresdottir, 2002 (26)	Family history
	Family history of MI determined from questionnaire is an independent risk factor for MI that cannot be explained by the conventional risk factors.
Andresdottir, 2003 (27); Danesh, 2004 (28); Saevarsdottir, 2005 (29)	Inflammation
	Erythrocyte sedimentation rate is an independent risk factor for MI.
	C-reactive protein is an independent risk factor for MI but does not add markedly to the conventional risk factors in the prediction of MI.
	Mannan-binding lectin is predictive of MI in high-risk persons, such as diabetics or those with raised cholesterol levels.
Tulinius, 1997 (30); Jonsson, 2004, (31)	Smoking and cancer
	Smoking was the most commonly associated risk factor for development of neoplasms among the cardiovascular risk factors.
	Family history of lung cancer was shown to be an independent risk factor for lung cancer, even accounting for smoking.

* MI, myocardial infarction.

controlled with a set of daily internal quality control samples, and quality assurance samples are measured monthly in accordance with the organization External Quality Assurance in Laboratory Medicine in Sweden (EQUALIS) (37). Imaging machines are also monitored with daily, weekly, and monthly measures.

Genotyping will be carried out at both the Icelandic Heart Association and other laboratories. With high-throughput genotyping becoming more available, collaborations with other studies with similar phenotypic data are planned for initial gene discovery and for replication.

AGES–Reykjavik was approved by the National Bioethics Committee in Iceland that acts as the institutional review board for the Icelandic Heart Association (approval number VSN-00-063) and by the National Institute on Aging Intramural Institutional Review Board. A multistage consent is obtained for AGES–Reykjavik to cover participation, use of specimens and DNA, and access to administrative records. All requests to merge AGES–Reykjavik data with administrative, genealogic, hospital, or nationally maintained databases are reviewed by the Icelandic Data Protection Authority. Release of data for analysis is governed by rules created by these bodies to protect the privacy of Icelandic participants.

Starting in 2007, all surviving AGES–Reykjavik participants will be recruited for a second examination that is restricted to components central to testing hypotheses related to the four study areas and will show change over time. The planned measurements are shown in tables 2 and 3.

Statistical methods

Selected cardiovascular risk factors are compared for all Reykjavik Study participants eligible for AGES–Reykjavik, for the first 1,310 men and 1,933 women invited to participate in AGES–Reykjavik, and for the first 976 men and 1,324 women enrolled. Not described are the additional 3,464 participants enrolled in AGES–Reykjavik. Those eligible are compared with those invited, and nonresponding invited persons are compared with those enrolled. The following factors are compared: total cholesterol, triglycerides (log-transformed and then back-transformed), fasting glucose, systolic blood pressure, and body mass index (weight in kilograms divided by height in meters squared)) (25). In AGES–Reykjavik, lipids and glucose were assessed by using a Hitachi 912 clinical chemistry analyzer (Roche Diagnostics, Basel, Switzerland, 1999) with quality assessment standards comparable to those used in the Reykjavik Study.

All age-adjusted regression models were created separately for men and women by using the SAS PROC GENMOD procedure (38) (tables 5 and 6). Midlife data were adjusted to age = 50 years and AGES–Reykjavik data to age = 76 years. Age-adjusted linear regression was used to compare groups regarding continuously distributed data; logistic regression models were used to study smoking.

Among the first 2,300 enrolled participants, we compared measures of cardiovascular risk factors from midlife with

TABLE 5. Midlife values (adjusted to age 50 years) for selected disease risk factors in eligible, invited, and the first 976 male AGES–Reykjavik† enrollees

Selected risk factors	Eligible from among the Reykjavik Study cohort members ($n = 4,800$)		Invited to participate in AGES–Reykjavik ($n = 1,310$)		Nonresponders to AGES–Reykjavik ($n = 334$)		AGES–Reykjavik enrollees ($n = 976$)	
	Mean	95% CI†	Mean	95% CI	Mean	95% CI	Mean	95% CI
Total cholesterol (mmo1/liter)	6.32	6.29, 6.35	6.39*	6.33, 6.45	6.34	6.22, 6.46	6.4	6.34, 6.47
Triglycerides (mmo1/liter)	1.15	1.13, 1.17	1.11*	1.08, 1.13	1.16	1.11, 1.23	1.08**	1.05, 1.11
Fasting glucose (mmol/liter)	4.48	4.46, 4.50	4.47	4.44, 4.50	4.52	4.46, 4.58	4.45†	4.41, 4.48
Systolic blood pressure (mmHg)	136.4	135.8, 137.0	137.6*	136.6, 138.6	142.5	140.2, 144.9	135.6***	134.5, 136.7
Body mass index(kg/m^2)	25.7	25.6, 25.8	25.5*	25.3, 25.7	25.7	25.3, 26.0	25.4	25.2, 25.6
Smoking (%)	50.2	48.7, 51.7	52.1	49.3, 54.8	55.1	49.6, 60.6	51	47.8, 54.2

* $p < 0.05$ between midlife data for invited and eligible Reykjavik Study cohort members; ** $p < 0.05$ between midlife data for nonresponders and AGES–Reykjavik enrollees; *** $p < 0.01$ between midlife data for nonresponders and AGES–Reykjavik enrollees.
† AGES–Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik Study; CI, confidence interval.

their current measurements (table 7). Repeated-measures generalized estimation models were used, with age at entry and time between visits as covariates.

To illustrate the power of obtaining detailed measures on several biologic systems, we identified a key measurement from each of the four focus areas of the study and assessed their joint prevalence in the first 2,300 of the total 5,764 persons enrolled in the cohort. We examined trabecular bone mass, performance on two cognitive tests, fasting insulin, and arterial calcification (table 8). Trabecular bone mass was measured from the quantitative computed tomography scans of the femoral neck and spine (39). For insulin, cognition, and trabecular bone density, scores below gender-specific medians were considered low (table 8). Higher arterial calcification, imaged with helical computed tomography and calculated as an Agatston score (40), was defined as calcification in four of the five sites examined, including the ascending and descending aorta, the combined coronary arteries, and the thoracic and abdominal aorta. For persons missing data on one site, if calcium was present at all other sites analyzed, they were considered at high risk. For this illustrative example, we selected cutpoints that would provide overlap between traits; if other cutpoints had been defined, the overlap proportions would have changed.

RESULTS

Total eligible Reykjavik Study cohort versus randomly selected AGES–Reykjavik invitees

As of March 2002, 11,549 Reykjavik Study participants were alive, including 4,800 men (41.6 percent of those alive). From this group, a random sample of 1,310 men was invited to the AGES–Reykjavik clinic through February 2004. We first compared mean midlife values of cardiovascular risk factors for the 4,800 living, eligible men with those for the 1,310 invited to the AGES–Reykjavik examination (table 5). Those invited had higher total cholesterol, lower triglycerides, higher systolic blood pressure, and lower body mass index in midlife than the average midlife values for the pool of men alive. A similar analysis for women also showed differences between women who participated in the Reykjavik Study and those

TABLE 6. Midlife values (adjusted to age 50 years) for selected disease risk factors in eligible, invited, and the first 1,324 female AGES–Reykjavik† enrollees

Selected risk factors	Eligible from among the Reykjavik Study cohort members ($n = 6,749$)		Invited to participate in AGES–Reykjavik ($n = 1,933$)		Nonresponders to AGES–Reykjavik ($n = 609$)		AGES–Reykjavik enrollees ($n = 1,324$)	
	Mean	95% CI†	Mean	95% CI	Mean	95% CI	Mean	95% CI
Total cholesterol (mmo1/liter)	6.32	6.28, 6.35	6.28	6.23, 6.33	6.36	6.25, 6.46	6.26	6.20, 6.32
Triglycerides (mmo1/liter)	0.91	0.90, 0.93	0.88*	0.87, 0.90	0.89	0.86, 0.93	0.88	0.86, 0.90
Fasting glucose (mmol/liter)	4.29	4.27, 4.31	4.25*	4.23, 4.28	4.29	4.22, 4.36	4.23***	4.21, 4.27
Systolic blood pressure (mmHg)	128.1	127.6, 128.7	128.5	127.6, 129.4	133.1	131.2, 135.0	126.7****	125.7, 127.8
Body mass index (kg/m^2)	24.9	24.8, 25.0	24.7**	24.5, 24.8	24.7	24.3, 25.1	24.6	24.4, 24.9
Smoking (%)	36.3	35.0, 37.7	32.3*	30.1, 34.5	36.3	32.1, 40.8	30.8‡	28.4, 33.5

* $p < 0.01$ between midlife data for eligible Reykjavik Study cohort members and those invited; ** $p < 0.05$ between midlife data for eligible Reykjavik Study cohort members and those invited; *** $p < 0.05$ between midlife data for nonresponders and AGES–Reykjavik enrollees; **** $p < 0.0001$ between midlife data for nonresponders and AGES–Reykjavik enrollees.
† AGES–Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik Study; CI, confidence interval.

TABLE 7. Comparison of midlife Reykjavik Study and late-life AGES–Reykjavik* measurements of selected cardiovascular risk factors

Gender	Variable	Reykjavik Study age- adjusted value	AGES–Reykjavik age- adjusted value	Pearson correlation between values	10-year change	26-year change	*p* for correlation
Men ($n = 976$)	Total cholesterol (mmol/liter)	6.40	5.27	0.26	−0.41	−1.06	<0.01
	Triglycerides (mmol/liter)†	1.08	1.07	0.44	−0.01	−0.02	0.24
	Serum glucose (mmol/liter)‡	5.52	5.97	0.24	0.17	0.43	<0.01
	Systolic blood pressure (mmHg)	135.6	141.9	0.20	2.4	6.2	<0.01
	Body mass index (kg/m^2)	25.4	26.7	0.66	0.4	1.16	<0.01
Women ($n = 1,324$)	Total cholesterol (mmol/liter)	6.26	6.11	0.27	−0.08	−0.21	<0.01
	Triglycerides (mmol/liter)†	0.88	1.15	0.46	0.10	0.26	<0.01
	Serum glucose (mmol/liter)‡	5.32	5.70	0.30	0.17	0.43	<0.01
	Systolic blood pressure (mmHg)	126.7	141.4	0.31	5.5	14.4	<0.01
	Body mass index (kg/m^2)	24.6	27.1	0.69	0.9	2.4	<0.01

* AGES–Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik Study.
† Analysis on log-transformed values. The 10-year change was back-transformed.
‡ The Reykjavik Study value is for blood sugar. Conversion to serum glucose: $1.47 + 0.91 \times$ (Reykjavik Study blood sugar).

invited to participate in AGES–Reykjavik, but the factors that differed were not the same as those for men. Of the 6,749 living, eligible women, a random sample of 1,933 women was invited to attend the AGES–Reykjavik examination. Compared with all living Reykjavik Study women, the 1,933 invited had significantly lower triglycerides, lower fasting blood glucose, and lower body mass index and included a smaller percentage of smokers (table 6).

TABLE 8. Cutpoints used to examine overlap in the four focus areas for AGES–Reykjavik* participants

	Men ($n = 976$)		Women ($n = 1,324$)	
	Median or %	25th and 75th percentiles	Median or %	25th and 75th percentiles
Trabecular bone mineral density (mg/cm^3)				
Lumbar spine	0.09	0.07, 0.11	0.07	0.05, 0.09
Femoral neck	0.03	0.01, 0.06	0.01	−0.01, 0.04
Glucose regulation				
Serum insulin (mU/liter)	8.52	5.67, 12.72	7.85	5.31, 11.20
Cognition				
Mini-Mental State Examination score	27	25, 29	28	26, 29
Digit Symbol Substitution Test score	28	21, 36	29	21, 36
Calcification of arteries (% with any calcification)†				
Coronary arteries	96.40		81.60	
Ascending aorta	98.70		98.60	
Descending aorta	84.50		84.80	
Abdominal aorta L1/L2	96.30		96.50	
Abdominal aorta L4/L5	91.80		89.50	
In four of five aortic areas and coronary arteries	91.10		85.10	

* AGES–Reykjavik, Age, Gene/Environment Susceptibility–Reykjavik Study.
† Agatston scores and calcification measurements in the abdominal aorta at vertebral levels L1/L2 and L4/L5 with values greater than zero indicate that some degree of calcification is present. The values reflect the percentage of the cohort with any calcification present at the noted location.

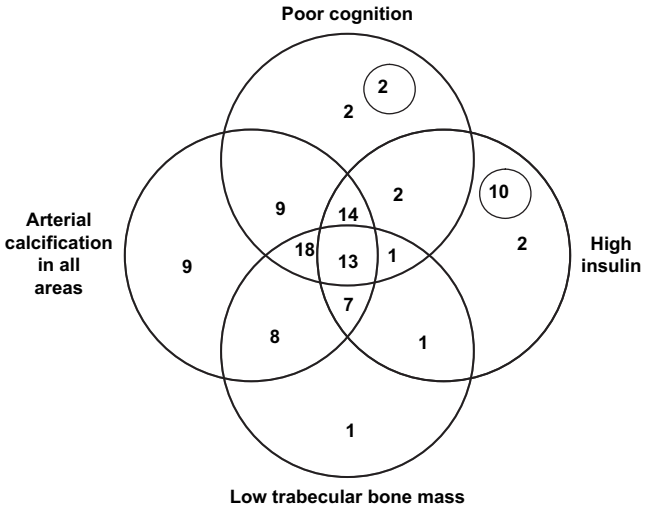

FIGURE 1. Independence and overlap of prevalent phenotypes in the Age, Gene/Environment Susceptibility–Reykjavik Study, Iceland, 2002–2004. Phenotypes are represented by the overlapping circles for the four traits of poor cognition, arterial calcification in all areas, high insulin, and low trabecular bone mass. The phenotypes are further defined in the Materials and Methods section of the text. Numbers in the circles represent the percentages of the cohort with each of these traits. Numbers in overlapping areas indicate the percentage of the cohort with more than one trait. Two percent of the cohort had none of the phenotypes, and only 13 percent shared all four traits. The number inside the small circle within the "poor cognition" phenotype represents the percentage of the cohort with both poor cognition and low trabecular bone mass. Similarly, the number inside the small circle within the "high insulin" phenotype represents the percentage of the cohort with both high insulin and arterial calcification in all areas.

Responders versus nonresponders through February 2004

Among the 1,310 men invited, 976 (response rate of 75 percent) agreed to participate in the study. Compared with those who refused, participants had significantly lower midlife triglycerides, fasting blood glucose, and systolic blood pressure (table 5). The percentage of men who smoked in midlife was similar in the two groups, as was midlife total cholesterol level and body mass index. Of the 1,933 women invited, 1,324 participated in the examination (response rate of 68 percent). Women who participated in AGES–Reykjavik had significantly lower midlife glucose and systolic blood pressure levels and were less likely than nonresponders to have been a smoker (table 6). Body mass index, total cholesterol, and triglycerides did not differ between these groups. For both men and women, nonresponse was greater among persons with a previously poor cardiovascular risk profile, particularly for systolic blood pressure and blood glucose.

Midlife versus late-life characteristics of the first 2,300 participants recruited for the AGES–Reykjavik Study

Among the first 2,300 participants, all measures differed significantly between midlife and late life, with the exception of triglyceride levels in men (table 7). Interestingly, other than body mass index, midlife and older-age measurements were only moderately correlated, with the lowest correlations for systolic blood pressure and fasting glucose. Body mass index, glucose, and systolic blood pressure all increased into old age, as did triglyceride levels in women; only total cholesterol levels decreased.

Joint prevalence of health measures

In this older population, overlap between measures representing the four focus areas of the study (trabecular bone mass, cognitive test performance, fasting insulin, and arterial calcification) was more common than the occurrence of a single characteristic (figure 1): the prevalence of each alone was less than 3 percent, except for arterial calcification, which was 9 percent. Forty percent of the participants had three of the four defined characteristics, with the most common combination being lower trabecular bone mass, more arterial calcification, and lower cognitive score (18 percent); the least common combination involved lower trabecular bone mass, poorer cognition, and higher insulin level (1 percent). Variation among these characteristics can be used to study successful aging, with few diseases, or to study the extreme of frailty, often accompanied by multiple health conditions.

DISCUSSION

A major goal of AGES–Reykjavik is intensive, quantitative trait identification, within and across biologic systems, for studying the genetic contribution to diseases of old age. Because of the in-depth characterization within and between multiple physiologic systems, this study should also create a valuable resource for a comprehensive study of aging.

Many system-specific studies of the contribution of genetics to complex disorders have been undertaken. To our knowledge, this is one of the few designed a priori to comprehensively phenotype a cohort for multiple diseases, where the target conditions were selected based on the potential of genetic factors that contribute either to the discrete disease state or to quantitative traits that might underlie these conditions. The comprehensive phenotyping in AGES–Reykjavik should allow for broader exploration of contributing genes and should be particularly valuable for analyzing markers of whole genome single nucleotide polymorphisms. The range of phenotypic characterization of the cohort, from clinically recognized conditions defined by criteria-based diagnoses to novel intermediate endophenotypes based on noninvasive technologies integrated with genetic, biochemical, physiologic, and performance-based measures of health and function, should provide a rich basis for newly proposed analytic approaches, such as reverse phenotyping (41).

As the world's population ages, a major challenge is to unravel the pathways to disease and disability in older persons. Iceland and other industrialized countries share the same major chronic diseases, with similar rates of cognitive and physical impairment. Focusing on this population will allow development of innovative approaches to studying how people reach old age and what factors enable older

persons to enjoy a healthy old age. Practically, studies such as this one, which require extensive long-term data, can be achieved only by leveraging longitudinal studies onto existing cohorts that have already accrued data, thereby facilitating a life-course approach to understanding the trajectories of disease and disability. Studies such as this one complement the ''organ-specific'' studies of health in old age and provide an opportunity for extending the findings in a context that can identify homologies between and among conditions that may better reveal factors that affect multiple conditions. From this perspective, measurements in the study were selected on the basis of well-designed population studies contemporary with AGES–Reykjavik, and collaborations with investigators outside of the study will continue to be sought to augment these measurements.

Studies such as AGES–Reykjavik that take advantage of existing data resources can also address methodological problems. The question of selective survival or selective participation often arises in studies of older populations, although it has been argued that the associations of risk factors within the survivors are unaffected by the bias. Because data from earlier life exist from the original study, it will be possible to model the effect that both survival and nonparticipation might have on the direction and strength of associations observed between risk factors and outcomes. This might be particularly important in estimating risks for older women, who tend to live longer but to be frailer and therefore have lower rates of study participation. Selective participation of healthier older persons in this cohort is reflected in at least two ways. First, the response rate for older women is lower than for older men because older women are frailer and more likely to be institutionalized. Second, the midlife profile of the nonresponders shows higher blood pressure and higher glucose, both major contributors to health in old age. Again, because the study was nested within the Reykjavik Study, these potential biases are known (unlike most studies of aging, where older persons are sampled de novo), and we hope to use the earlier data to model sensitivity of our results to these factors.

The design of the AGES–Reykjavik Study represents an integrative approach to methodological problems that may affect studies of genetics and studies of aging. As with many of the ongoing major cohort studies, it is hoped that this one will serve as the basis for ancillary studies that utilize the biologic specimens and the image database for studies consistent with the original consent obtained from the participants.

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