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Original Article

Inflammatory Biomarkers as Mediators between Chronic Diseases and Physical Functioning among Older Chinese Adults: A Longitudinal Mediational Analysis

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SUMMARY

Background: Little research has been conducted on the mediational role of inflammation on the association between chronic diseases and physical functioning among older Chinese adults.
Methods: Data were from the China Health and Retirement Longitudinal Study (CHARLS in 2011, 2015, and 2018). Chronic diseases were assessed by the summed scores of self-reported physician diagnosed of 14 chronic diseases in 2011. High-sensitivity C-reactive protein (CRP) and white blood cell (WBC) counts were used to measure inflammation in 2015. Physical functioning was measured by activities of daily living (ADLs) and instrumental activities of daily living (IADLs) in 2018. Longitudinal mediational models adjusting sex, age, residential areas, marital status, and health behaviors were used.
Results: The sample size was 3,328 for CRP and 3,349 for WBCs, respectively. Chronic diseases in 2011 had direct effects on CRP in 2015 ($b = 0.06$, $p < 0.001$) and ADLs in 2018 ($b = 0.25$, $p < 0.001$), whereas the association between CRP and ADLs was not statistically significant ($b = 0.07$, $p > 0.05$). Higher number of chronic diseases were associated with higher levels of WBCs ($b = 0.12$, $p < 0.001$) and greater ADLs ($b = 0.22$, $p < 0.001$), and WBCs were also associated with greater ADLs ($b = 0.04$, $p < 0.05$). Similar results were found except that CRP was also associated with greater IADLs ($b = 0.13$, $p < 0.001$).
Conclusion: Inflammatory biomarkers partially mediate the association between chronic diseases and physical functioning. A better understanding of the social and biological processes that lead to disability could potentially improve the health status of the Chinese adults in the future.

1. Introduction

The risk of chronic disease increases with aging. It has been reported that nearly 50% of older Chinese adults have one chronic condition, 18.9% have two conditions, 5.8% have three conditions, and 1.4% have four or more conditions.[1] Many older people with chronic disease do not have a single condition, but rather, they experience chronic diseases — the presence of two or more chronic diseases in an individual at the same time.[2] People living with multimorbidity often have complex health needs and report poorer overall quality of life.[3] As an ongoing cause of poor health, disability, and premature death, multimorbidity have been an important global, national, and individual health concern.[4]

Cross-sectional and longitudinal studies have suggested a positive association between the number of chronic diseases and the risk of physical disability,[5,6] underscoring the need to understand the mechanisms by which chronic diseases results in physical disability. Previous studies have suggested that specific chronic condition may cause functional limitation. For example, heart disease may limit physical exertion because of cardiovascular dysfunction.[7] Hypertension and asthma predicted muscle strength decline, resulting in impaired physical functioning.[8] However, the mechanisms of chronic diseases and physical disability are still not fully understood. Several studies have found that inflammation may play an important role in the association between chronic diseases and physical functioning.[9,10] For example, chronic lung disease may promote systemic inflammation (e.g. C-reactive protein [CRP]);[11] higher levels of inflammation also increase the risk of physical disability over time.[12] The direct effect of inflammatory biomarkers on functional limitation, along with the knowledge that inflammation is elevated with aging,[13] provide the rationale for considering inflammation as a potential mechanism for functional decline. Thus, inflammation represents a potential biological mechanism linking chronic diseases and physical functioning.[14]

Little research has been done to test the potential mediational role of inflammation in the association between chronic diseases and physical functioning among older Chinese adults. Previous studies have found the differences in the associations and mechanisms of inflammation and physical functioning between different races (e.g., African Americans and European Americans),[15] it is still unknown whether this association exists among older Chinese adults. Compared with their counterparts in Western societies, Chinese older adults have undergone significant changes in their lifetime given the rapid social and economic transitions in China decades ago. The aim was to examine whether inflammatory biomarkers mediated the relationship between the number of chronic diseases and physical functioning (activities of daily living [ADLs] and instrumental activities of daily living [IADLs]) over a 7-year follow-up period using a longitudinal mediation analysis.

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2. Materials and methods

2.1. Sample

The data were obtained from the China Health and Retirement Longitudinal Study (CHARLS), an ongoing nationally representative study of Chinese community-dwelling adults aged 45 years and older. The sample was randomly selected from 150 counties in 28 provinces using multistage probability sampling. The baseline survey (Wave 1) was conducted from 2011 to 2012; three follow-up surveys were carried out in 2013 (Wave 2), 2015 (Wave 3), and 2018 (Wave 4). All data were collected using face-to-face personal interviews, and there was a response rate of over 80% at the baseline. Blood samples containing inflammatory biomarkers were collected in 2015 (Wave 3). The fieldwork for blood was administered by the National Center for Chronic and Non-Communicable Disease Control and Prevention of the Chinese Center for Disease Control and Prevention. The lab work was done at Capital Medical University in Beijing. All blood samples were placed in a deep freeze and stored at –80 °C until the assay. CHARLS was approved by the Ethical Review Committee of Peking University (IRB00001052-11015), and all participants provided written informed consent.[16]

The sample size at baseline in 2011 was 17,708. Participants who were aged under 60 years old in 2011 were excluded from the sample, leaving 8,028 participants in the dataset at baseline. Because the inflammatory biomarkers were only available in 2015, the samples in this study were selected from Wave 1 in 2011 (T1, chronic diseases), Wave 3 in 2015 (T2, inflammatory biomarkers), and Wave 4 in 2018 (T3, physical functioning) of the CHARLS dataset to examine the longitudinal mediational effects. Missing values on all variables and values in excess of 10 mg/L (4,042) or 10×10^9/L (3,957) for CRP or WBCs were excluded from the sample, producing a sample size of 3,328 for CRP and 3,349 for WBCs, respectively.

2.2. Variables

2.2.1. Chronic diseases

Consistent with previous studies measuring the association between chronic diseases and physical functioning,[7,8] the number of chronic diseases (ranged from 0 to 14) was captured by measuring the count number of 14 self-reported physician-diagnosed chronic diseases (0 = no, 1 = yes) for each individual, including high blood pressure, diabetes, cancer, lung disease, heart problems, stroke, psychiatric problems, arthritis, dyslipidemia, liver disease, kidney disease, digestive disease, asthma, and memory problems.

Physical functioning was measured by self-reported ADL and IADL measures. ADL and IADL have been extensively used worldwide to measure the physical status and mobility of older adults in ageing and gerontology studies.[17–19] ADL encompasses the personal basic activities of daily life. The respondents were asked whether they had difficulty in completing the following six basic tasks: bathing, dressing, using the toilet, getting into or out of bed, incontinence, and eating (coded with 1 = have no difficulty, 2 = have difficulty but can still do it, 3 = have difficulty and need help, and 4 = cannot do it). The term IADL covers managing money, shopping for groceries, preparing meals, cleaning the house, making phone calls, and taking medications (coded with 1 = have no difficulty, 2 = have difficulty but can still do it, 3 = have difficulty and need help, and 4 = cannot do it). Total ADL or IADL scores ranged from 6 to 24; higher ADL and IADL scores indicated poorer physical functioning. The Cronbach's alphas for ADL and IADL were 0.84 and 0.82, respectively, indicating good internal consistency. We used continuous ADL and IADL scores to assess each individual's physical functioning.

2.3. Inflammatory biomarkers

Due to the unavailability of serum IL-6 and fibrinogen in the survey dataset, high-sensitivity C-reactive protein (CRP) and white blood cell counts (WBCs) were used to measure inflammatory biomarkers suggested by previous studies.[9,20] Values in excess of 10 mg/L or 10×10^9/L for CRP or WBCs were thought to indicate acute infectious illness, and participants with them were then excluded from the dataset.[9,21] The two measurements were ln-transformed for statistical analyses due to the positive skewed distributions.

2.4. Covariates

The analyses controlled for the participants' sociodemographic characteristics, including age, sex (0 = male, 1 = female), educational attainment (illiterate = 0 year, can read and write = 1 year, primary school = 6 years, junior high school = 9 years, senior high school = 12 years, college and above = 16 years), area of residence (0 = rural, 1 = urban), marital status (0 = married, 1 = unmarried), current smoking status (whether the respondents smoke currently, 0 = no, 1 = yes), and drinking status (whether the respondents drink in the last 12 months, 0 = no, 1 = yes), which were measured in 2011. The average grip strength of both the left and right hands and walking speed measured in 2015 were also adjusted to indicate the muscle strength, as previous studies have suggested a negative association between inflammation, muscle strength.[22]

2.5. Statistical analyses

Analyses were performed using Stata 15.1 (Stata Corporation, College Station, TX, USA). Descriptive statistics of the variables are presented in Table 1. Path analysis with longitudinal data was performed to test the mediating effects of inflammatory biomarkers (T2, 2015) on the association between the number of chronic diseases (T1, 2011) and physical functioning (T3, 2018), adjusting covariates at T1. The sgmediation command in Stata was used to calculate total, direct, and indirect effects, and the significance of the indirect effect was tested using the Sobel test.[23] The total effect (path c) of an independent variable (IV) on a dependent variable (DV) consists of a direct effect (path c') of the IV on the DV and an indirect effect (path a × b) of the IV on the DV via a proposed mediator. Path a represents the effect of the IV on the mediator, and path b represents the effect of the mediator on the DV. In the present study, the number of chronic diseases were the IV, ADL/IADL was the DV, and the inflammatory biomarkers were the mediators. The 95% confidence interval (CI) was estimated using bootstrapping with 5,000 sampling replications because the mediator and outcome variables were not normally distributed.[24] The Skewness and Kurtosis tests for normality for CRP, WBCs, ADL, and IADL indicated that these variables were all not normally distributed ($p < 0.001$). Bootstrapping method was preferable to the Sobel tests for testing the significance of indirect effects because it did not assume a normal distribution and therefore reduced the likelihood of type 2 error.[25] A 95% CI that did not include zero indicates a significant indirect effect at $p < 0.05$.[24]

3. Results

Table 1 presents descriptive statistics of the variables used in the analyses. The average number of chronic diseases were 1.7,

Table 1
Descriptive statistics for the sample.

Variable	CRP sample %/Mean (SD)	WBCs sample %/Mean (SD)
Chronic diseases (T1)	1.7 (1.5)	1.7 (1.5)
CRP (mg/L, T2)	2.0 (1.8)	-
WBCs (10^9/L, T2)	-	5.8 (1.5)
ADL (T3)	7.2 (2.5)	7.2 (2.5)
IADL (T3)	8.3 (4.0)	8.4 (4.0)
Age (years)	67 (5.9)	67 (5.9)
Education level	3.6 (3.9)	3.6 (3.9)
Grip strengths	24.7 (9.2)	24.6 (9.2)
Walking speed	3.8 (6.1)	3.9 (6.3)
Male (%)	50.0	50.0
Rural residence (%)	65.3	65.4
Married (%)	81.7	81.5
Drinkingin last 12 months (%)	28.8	28.7
Current smoking (%)	27.7	27.9
N	3,328	3,349

Note: ADL: activities of daily living; CRP: high-sensitivity C-reactive protein; IADL: instrumental activities of daily living; SD: standard deviation; T1: 2011, T2: 2015, T3: 2018; WBCs: white blood cell counts.

which means that the participants had nearly two chronic diseases at T1. The mean age of the sample was 67 years, and the average years of education were 3.6. The mean value of ADL or IADL in 2018 was 7.2 or 8.3 for the CRP sample and 7.2 or 8.4 for the WBCs sample.

Results from the mediation analyses of ADL and IADL are presented in Table 2 and Figure 1. For ADL, the number of chronic diseases at T1 had direct effects on CRP at T2 (b = 0.06, p < 0.001) and ADL at T3 (b = 0.25, p < 0.001), while the association between CRP and ADL was not statistically significant (b = 0.07, p > 0.05). Higher number of chronic diseases were associated with higher levels of WBCs (b = 0.12, p < 0.001) and greater ADL (b = 0.22, p < 0.001), and higher WBCs were associated with greater ADL (b = 0.04, p < 0.05). For IADL, the number of chronic diseases had a direct effect on CRP (b = 0.06, p < 0.001) and IADL at T3 (b = 0.33, p < 0.001). Higher level of CRP was also associated with greater IADL (b = 0.13, p < 0.001). For WBCs, higher number of chronic diseases were associated with higher levels of WBCs (b = 0.10, p < 0.001) and greater ADL (b = 0.30, p < 0.001), and higher WBCs were also associated with greater IADL (b = 0.11, p < 0.001). Although the associations between chronic diseases, CRP/WBCs, and ADL/IADL were statistical significance, the absolute effects of each regression path were relatively small.

Mediation effects were presented in Table 2. In the longitudinal mediation model, the indirect effects of chronic diseases at T1 on physical functioning at T3 through CRP and WBCs at T2 were significant (indirect effect = 0.005, p < 0.05, 95% CI, 0.001–0.011; indirect effect = 0.008, p < 0.05, 95% CI, 0.001–0.016; indirect effect = 0.011, p < 0.05, 95% CI, 0.003–0.020).

Table 2
Mediation of inflammatory biomarkers on ADL and IADL.

	CRP (T2)	ADL (T3)	WBCs (T2)	ADL (T3)
Chronic diseases (T1)	0.06***	0.25***	0.12***	0.22***
CRP (T2)		0.07		
WBCs (T2)				0.04*
Mediation	95% CI		95% CI	
T1 → T2 → T3	-0.001–0.009		0.001–0.011	
N	3,328		3,349	
	CRP (T2)	IADL (T3)	WBCs (T2)	IADL (T3)
Chronic diseases (T1)	0.06***	0.33***	0.10***	0.30***
CRP (T2)		0.13**		
WBCs (T2)				0.11**
Mediation	95% CI		95% CI	
T1 → T2 → T3	0.001–0.016		0.003–0.020	
N	3,328		3,349	

Note: * p < 0.05. ** p < 0.01. *** p < 0.001.
ADL: activities of daily living; CRP: high-sensitivity C-reactive protein; IADL: instrumental activities of daily living; T1: 2011, T2: 2015, T3: 2018; WBCs: white blood cell counts.
Results of covariates were not shown.

4. Discussion

This study examined the mediational role of inflammation on the association between chronic diseases and physical functioning using a nationally representative longitudinal survey data in China. The results suggested that higher levels of inflammatory biomarkers measured by CRP and WBCs predicted poorer physical functioning. Moreover, there was a mediational effect of inflammation on the pathway between the number of chronic diseases and physical functioning. All analyses adjusted for a set of sociodemographic confounders — age, sex, residential areas, and educational level. Health behaviors (smoking and drinking), grip strength, and walking speed. The role of inflammation has not been examined previously among older Chinese adults. The results in the current study indicate that chronic diseases were associated with physical disability through the effects of inflammatory biomarkers.

The possibility that inflammation might mediate the association between chronic diseases and physical functioning is consistent with previous studies that have linked chronic diseases, inflammatory biomarkers, and physical functioning.[26] Evidence suggests that increased systemic inflammation is closely associated with aging and age-related chronic diseases.[27] First, chronic inflammation is caused by a variety of factors, including bacterial and viral infections and

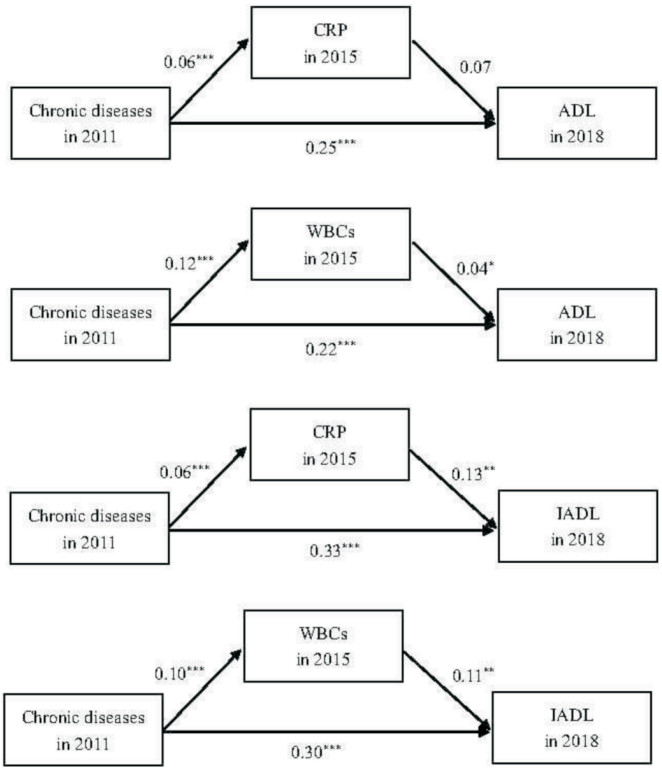

Figure 1. Mediational effects of inflammatory biomarkers (CRP and WBCs) between chronic diseases and physical functioning (ADL and IADL). Note: * p < 0.05. ** p < 0.01. *** p < 0.001. CRP: high-sensitivity C-reactive protein; WBCs: white blood cell counts; ADL: activities of daily living; IADL: instrumental activities of daily living.

chronic diseases. Some chronic diseases (e.g., hypertension and stroke) may keep the body in a state of chronic inflammation, which in turn further promotes the occurrence of metabolic symptoms.[28] Biological evidence suggests that oxidative stress and inflammation initiate atherosclerosis, hypertension, and alteration of metabolic markers, thus causing major adverse cardiovascular events.[29] Second, higher levels of inflammation have been associated with greater physical disability and lower levels of physical functioning.[30] Furthermore, chronic diseases also increases the risk of functional disability.[5,31] The pathological basis of reduced physical functioning was thought to be muscle strength, which was the sequela of chronic inflammation. Chronic inflammation accelerates protein catabolism and is thus related to muscle wasting and sarcopenia.[32,33] Previous studies have found that inflammatory proteins reduce the production of muscle cells and increase muscle catabolism.[34] In the current study, grip strength and walking speed have already been controlled for in the analyses, suggesting that inflammation has a robust mediational role in the pathway linking chronic diseases and physical functioning.

The results of the study aid understanding of the biological pathology from chronic diseases to physical functioning. Chronic diseases may lead to long-term inflammation, resulting in decreasing level of physical functioning eventually.[35] In such a context, the current study also highlights the clinical implications of inflammatory biomarkers for the process of disablement. As independent predictors of chronic diseases, elevated levels of CRP and WBCs may be important indicators of risk for the functional limitation of older adults. Measurement of CRP levels may be useful in identifying and targeting older individuals who may require intervention to prevent loss of function and disability.

The strengths of the study were that a nationally representative survey sample was used in the analyses and longitudinal mediation modeling was used to exclude the possibility of reverse relationships between chronic diseases, inflammation, and physical functioning. Potential limitations should be noted as well. Firstly, chronic diseases and physical functioning (ADL/IADL) were based on self-reporting, which may introduce the possibility of recall errors. However, previous studies have suggested that self-reporters would tend to underestimate these associations.[14] Secondly, inflammatory biomarkers in this study were measured only for one time and it may indicate acute or long-term low-grade inflammation. Further study measured in long-term inflammation is warranted. Thirdly, we found significant associations between chronic diseases, CRP/WBCs, and physical functioning, but the absolute effects were relatively small in the meditational regressions, thus extending the associations into clinical implications should be cautious.

In summary, this study supplies evidence that inflammation plays a mediational role in the pathway linking chronic diseases and physical functioning among older Chinese adults. As China's population ages, the number of older people living with multiple chronic diseases and physical limitations or disabilities will also increase. As a public concern, a better understanding of the social and biological processes that lead to disability can potentially improve the health status of Chinese adults in the future.

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Conflict of interest

The authors declare no conflict of interest.

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