Published in final edited form as:

Res Aging. 2011 May 1; 33(3): 312–326. doi:10.1177/0164027511399105.

Age-Related Changes in Biomarkers: Longitudinal Data from a Population-Based Sample

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Abstract

Identifying how biological parameters change with age can provide insights into the physiological determinants of disease, and ultimately, death. Most prior studies of age-related change in biomarkers are based on cross-sectional data, small or selective samples, or a limited number of biomarkers. We use data from a nationally-representative longitudinal sample of 639 Taiwanese aged 54 and older in 2000 to assess changes over a six-year period in a wide range of biomarkers. Markers that increased most with age were glycosylated hemoglobin, interleukin-6, and norepinephrine. Markers that decreased most with age were diastolic blood pressure and creatinine clearance. For example, glycosylated hemoglobin increased by 8-13%, on average, over this six-year period. Several standard clinical risk factors exhibited little evidence of age-related change. Further research is needed to determine whether the observed variation between individuals in biomarker changes represents differences in underlying physiological function that are predictive of future health and survival.

Although chronological age is one of the strongest predictors of mortality and various types of morbidity, it undoubtedly serves as a proxy for physiological processes related to disease and survival. By determining how biological parameters change with age, we may obtain insights into the physiological determinants of disease, and ultimately, death. Previous research underscores the importance of understanding age-related changes in biomarkers: Many standard clinical risk factors are less predictive of old-age survival than of mortality in mid-life, perhaps because the cutoff points designating high risk of disease differ at the older ages.

Much of the documentation of age-related change in biological parameters may give a misleading picture of individual change over time because it is based on cross-sectional data. Some studies use longitudinal biomarker data, but most are limited by sampling constraints (small sample, clinical population, or convenience samples) or by the collection of only a small set of markers (e.g., blood pressure, lipids).

This study uses data from a nationally-representative longitudinal sample of older Taiwanese to assess changes over a six-year period in biomarkers pertaining to diverse physiological systems. We begin by reviewing prior evidence regarding the association between these biomarkers and age; highlight some of the problems associated with use of

cross-sectional data; and summarize existing longitudinal studies that have examined change in at least one of the following biomarkers: systolic blood pressure (SBP), diastolic blood pressure (DBP), total and HDL cholesterol, triglycerides, glycosylated hemoglobin (HbA_{1c}), body mass index (BMI), waist circumference, waist-hip ratio, creatinine clearance, albumin, leukocyte count (WBC), interleukin-6 (IL-6), and urinary measures of cortisol, epinephrine, norepinephrine, or dopamine. Then we investigate changes in these biomarkers within our Taiwan cohort over a six-year period and compare those results with previously-documented age patterns.

BIOMARKERS ASSOCIATED WITH AGE AMONG OLDER ADULTS

Previous studies—most of which rely on cross-sectional data—suggest that numerous biomarkers are associated with age among older adults. We review here the age patterns among older adults as indicated by the preponderance of available evidence, whether cross-sectional or longitudinal. Some biomarkers appear to decline with age: creatinine clearance (Boss and Seegmiller 1981; Lindeman, Tobin, and Shock 1985; Rowe et al. 1976) and albumin (Danesh et al. 1998; Gillum 2000). Others seem to increase with age: SBP (Burt et al. 1995; Landahl et al. 1986), triglycerides (Frishman et al. 1992; Schubert et al. 2006; Siervogel et al. 1998; Ueno et al. 2003), HbA_{1c} (Chiu, Martinez, and Chu 2005; Kilpatrick, Dominiczak, and Small 1996; Nuttall 1999; Yates and Laing 2002), waist circumference (Noppa et al. 1980; Shimokata et al. 1989; Zamboni et al. 2005), IL-6 (Bruunsgaard 2002; Crimmins et al. 2008; Roubenoff et al. 1998; Sparkman and Johnson 2008), and urinary norepinephrine (measured per g of creatinine) (Gerlo, Schoors, and Dupont 1991; Jenner et al. 1987).

A few biomarkers reveal a non-monotonic relationship with age, typically a reversal at the older ages of the pattern observed earlier in the life span. DBP increases with age but declines above age 60 (Burt et al. 1995; Landahl et al. 1986; Yashin et al. 2006). Similarly, total cholesterol increases up to middle age but declines at older ages (Bakx et al. 2000; Schubert et al. 2006; Siervogel et al. 1998; Weijenberg, Feskens, and Kromhout 1996; Wilson et al. 1994; Yashin et al. 2006). Most studies find no systematic age variation in HDL cholesterol (Schubert et al. 2006; Siervogel et al. 1998; Weijenberg, Feskens, and Kromhout 1996). Body weight tends to increase until around age 60-65, or later in women, and decline thereafter (Elia 2001; Lissner et al. 1994; Zamboni et al. 2005). Although height appears to decrease at older ages (Hughes et al. 2004; Noppa et al. 1980), BMI may follow an inverted-U-shaped age pattern if the decline in weight at the oldest ages more than compensates for any decrease in height. Such an age pattern has been observed in other studies (Elia 2001; Shimokata et al. 1989; Wilson et al. 1994; Yashin et al. 2006).

LIMITATIONS OF CROSS-SECTIONAL DATA FOR INFERRING AGE-RELATED CHANGE

Inferring individual-level change from cross-sectional data can be misleading because of selection biases and cohort effects. For example, if persons with a high level of a given biomarker are at greater mortality risk, then the average level of that biomarker may level off or even decline at the oldest ages because of selective mortality. Cross-sectional data also do not permit one to distinguish between age and cohort effects. For example, an inverse relationship between BMI and age may arise from an increasing prevalence of obesity among successively younger cohorts but may be incorrectly attributed to aging.

By following the same cohort of individuals as they age, longitudinal data permit researchers to avoid these problems. Estimates of age-related change in biomarker levels can be derived from within-individual changes over time, implicitly controlling for stable

characteristics that differ between individuals. Biases associated with selective mortality can be minimized by restricting the analysis to the population that survived to the end of observation. Admittedly, this restriction may exclude the most vulnerable population; there is no way to know how much biomarker levels might have changed over time if the decedents had instead survived. In addition, longitudinal analyses cannot distinguish between age and period effects. For example, increased use of medication over time could attenuate the level of change in certain biomarkers. Cross-sectional results may be biased by medication use as well; for example, if blood pressure increases with age, but individuals adopt medication in response, then effective treatment could mask the underlying age-related increase.

PRIOR LONGITUDINAL STUDIES OF CHANGES IN BIOMARKERS

Longitudinal studies that examine changes in biomarkers over time (as the individual ages) are much less common than cross-sectional studies. Appendix Table A-1 summarizes the longitudinal studies that examine changes in at least one of the biomarkers listed above. Most of these studies include only a small set of biomarkers. Many are based on small ($n < 500$) samples, while others rely on clinical or convenience samples. Only four of the datasets used in these studies comprise a representative sample of at least 500 individuals: Framingham (James et al. 2003; Wilson et al. 1994; Yashin et al. 2006); Göteborg (Landahl et al. 1986; Noppa et al. 1980); LASA (Schalk et al. 2006); and SENECA (Grunenberger et al. 1996). None of these samples is nationally representative.

METHODS

Data

The 2000 wave of the Social Environment and Biomarkers of Aging Study (SEBAS) comprised a nationally representative sample of Taiwanese aged 54 and older; older persons (71+) and urban residents were oversampled. In-home interviews were completed with 1497 respondents; 1023 of them also completed the physical examination. Exam participants did not differ significantly from nonparticipants in ways likely to introduce serious bias (Goldman et al. 2003). Six years later, a follow-up was conducted with those who completed the 2000 exam and survived to 2006: 757 completed the in-home interview and 639 participated in the physical examination. See the Appendix for more detailed information regarding response rates, sample attrition, and exam participation.

The physical examination followed a similar protocol in both waves. Several weeks after the household interview, participants collected a 12-hour overnight urine sample (7pm to 7am), fasted overnight, and visited a nearby hospital the following morning for a physical examination that included collection of a blood specimen and measurements of blood pressure, height, weight, waist and hip circumference. Compliance was high: in 2000, 96 percent fasted overnight and provided a urine specimen deemed suitable for analysis; the comparable figure was 88 percent in 2006.

Blood and urine specimens were analyzed at Union Clinical Laboratories (UCL) in Taipei. In addition to the routine standardization and calibration tests, triplicate sets of specimens were contributed by individuals outside the target sample ($n=9$ in 2000; $n=10$ in 2006): two sets were sent to UCL and the third set was sent to Quest Diagnostics in the US (San Juan Capistrano, CA). The results indicated high intra-lab reliability for duplicates sent to UCL (2000: ≥ 0.86 ; 2006: ≥ 0.83). With a few exceptions, inter-lab correlations between results from UCL and Quest Diagnostics exceeded 0.90 in both waves.

Biomarker Measures

DBP and SBP were calculated as the average of two seated readings (1-2 minutes apart) using a mercury sphygmomanometer at least 20 minutes after the respondent arrived at the hospital. Creatinine clearance was estimated using the Cockcroft-Gault Formula (Cockcroft and Gault 1976). Measurements of cortisol, epinephrine, norepinephrine, and dopamine were obtained from the overnight urine specimen, which provided integrated values of basal operating levels during a period when most participants were resting; values were standardized for diuresis by dividing by the level of urinary creatinine. See the Appendix for details regarding assay methods for blood and urine specimens.

Analytical Strategy

The analysis sample included 639 persons who participated in the 2000 and 2006 exams. All estimates and standard errors are calculated using the survey commands in Stata 10.1 (StataCorp 2007) in order to take into account the sampling design (i.e., stratification, clustering, sampling weights). We use probability weights that adjust for oversampling and for differential response rates by age, sex and other covariates.

We evaluated changes in biomarker levels (2000-2006), implicitly controlling for individual characteristics that remained stable over time. To reduce the possibility that a few extreme values could unduly influence the results, we trimmed outliers before computing the change; when the analyses were repeated using the untrimmed versions, the results were generally similar (see the Appendix for details).

For each sex, we regressed the change (2006 – 2000 value for a given individual) in each biomarker on age at baseline (in completed years) and age-squared (to allow for a non-linear pattern). We retained the quadratic term for age in the model for creatinine clearance among males, the only model in which the coefficient was significant at $p < 0.01$. Given the large number of statistical tests conducted in this study, we use this conservative p -value throughout our analyses. We also controlled for relevant medication use in models of blood pressure (anti-hypertensives), lipids (lipid-lowering medication), and HbA_{1c} (hypoglycemic agents)—see Table A-2 for details. Using the coefficients from these models, we calculated the predicted change over a six-year period for each biomarker when age at baseline equals 55, 65, and 75; that is, these estimates represent the expected changes as the respondent ages from 55 to 61, 65 to 71, and 75 to 81. We selected these particular ages in order to demonstrate how the change in biomarkers varies across an age range that includes most (85%) of our sample.

RESULTS

Table 1 shows the descriptive statistics for the biomarkers at both waves. The sample mean decreased significantly between 2000 and 2006 for some biomarkers (DBP, total cholesterol, HDL, triglycerides, height, hip circumference, creatinine clearance, albumin), but increased for others (HbA_{1c}, waist-hip ratio, IL-6, epinephrine, norepinephrine).

Using the coefficients from the regression models (Table A-2), we calculated the predicted change (over a six-year period) in a given biomarker for each sex when age at baseline is set at 55, 65, and 75. The predicted changes that differ significantly from zero are presented in Tables 2 and 3 in two ways: an absolute change and a percentage change. We divide the absolute change by the mean for that marker in 2000 to convert it into a percentage change in order to compare the relative magnitude across biomarkers (which vary in scale). For example, men aged 55 at baseline are estimated to exhibit a 6.5 mmHg (or 8%) decline in DBP by the end of the six-year interval (when they reach age 61). The coefficients from the regression models are provided in Appendix Table A-2.

Among the cardiovascular and metabolic markers, HbA_{1c} and DBP exhibited the biggest changes (in relative terms) over the six-year period (Table 2). HbA_{1c} rose 8-13% on average. Over the same period, DBP declined by 6-9 mmHg (8-11%) as the cohort aged six years. [These results refer to respondents who were not using anti-hypertensive medication. Among those using anti-hypertensive medication, the predicted decrease in DBP was greater (Table A-2).] Among women, there was little change in total cholesterol below age 75, but levels fell at the oldest ages. Despite no significant change in waist circumference, there was a small but significant increase in waist-hip ratio that stemmed from a decline in hip circumference, especially among older women. Compared with men and with younger women, the oldest women lost more weight over the six-year period; it may be that excess fat and weight loss were more concentrated on the hips, especially for women.

Among other biomarkers (Table 3), the biggest relative changes were observed in IL-6 and norepinephrine: as the cohort aged six years, IL-6 rose among older men and women, while norepinephrine increased among all groups. There were also large decreases in creatinine clearance at older ages.

Comparisons with Previously-Documented Age Patterns

In many cases (e.g., HDL, HbA_{1c}, creatinine clearance, IL-6, norepinephrine), our results are consistent with the previously-documented age pattern (see Appendix Table A-3). For two other biomarkers, our results are partly consistent with the previously-documented age patterns. Prior studies indicated that DBP and total cholesterol follow an inverted U-shaped pattern with age. We find a monotonic decline in DBP, possibly because we capture only the declining portion of the age pattern in our older sample. For total cholesterol, we see evidence of a decline among the oldest women.

Unlike previous studies that suggested age-related increases in SBP, waist circumference, and waist-hip ratio, we find little change in these markers. Increased use of anti-hypertensive medication (from 21% of our sample in 2000 to 36% in 2006) may have attenuated the underlying change in SBP.

BMI has been shown by others to decline at the oldest ages (Elia 2001; Shimokata et al. 1989; Wilson et al. 1994; Yashin et al. 2006), but we see little change in our sample. When we look at our data cross-sectionally (not shown), the results are more consistent with the previously-documented decline in BMI at older ages, but the apparent cross-sectional decline in BMI with age could be due, at least in part, to selective mortality or a cohort effect (i.e., increasing prevalence of obesity among younger cohorts).

DISCUSSION

Biomarkers that demonstrate a strong relationship with age could serve as early warning signs that can help predict subsequent illness and mortality, before any clinical manifestation of disease is evident. Several biomarkers exhibited substantial age-related change in our sample of older Taiwanese: DBP, HbA_{1c}, IL-6, and norepinephrine. The dramatic increase in HbA_{1c} may foreshadow a growing problem with diabetes. The age-related increase we observed in norepinephrine appears to be larger than estimates from earlier cross sectional studies (Gerlo, Schoors, and Dupont 1991; Jenner et al. 1987) and contrasts with the decline identified in a longitudinal study (Karlamangla et al. 2006). Further study is needed to determine the magnitude and direction of changes in norepinephrine at older ages and assess whether these changes represent an important indicator of impending health decline. In contrast, we observed little evidence of age-related change for several standard clinical risk factors (e.g., SBP, total/HDL cholesterol ratio, BMI, waist circumference, waist hip ratio).

Longitudinal analysis of changes in biomarkers provides important information that may be obscured in cross-sectional comparisons of different ages in the same time period. For example, we found an increase in HbA_{1c} as the respondents aged six years, but the cross-sectional data from either 2000 or 2006 indicated little association or a slight decline at the oldest ages (data not shown). As suggested by Crimmins et al. (2008), the lack of variation in HbA_{1c} by age could be a result of selective mortality of those with higher values. Indeed, we discovered that respondents with levels of HbA_{1c} greater than 7.0% in 2000 were much more likely to die by the end of 2006 (22%) than those with lower levels of HbA_{1c} (14%) (data not shown). Consequently, the cross-sectional association with age is likely to underestimate the age-related increase in HbA_{1c}.

Variation between individuals in biomarker changes is likely to reflect meaningful differences in underlying physiological function that are predictive of future health and survival. For example, Yashin et al. (2006) have demonstrated that individual-level trajectories of various biomarkers between ages 40 and 60 predict subsequent survival. Nonetheless, some of the variation may result from measurement error or short-term fluctuations in the biomarker level. An important test of the utility of information on changes in biomarker levels is their ability to predict subsequent health outcomes. The 2011 wave of TLISA will provide follow-up information about morbidity and mortality for these cohorts, which will allow us to investigate the relationship between the changes in biomarkers examined in the present study and health decline over the ensuing five-year period.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the Demography and Epidemiology Unit of the Behavioral and Social Research Program of the National Institute on Aging [R01AG16790, R01AG16661]; and the Eunice Kennedy Shriver National Institute of Child Health and Human Development [R24HD047879]. We are grateful to Dr. Min-Long Lai and Ms. Susana Ong at Union Clinical Laboratory in Taipei for their assistance with the laboratory assays. Furthermore, we appreciate the statistical advice provided by Germán Rodríguez at Princeton University.

REFERENCES

- Bakx JC, van den Hoogen HJ, Deurenberg P, van Doremalen J, van den Bosch WJ. Changes in Serum Total Cholesterol Levels Over 18 Years in a Cohort of Men and Women: The Nijmegen Cohort Study. *Preventive Medicine*. 2000; 30(2):138–145. [PubMed: 10656841]
- Boss GR, Seegmiller JE. Age-Related Physiological Changes and their Clinical Significance. *The Western Journal of Medicine*. 1981; 135(6):434–440. [PubMed: 7336713]
- Brunsgaard H. Effects of Tumor Necrosis Factor-Alpha and Interleukin-6 in Elderly Populations. *European Cytokine Network*. 2002; 13(4):389–391. [PubMed: 12517724]
- Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D. Prevalence of Hypertension in the US Adult Population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension*. 1995; 25(3):305–313. [PubMed: 7875754]
- Chiu KC, Martinez DS, Chu A. Comparison of the Relationship of Age and Beta Cell Function in Three Ethnic Groups. *Clinical Endocrinology*. 2005; 62(3):296–302. [PubMed: 15730410]
- Cockcroft DW, Gault MH. Prediction of Creatinine Clearance from Serum Creatinine. *Nephron*. 1976; 16(1):31–41. [PubMed: 1244564]
- Crimmins E, Vasunilashorn S, Kim JK, Alley D. Biomarkers Related to Aging in Human Populations. *Advances in Clinical Chemistry*. 2008; 46:161–216. [PubMed: 19004190]

- Danesh J, Collins R, Appleby P, Peto R. Association of Fibrinogen, C-Reactive Protein, Albumin, Or Leukocyte Count with Coronary Heart Disease: Meta-Analyses of Prospective Studies. *JAMA : The Journal of the American Medical Association*. 1998; 279(18):1477–1482. [PubMed: 9600484]
- Elia M. Obesity in the Elderly. *Obesity Research*. 2001; 9(Suppl 4):244S–248S. [PubMed: 11707549]
- Frishman WH, Ooi WL, Derman MP, Eder HA, Gidez LI, Ben-Zeev D, Zimetbaum P, Heiman M, Aronson M. Serum Lipids and Lipoproteins in Advanced Age. Intraindividual Changes. *Annals of Epidemiology*. 1992; 2(1-2):43–50. [PubMed: 1342263]
- Gerlo EA, Schoors DF, Dupont AG. Age- and Sex-Related Differences for the Urinary Excretion of Norepinephrine, Epinephrine, and Dopamine in Adults. *Clinical Chemistry*. 1991; 37(6):875–878. [PubMed: 2049852]
- Gillum RF. Assessment of Serum Albumin Concentration as a Risk Factor for Stroke and Coronary Disease in African Americans and Whites. *Journal of the National Medical Association*. 2000; 92(1):3–9. [PubMed: 10800280]
- Goldman N, Lin IF, Weinstein M, Lin YH. Evaluating the Quality of Self-Reports of Hypertension and Diabetes. *Journal of Clinical Epidemiology*. 2003; 56(2):148–154. [PubMed: 12654409]
- Grunenberger F, Lammi-Keefe CJ, Schlienger JL, Deslypere JP, Hautvast JG. Longitudinal Changes in Serum Lipids of Elderly Europeans. SENECA Investigators. *European Journal of Clinical Nutrition*. 1996; 50(Suppl 2):S25–31. [PubMed: 8841782]
- Hughes VA, Roubenoff R, Wood M, Frontera WR, Evans WJ, Singh M. A. Fiatarone. Anthropometric Assessment of 10-y Changes in Body Composition in the Elderly. *The American Journal of Clinical Nutrition*. 2004; 80(2):475–482. [PubMed: 15277173]
- James K, Weitzel LR, Engelman CD, Zerbe G, Norris JM, Framingham Heart Study. Genome Scan Linkage Results for Longitudinal Systolic Blood Pressure Phenotypes in Subjects from the Framingham Heart Study. *BMC Genetics*. 2003; 4(Suppl 1):S83. [PubMed: 14975151]
- Jenner DA, Harrison GA, Prior IA, Leonetti DL, Fujimoto WY. 24-H Catecholamine Excretion: Relationships with Age and Weight. *Clinica Chimica Acta; International Journal of Clinical Chemistry*. 1987; 164(1):17–25.
- Karlamangla AS, Singer BH, Seeman TE. Reduction in Allostatic Load in Older Adults is Associated with Lower all-Cause Mortality Risk: MacArthur Studies of Successful Aging. *Psychosomatic Medicine*. 2006; 68(3):500–507. [PubMed: 16738085]
- Kilpatrick ES, Dominiczak MH, Small M. The Effects of Ageing on Glycation and the Interpretation of Glycaemic Control in Type 2 Diabetes. *QJM : Monthly Journal of the Association of Physicians*. 1996; 89(4):307–312. [PubMed: 8733518]
- Kuzuya M, Ando F, Iguchi A, Shimokata H. Effect of Smoking Habit on Age-Related Changes in Serum Lipids: A Cross-Sectional and Longitudinal Analysis in a Large Japanese Cohort. *Atherosclerosis*. 2006; 185(1):183–190. [PubMed: 16051249]
- Landahl S, Bengtsson C, Sigurdsson JA, Svanborg A, Svardsudd K. Age-Related Changes in Blood Pressure. *Hypertension*. 1986; 8(11):1044–1049. [PubMed: 3770866]
- Lindeman RD, Tobin J, Shock NW. Longitudinal Studies on the Rate of Decline in Renal Function with Age. *Journal of the American Geriatrics Society*. 1985; 33(4):278–285. [PubMed: 3989190]
- Lissner L, Sjostrom L, Bengtsson C, Bouchard C, Larsson B. The Natural History of Obesity in an Obese Population and Associations with Metabolic Aberrations. *International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity*. 1994; 18(6):441–447. [PubMed: 8081436]
- Noppa H, Andersson M, Bengtsson C, Bruce A, Isaksson B. Longitudinal Studies of Anthropometric Data and Body Composition. the Population Study of Women in Gotenberg, Sweden. *The American Journal of Clinical Nutrition*. 1980; 33(1):155–162. [PubMed: 7355777]
- Nuttall FQ. Effect of Age on the Percentage of Hemoglobin A1c and the Percentage of Total Glycohemoglobin in Non-Diabetic Persons. *The Journal of Laboratory and Clinical Medicine*. 1999; 134(5):451–453. [PubMed: 10560937]
- Roubenoff R, Harris TB, Abad LW, Wilson PW, Dallal GE, Dinarello CA. Monocyte Cytokine Production in an Elderly Population: Effect of Age and Inflammation. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. 1998; 53(1):M20–6.

- Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW. The Effect of Age on Creatinine Clearance in Men: A Cross-Sectional and Longitudinal Study. *Journal of Gerontology*. 1976; 31(2):155–163. [PubMed: 1249404]
- Schalk BW, Visser M, Bremmer MA, Penninx BW, Bouter LM, Deeg DJ. Change of Serum Albumin and Risk of Cardiovascular Disease and all-Cause Mortality: Longitudinal Aging Study Amsterdam. *American Journal of Epidemiology*. 2006; 164(10):969–977. [PubMed: 16980573]
- Schubert CM, Rogers NL, Remsberg KE, Sun SS, Chumlea WC, Demerath EW, Czerwinski SA, Towne B, Siervogel RM. Lipids, Lipoproteins, Lifestyle, Adiposity and Fat-Free Mass during Middle Age: The Fels Longitudinal Study. *International Journal of Obesity*. 2006; 30(2):251–260. (2005). [PubMed: 16247511]
- Shimokata H, Andres R, Coon PJ, Elahi D, Muller DC, Tobin JD. Studies in the Distribution of Body Fat. II. Longitudinal Effects of Change in Weight. *International Journal of Obesity*. 1989; 13(4): 455–464. [PubMed: 2676875]
- Siervogel RM, Wisemandle W, Maynard LM, Guo SS, Roche AF, Chumlea WC, Towne B. Serial Changes in Body Composition Throughout Adulthood and their Relationships to Changes in Lipid and Lipoprotein Levels. the Fels Longitudinal Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1998; 18(11):1759–1764.
- Sparkman NL, Johnson RW. Neuroinflammation Associated with Aging Sensitizes the Brain to the Effects of Infection Or Stress. *Neuroimmunomodulation*. 2008; 15(4-6):323–330. [PubMed: 19047808]
- StataCorp.. *Stata Statistical Software: Release 10*. StataCorp LP; College Station, TX: 2007.
- Ueno LM, Yamashita Y, Moritani T, Nakamura E. Biomarkers of Aging in Women and the Rate of Longitudinal Changes. *Journal of Physiological Anthropology and Applied Human Science*. 2003; 22(1):37–46. [PubMed: 12672981]
- Weijenberg MP, Feskens EJ, Kromhout D. Age-Related Changes in Total and High-Density-Lipoprotein Cholesterol in Elderly Dutch Men. *American Journal of Public Health*. 1996; 86(6): 798–803. [PubMed: 8659652]
- Wilson PW, Anderson KM, Harris T, Kannel WB, Castelli WP. Determinants of Change in Total Cholesterol and HDL-C with Age: The Framingham Study. *Journal of Gerontology*. 1994; 49(6):M252–7. [PubMed: 7963277]
- Yashin AI, Akushevich IV, Arbeev KG, Akushevich L, Ukraintseva SV, Kulminski A. Insights on Aging and Exceptional Longevity from Longitudinal Data: Novel Findings from the Framingham Heart Study. *Age (Dordrecht, Netherlands)*. 2006; 28(4):363–374.
- Yates AP, Laing I. Age-Related Increase in Haemoglobin A1c and Fasting Plasma Glucose is Accompanied by a Decrease in Beta Cell Function without Change in Insulin Sensitivity: Evidence from a Cross-Sectional Study of Hospital Personnel. *Diabetic Medicine : A Journal of the British Diabetic Association*. 2002; 19(3):254–258. [PubMed: 11918628]
- Zamboni M, Mazzali G, Zoico E, Harris TB, Meigs JB, Di Francesco V, Fantin F, Bissoli L, Bosello O. Health Consequences of Obesity in the Elderly: A Review of Four Unresolved Questions. *International Journal of Obesity*. 2005; 29(9):1011–1029. (2005). [PubMed: 15925957]

Table 1
Descriptive Statistics for Biomarkers in 2000 and 2006, SEBAS Longitudinal Cohort

	N	2000		2006		Test of the Difference in Means
		Mean	SD	Mean	SD	
<u>Standard cardiovascular and metabolic markers</u>						
SBP (mmHg)	637	136.1	19.7	135.2	20.8	$p \sim 0.655$
DBP (mmHg)	637	82.4	10.9	72.8	10.9	$p < 0.001$
Total/HDL ratio	635	4.4	1.5	4.3	1.2	$p \sim 0.357$
Total cholesterol (mg/dL)	635	202.3	38.1	197.6	38.0	$p \sim 0.001$
HDL cholesterol (mg/dL)	635	49.2	13.5	48.1	13.9	$p \sim 0.032$
Triglycerides (mg/dL)	635	122.8	97.0	110.8	63.8	$p \sim 0.007$
HbA _{1c} (%)	635	5.7	1.2	6.2	1.3	$p < 0.001$
Weight (kg)	628	62.0	10.4	61.6	10.9	$p \sim 0.189$
Height (cm)	628	158.5	8.1	157.6	8.5	$p < 0.001$
BMI (weight in kg / (height in m) ²)	627	24.7	3.5	24.8	3.7	$p \sim 0.530$
Waist circumference (cm)	627	85.3	9.3	84.9	9.9	$p \sim 0.443$
Hip circumference (cm)	626	97.2	7.7	94.9	7.4	$p < 0.001$
Waist-hip ratio	626	0.88	0.06	0.90	0.07	$p < 0.001$
<u>Other markers</u>						
Creatinine clearance (ml/min)	624	64.6	16.8	59.8	20.1	$p < 0.001$
Albumin (g/dL)	635	4.5	0.3	4.4	0.3	$p < 0.001$
Leukocyte count (10 ³ /μL)	624	6.0	1.5	6.1	1.8	$p \sim 0.133$
Interleukin-6 (pg/mL) [*]	624	3.3	4.6	4.5	9.6	$p \sim 0.001$
Urinary cortisol (μg/g creatinine) [*]	603	24.5	23.8	22.4	38.7	$p \sim 0.383$
Urinary epinephrine (μg/g creatinine) [*]	611	3.6	2.1	4.1	2.6	$p \sim 0.003$
Urinary norepinephrine (μg/g creatinine)	611	21.4	8.8	27.1	15.0	$p < 0.001$
Urinary dopamine (μg/g creatinine) [*]	611	185.4	485.1	321.7	2102.3	$p \sim 0.129$

* In some cases, the laboratory reported that the value was below assay sensitivity (BAS) for one or both duplicate assays: IL-6 (N=80 in 2000, N=9 in 2006), cortisol (N=131 in 2006), epinephrine (N=334 in 2000, N=350 in 2006), and dopamine (N=1 in 2006). In these cases, we coded the BAS values to the detection limit before calculating the mean across duplicate assays.

SD: Standard deviation

Table 2
Predicted Six-Year Change* in Cardiovascular and Metabolic Markers at Selected Ages, by Sex

	Males				Females			
Age at baseline (2000)	55	65	75	55	65	75		
Age at followup (2006)	61	71	81	61	71	81		
SBP (mmHg)	NS	NS	NS	NS	NS	NS		
DBP (mmHg)	-6.47	-7.67	-8.88	-9.19	-7.79	-6.40		
% Change [‡]	-8%	-9%	-11%	-11%	-9%	-8%		
Total/HDL ratio	NS	NS	NS	NS	NS	NS		
Total cholesterol (mg/dL)	NS	NS	NS	NS	NS	-12.01	[†]	
% Change [‡]						-6%		
HDL cholesterol (mg/dL)	NS	NS	NS	NS	NS	NS		
Triglycerides (mg/dL)	NS	-10.65	NS	NS	NS	NS		
% Change [‡]		-9%						
HbA _{1c} (%)	0.71	0.61	0.51	0.65	0.55	0.44	[†]	
% Change [‡]	13%	11%	9%	11%	10%	8%		
Weight (kg)	NS	NS	NS	NS	NS	-2.11	[†]	
% Change [‡]						-3%		
Height (cm)	NS	-0.48	-0.80	NS	-1.27	-1.71		
% Change [‡]		0%	-1%		-1%	-1%		
BMI	NS	NS	NS	0.57	NS	NS	[†]	
% Change [‡]				2%				
Waist (cm)	NS	NS	NS	NS	NS	NS		
Hips (cm)	-1.67	-1.93	-2.20	NS	-3.31	-5.01	[†]	
% Change [‡]	-2%	-2%	-2%		-3%	-5%		
Waist-hip ratio	0.02	0.02	0.02	NS	0.02	0.04	[†]	
% Change [‡]	2%	2%	2%		3%	4%		

* We modeled the change in each marker, separately by sex, using a weighted regression model that controls for age. We also controlled for medication use where appropriate: anti-hypertensives for blood pressure; lipid-lowering medication for lipids; hypoglycemic agents for HbA1c. Standard errors were corrected for sampling design. Using the coefficients shown in Table A-2, we calculated predicted changes by setting age at baseline to the specified value and, if the model controls for medication use, setting those variables to zero.

[†] Change in biomarker varied significantly ($p < 0.01$) by age at baseline.

[‡] Calculated as a percentage of the average value for the specified biomarker in 2000.

NS = Predicted change did not differ significantly from zero (at the $p < 0.01$ level based on an F -test).

Table 3

Predicted Six-Year Change* in Other Biomarkers at Selected Ages, by Sex

	Males				Females			
Age at baseline (2000)	55	65	75	75	55	65	75	75
Age at followup (2006)	61	71	81	81	61	71	81	81
Creatinine clearance (ml/min)	NS	-5.27	-6.47	†	NS	-5.74	-8.28	†
% Change [‡]		-8%	-10%			-9%	-13%	
Albumin (g/dL)	-0.19	-0.18	-0.17	-0.13	-0.15	-0.15	-0.17	
% Change [‡]	-4%	-4%	-4%	-3%	-3%	-3%	-4%	
Leukocyte count (10 ³ /μL)	NS	NS	0.39	NS	NS	NS	NS	NS
% Change [‡]			7%					
Interleukin-6 (pg/mL)	NS	0.69	1.33	†	NS	NS	1.02	
% Change [‡]		21%	41%				31%	
Cortisol (μg/g creatinine)	NS	NS	NS	NS	-5.98	-5.98	NS	NS
% Change [‡]					-24%	-24%		
Epinephrine (μg/g creatinine)	NS	0.44	NS	NS	NS	NS	NS	NS
% Change [‡]		12%						
Norepinephrine (μg/g creatinine)	4.10	5.09	6.08	4.63	6.39	6.39	8.14	
% Change [‡]	19%	24%	28%	22%	30%	30%	38%	
Dopamine (μg/g creatinine)	19.96	14.09	NS	NS	16.52	16.52	NS	NS
% Change [‡]	11%	8%			9%	9%		

* Refer to notes on Table 2. The model for creatinine clearance among men also includes a quadratic term for age.

† Change in biomarker varied significantly ($p < 0.01$) by age at baseline. For the model of creatinine clearance among men, we performed a joint test for age and age².

‡ Refer to notes on Table 2.

NS = Predicted change did not differ significantly from zero (at the $p < 0.01$ level based on an F -test).