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Multiple inflammatory markers and 15-year incident ADL disability in admixed older adults: The Bambui-Epigen Study

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ABSTRACT

Background: The ability of inflammatory markers to predict disability in later life has received growing attention. However, the current evidence came predominantly from Caucasians and the role of genomic ancestry has not been investigated.
Objective: We investigated the prognostic value of multiple citokynes and chemokines for incident disability in admixed older Brazilians and whether genomic African and Native American ancestry affects the association.
Design: Population-based longitudinal study.
Setting: The Bambui-Epigen (Brazil) Cohort Study of Aging.
Subjects: 1171 males and females aged ≥60 years over 15-year of follow-up.
Methods: Outcome examined was incident activity of daily living (ADL) disability assessed annually (10,039 measures were performed). Serum levels of citokynes (IL6, IL12, TNF, IL10, and IL1β) and chemokines (CCL2, CCL5, CXCL8, CXCL9 and CXCL10) were measured at baseline. We used 370,539 Single Nucleotide Polymorphisms (SNPs) to estimate each individual genomic ancestry proportions. Potential confounding variables included a wide range of socio-demographic variables and health indicators. Statistical analyses were based on competing risk framework.
Results: The incidence rate of disability was 57.9 per 1000 person-years. IL6 level at the highest quartile showed an independent association with ADL disability (SRH = 1.32; 95% CI: 1.03, 1.70). Other inflammatory markers showed no statistically significant associations with the outcome. Neither genomic African nor Native American ancestry had an effect modifier on the associations (P for interaction > 0.05 for all).
Conclusion: Among multi-inflammatory markers, only IL6 had the potential to identify people at increased risk of ADL disability, independently of ethno-racial background.

1. Introduction

Disability in later life is a public health concern worldwide due to increase in demand and cost of long-term care (National Institute of Aging, 2016). Identifying predictors of disability can potentially contribute not only to a better understanding of underlying mechanisms, but also to targeting vulnerable groups for timely prevention. Given that there is evidence linking inflammation to the process of ageing and age-related diseases, the ability of inflammatory markers to predict disability in old age has received growing attention (Singh & Newman, 2011).

Cytokines and chemokines are important players in the immune responses (Singh & Newman, 2011). There is considerable evidence showing that elevated baseline levels of Interleukin-6 (IL6), a pro-inflammatory cytokine, has a prognostic value for activities of daily living (ADL) disability or impairment in mobility (Adriaensen et al., 2014; Ferrucci et al., 1999; Penninx et al., 2004), muscle strength loss (Barbieri et al., 2003; Cesari et al., 2004; Ferrucci et al., 2002; Schaap

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et al., 2006; Schaap et al., 2009) and sarcopenia (Payette et al., 2003) in short and medium terms (up to 5 years). The prognostic value of IL6 for long-term physical functioning is unknown. In the MacArthur Studies of Sucessful Aging, baseline IL6 level did not predict physical functioning performance 7 years later (Taaffe, Harris, Ferrucci Rowe, & Seeman, 2000). Studies examining the prognostic value of other cytokines and chemokines for physical functioning are still scarse and have reported inconsistent results (Adriaensen et al., 2014; Penninx et al., 2004; Schaap et al., 2009).

The above-mentioned evidence came predominantly from Caucasians (Adriaensen et al., 2014; Barbieri et al., 2003; Cesari et al., 2004; Ferrucci et al., 1999, 2002; Payette et al., 2003; Penninx et al., 2004; Singh & Newman, 2011; Schaap et al., 2006; Schaap et al., 2009; Taaffe et al., 2000). To the best of our knowledge, no previous study has specifically examined the influence of genetic ancestry on those associations. Brazil, the largest Latin American country, offers a valuable opportunity to explore this issue. The Brazilian population originates from African, European and Native American ancestral roots (Kehdy et al., 2015). The absence of legal segregation and other factors contributed to an emergence of a highly-admixed population (Lima-Costa et al., 2015).

We used 15-year follow-up data from the Bambui-Epigen study (Lima-Costa et al., 2011), the longest running cohort study of aging in Brazil, with two main objectives: (1) to examine the association between multiple inflammatory markers and long term ADL disability; and (2) to investiagate whether genomic African and Native American ancestry levels affect the ability of those biomarkers to predict the outcome.

2. Methods

2.1. Study population

The Bambui cohort study of aging is ongoing in Bambuí, a city of approximately 15,000 inhabitants in Southeast Brazil. From an ethnoracial perspective, the cohort population consists of an admixture of African (≅10%), Native American (≅5%), and European (≅85%) genomic ancestries, in similar proportions to that estimated for the Brazilian population, excluding the Amazon region (Lima-Costa et al., 2015). Detailed information on this cohort can be found elsewhere (Lima-Costa, Firmo & Uchoa, 2011). Briefly, the population eligible for the cohort consisted of all residents aged 60 years and older on the 1 st of January 1997 (92% of the 1742 inhabitants in this age group participated). Annually, from 1997 to 2011, cohort members underwent subsequent annual follow-up by face-to-face interview. Blood collection and other procedures for the current analysis where performed at the baseline survey. Deaths occurring from study enrollment to December 31, 2011, were considered in this analysis. Deaths were reported by next of kin during the annual follow-up interview and were ascertained through the Brazilian mortality information system. Death certificates were obtained for 95.5% of all deceased participants. Cohort members with an ADL disability at baseline (n = 171) were excluded from the current analysis (see bellow).

2.2. Activity of daily living disability

Annually, from 1997 to 2011, physical functioning was measured as self-reported limitations in the following basic ADL: dressing, walking across a room, bathing or showering, eating, getting in or out of bed, using the toilet. The questions had four possible answers: no difficulty, some difficulty, great difficulty and unable to perform. Onset of disability was considered when a participant reported, for the first time, great difficulty or unability to perform one or more tasks.

2.3. Inflammatory markers (cytokines and chemokines)

Blood samples for measurement of cytokines and chemokines were collected at the baseline survey in early morning. The Cytometric bread array assay (CBA immunoassay kit; Becton Dickinson, California) was used for the quantitative determination of the serum cytokines (Human Inflammatory kit) and chemokines (Human Chemokines kit) levels according to the instructions of the manufacturer. Data was acquired using a FACSVerse flow cytometer (Becton Dickinson, California). BD FCAP Array 3.0 software (Becton Dickinson, California) was used for sample analysis. The coefficients of variation intra and inter-assays were 5–10% and 7–12%, respectively. Based on their distributions, IL6, CXCL8, CCL2, CXCL9, CCL5 and CXCL10 were log-transformed and considered as continuous variables in our analysis. IL1β, IL10, IL-12 and TNF showed very low detectable levels and were considered as dichotomous variables.

2.4. Genetic and ancestry analyses

Cohort participants were genotyped with the Omni 2.5 M array (Illumina, California) (Kehdy et al., 2015). Ancestry inference was performed by using the model-based method (Alexander, Novembre, & Lange, 2009). We used 370,539 SNPs to estimate each individual African, European and Native American tri-hybrid ancestry proportions, based on public datasets parental populations. We used the matrix of kinship coefficients and a network-based approach to identify families, and identified them as categorical variables for the association tests described below. Pairs of individuals were considered as related if they had a kinship coefficient > 0.1 (first and second-degree relatives). Further details are described elsewhere (Kehdy et al., 2015).

2.5. Covariates

Covariates comprised baseline socio-demographic characteristics (age, sex, education and household income), lifestyle (smoking, alcohol consumption and physical activity), body mass index and health conditions. We categorized schooling into < 4 years, 4–7 and ≥8 years. Monthly household income per capita was divided into tertiles (< USD 90.00 is the lowest tertile). Current smokers were participants who had smoked at least 100 cigarettes during their lifetime and who still smoke. Leisure-time physical activity was defined as activity of any intensity for 20–30 min in the previous 3 months, and categorized into at ≥3 times a week, < 3 times a week and never. Alcohol consumption was defined by consumption of 14 doses per week in previous 12 months. Body mass index was categorized into < 18.5, 18.6-24.9 and ≥24 kg/m^2. Health conditions considered were: hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and/or treatment); diabetes (fasting blood glucose ≥126 mg/dL and/or treatment); arthritis (previous medical diagnosis of any joint condition); coronary heart disease (medical diagnosis of myocardial infartion or angina pectoris as assessed by the Rose's questionnaire); intermitent claudication (Rose's questionnaire), stroke (medical diagnosis), fasting high non-HDL cholesterol (≥130 mg/dL); heart failure (plasma B-type natriuretic peptide level > 100 pg/mL); anaemia (hemoglobin < 13 g/dL for men and < 12 g/dL for women), depressive symptoms (defined by a 12-item version of the General Health Questionnaire score ≥5 (Costa et al., 2006)); cognitive impairment (defined by a Mini-Mental State Examination score < 22 − below the 25th percentile- or by the need for a proxy interview- 87 participants). Based on the health conditions described above (all as dichotomous variables) we used principal component analysis (Ismail, 2008) to create a morbidity score that ranged from − ∞ to + ∞ (higher scores indicated worse health). Scores were divided into quartiles.