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Social Relationships, Inflammation, and Cognitive Function among Older Mexican Americans

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Social Relationships, Inflammation, and Cognitive Function among Older Mexican

Americans

A thesis submitted in partial satisfaction of

the requirements for the degree Master of Science

in Epidemiology

by

Yingyan Wu

2021

ABSTRACT OF THE THESIS

Social Relationships, Inflammation, and Cognitive Function among Older Mexican

Americans

by

Yingyan Wu

Master of Science in Epidemiology

University of California, Los Angeles, 2021

Professor Roch Arnaud Kibsa Nianogo, Chair

Studies have suggested that social relationships may be a protective factor for cognitive

decline. Elevated levels of inflammatory biomarkers have been associated with cognitive

decline. We aim to estimate the effect of social relationships (family support and local ties

in particular) on cognitive function and investigate whether inflammation measured by the

elevated level of inflammatory biomarkers mediates this effect among 1,374 Hispanic

participants from the Sacramento Area Latino Study on Aging (1998–2007). At baseline

and during follow-up wave 4 & 6 the Modified Mini Mental State Exam (3MSE) and the

Spanish and English Verbal Learning Test (SEVLT) measures were used to assess

cognitive function. Generalized linear models were used to assess the total effect of family

support and local ties as well as the components of these social relationship measures on

cognitive function measured in follow-up waves. A causal mediation analysis within a potential outcome framework was applied to decompose direct and indirect effects. The results are compatible with a protective effect of family support on cognitive function with a larger effect estimated for the follow-up in wave 4 than wave 6. The 95% CI of indirect effect estimates were null. Our results suggest it is unlikely that there are mediated effects through inflammatory biomarkers within this study sample.

The thesis of Yingyan Wu is approved.

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2021

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# SUPPLEMENTARY MATERIALS

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SALSA: Sacramento Area Latino Study on Aging
3MSE: Modified Mini Mental State Exam
SEVLT: Spanish and English Verbal Learning Test
hs-CRP: High-sensitive CRP
CRP: C-reactive protein
IL-6: interleukin 6
TNF-$\alpha$: tumor necrosis factor $\alpha$
ADLs: Activities of daily livings

IADLs: instrumental activities of daily living
IPCW: Inverse Probability Censored Weighting
GLM: General linear regression models
MD: mean difference
CI: Confidence Interval
SAGE: Study on Global Ageing
AgeCoDe: Ageing, Cognition, and Dementia in Primary Care Patients

## Introduction

Cognitive decline represents a major public health concern among older adults because it often progresses to cognitive impairment and dementia[1]. There are more than 6.2 million people in the US aged 65 and over who have Alzheimer's dementia[2]. More than 16 million people in the US are living with cognitive impairment[3]. Prevention of cognitive decline and dementia in late life is imperative given that the population of older adults will approach 71.5 million by 2060[4]. Evidence from various studies has shown that older Hispanic Americans are more likely to have cognitive impairment and Alzheimer's disease and related dementia compared to older non-Hispanic Whites[2,5–7]. The population of older Mexican Americans adults are growing and are projected to be the largest older adult minority population by 2050[8–10].

Social relationships or Local social support and social activities (noted as local ties in this study) have been described as beneficial factors to prevent health problems. As opposed to cross-border support and cross-border ties which indicate support and ties from the communities of origin, local social support and local ties for immigrants represent the social support from local social relationships. A growing body of evidence suggests the buffering effect of social support and social ties against psychological and cognitive function decline[11–13]. Prior work using the German prospective longitudinal multicenter study on Ageing, Cognition, and Dementia in Primary Care Patients(AgeCoDe) indicates the influence of local social support on cognitive function is limited, as shown by null results. This work suggests that further research is needed to explore the effect of different

components of social support on cognitive function and also assess the possibly complex interactions between the components[14].

Various studies have suggested that inflammation is involved in the development of cognitive decline and dementia[15–18]. Accumulating evidence links elevated C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α) levels to declining cognitive functioning[19–23]. Other studies have shown associations between CRP levels and verbal fluency function in a cognitively normal population of Mexican-Americans[24]. Longitudinal studies found that support from family, friends, and/or spouse modestly protected against inflammation measured as the elevated level of inflammatory biomarkers[25,26]. Another study has shown that inflammation may mediate the relationship between age and cognitive deficits[27]. However, whether local social support, family support in particular, is protective of cognitive decline among older Americans of Mexican descent, and whether inflammation mediates this effect, has rarely been studied.

This study aimed to estimate the effect of the components and combinations of components of family support and local ties on cognitive function as well as assess whether family support acts on cognitive function via the inflammation pathway, reflected by the change in levels of inflammatory biomarkers, CRP, IL-6, and TNF-α. We hypothesized that among older Mexican Americans, more family support and local ties would be associated with better cognitive function and that part of the effect would be mediated through inflammation.

## Methods

### Study population

Data from the Sacramento Area Latino Study on Aging (SALSA)[28] are used in the study. SALSA is a prospective cohort study of Mexican Americans in California, which collected data from residents. The study population was recruited in the Sacramento Metropolitan Statistical Area and surrounding counties (Sacramento, Yolo, Sutter, Solano, San Joaquin, and Placer counties) in California. Those who were aged 60 and over during 1998-1999 and had a Latino surname were contacted by mail, phone, and door-to-door enumeration reaching a response rate of 85%. 1789 participants aged 60 to 101 years who self-identified as Latino, Mexican, Central American, and Mexican American were enrolled at baseline in 1998 - 1999 and attempted to be followed up every 12-15 months for up to 7 study visits until 2007[29]. From the interviewer-administered surveys in English or Spanish, sociodemographic information, health, lifestyle data was obtained. Biological and clinical assessments were completed during home visits. Details of the study design and sampling strategies are provided elsewhere[29].

Of 1,789 participants, the following participants were excluded:

- those without baseline family support information (n = 11),
- those without baseline inflammatory biomarkers (n = 224),
- those who were diagnosed with dementia or CIND at baseline (n = 108),
- those who were lost to follow up (n = 23),
- those without gross income information (n = 25),
- those without occupation information (n = 14),

- and those without an IADL summary score (n = 10)

The final analytical sample of SALSA participants followed through 2007 (wave 6) included 1,374 participants (Figure 1).

**Measures**

*Family support and local ties*

At baseline, participants were asked to answer questions regarding family support and local ties. Responses to the following 3 questions were used to measure family support in the current living situation: "Do you live with a spouse?", "Do you live with children?", "Do you live with other family members?" Assigning value 1 for "yes" and 0 for "no," the responses to these three questions were then combined into a dichotomized family support variable: living with family members (children, spouse, or other family members) vs. not living with family members.

As done in the study by Torres et al [30], responses to the following 2 questions were used to measure local ties: "How often did you meet with or talk to family and friends?", "How often did you see the person you had the most contact with?". For the first question, the response was categorized as "always," "a lot of the time," "some of the time," or "never." For the second question, the frequency of seeing the person with whom they had the most contact was categorized as "daily" or "less than daily." The responses to these two questions were summed and dichotomized at 0 vs. 1-2.

*Cognitive function*

The Modified Mini-Mental State Exam (3MSE) and the Spanish English Verbal Learning Test (SEVLT) were used to assess cognitive function. 3MSE is a validated global test with scores ranging from 0 – 100. Compared to the Mini-Mental State Examination, the 3MSE shows better reliability, test-retest properties, sensitivity, as well as specificity, and has fewer ceiling effects[31,32]. Errors on the 3MSE were calculated as 101 – 3MSE score and log-transformed to correspond to a normal distribution. Higher log(errors) denote worse cognitive function[33–35]. The SEVLT is a 15-point verbal memory recall test with five 15-word memory trials and usually, the final trial score is taken. The SEVLT was developed for use in SALSA which has been validated in English and Spanish[36–38]. The SEVLT score has a range from 0-15. A higher score indicates better cognitive function. Measures from wave 4 (around 5-7 years after the baseline interview) and wave 6 (around 7-9 years after the baseline interview) were used in further analysis.

*Inflammatory Biomarkers*

Fasting blood samples were collected on the day of the interview and processed/stored at the Medical Center Clinical Laboratory at baseline at the University of California, Davis. High-sensitive CRP (hs-CRP), IL-6, TNF- α level was assessed for the participants. CRP levels were tested using the CRP Ultra-Wide Range Reagent Kit latex-enhanced turbidimetric immunoassay(Equal Diagnostics, Exton, Pennsylvania)[39]. TNF-α and IL-6 levels were determined by using the Quantiglo Chemiluminescent Immunoassay.[40,41] Level of the biomarkers were categorized as high versus low at a clinically relevant cut point (HsCRP: $\leq 1.0$ mg/L[42], IL-6: $\leq 1.8$ pg/mL[43], TNF- α $\leq 8.1$ pg/mL[44]).

*Covariates*

At the baseline interview, age, sex, education level, marital status, income level, and occupations grouped by type of main lifetime job were reported. Education level was indicated by years of completed education and was dichotomized at $\geq 12$ years. Marital status was recategorized as married or not. The income level of the participants was calculated using the household income measures in SALSA which reported household gross income (without deductions) or pension one month before the baseline interview. The household income was first categorized in 5 categories (less than \$1000/month, \$1000 to \$1499/month, \$1500 to \$1999/month, \$2000 to \$2499/month, \$2500 or more/month). We recoded the household income to the mid-point of each category (\$500, \$1249.5, \$1749.5, \$2249.5, \$2479.5). Individual income values were calculated by dividing the recoded value by the square root of the number of household members[45]. Since the distribution of individual income values was highly skewed, the logarithm of individual income values was used in the models. The occupational categories were recategorized as low (unskilled/semiskilled, skilled trade or craft, and clerical/office worker) and high (manager business/government and professional/technical) professional levels[46]. Activities of daily livings (ADLs) and instrumental activities of daily living (IADLs) were measured using a standard Likert-type scale[47]. If the participant reported having difficulty with $\geq 1$ activity for ADL level or $\geq 3$ activities for IADL level, the participant was categorized as having ADL difficulty or IADL difficulty.

**Statistical analysis**

In order to reduce potential selection bias due to differential lost-to-follow-up, Inverse Probability Censored Weighting (IPCW) was generated and used in the statistical models for each set of exposures and outcomes. The numerator for the stabilized IPCW was the proportion who remained in the sample. The denominator was the predicted values of the probabilities of remaining in the sample obtained from modeling "remaining in the sample" on exposure measures, age, sex, and education level, the language they used for completing the survey, individual income, main lifetime job category, marital status, diabetes, ADL, and IADL difficulties. The mean of each IPCW was around 1 with a standard deviation of around 0.25.

General linear regression models (GLM) were used to estimate the associations between having family support and cognitive function (log 3MSE error and SEVLT) adjusting for potential confounders. GLMs were also used for obtaining the effect estimates of the associations between local ties measures (always meet with family/friends as well as having daily contact) and cognitive function measures. Different covariates were included in various models. Age, sex, and education level were adjusted for in model 1. Individual income, occupational main lifetime job category, and marital status were adjusted for in model 2. In model 3, we further adjusted for ADL and IADL difficulties.

Mediation analysis was conducted to determine whether there is an indirect effect through inflammatory biomarkers which would partly explain the association between family support and cognitive function utilizing the G-computation algorithm[48]. Potential

confounders which were included in GLM model 3 were adjusted for in mediation analysis (Figure 2). Details on G-computation steps for mediation analysis can be found elsewhere[49]. To obtain parameters of the variable distributions, the marginal expectation of the exposure was estimated using parametric models. Models for the mediator and the outcome were fitted. The aim of obtaining the marginal expectation of the exposures is to create intervened exposures (the counterfactuals) that are independent of the potential confounders in the causal structure. Then, the distribution of the post-intervention variables (exposure, mediator, outcome) was simulated using the parameters obtained from the previous step. The intervention exposure and the covariates were marginally independent of each other. The potential mediator variables were simulated by a function of covariates and intervention exposure using the coefficients obtained from the first step. Potential outcome variables were similarly simulated according to different effect decompositions as equations of intervention exposure, potential mediator, and covariates (Table S1). Marginal structural modeling was used to obtain estimates of each effect component by regressing each potential outcome on the intervention exposure. The analysis was then repeated on 1,000 bootstrapped samples to estimate the robust 95% confidence intervals. The natural effects of family support and local ties on cognitive function were estimated through this process. In addition, the proportion of the effect mediated by inflammatory biomarkers was calculated by dividing the total effect by the indirect effect for each exposure-mediator combination. Statistical analysis was conducted using R, version (4.0.4).

**Results**

Table 1 shows the sample characteristics at baseline. The mean age of the final analysis sample was 70.0 years (SD = 6.60). Among them, 41.9% are female and 45.6% of participants answered the survey in English, and 54.4% in Spanish. There was less baseline family support in participants with less daily activity difficulty, higher education levels, and those who were not married. Those participants with local ties had higher education levels, generally higher incomes, less daily activity difficulty, and were married. Those participants with local ties scored 0 or living alone reported generally worse health than the group with local ties or living with people.

Table 2 presents the results of general linear models of the overall association between family support measures, local ties measures, and cognitive function obtained in wave 4 and wave 6. Having family support score was associated with lower 3MSE error (wave 4 mean difference (MD) = -0.06, 95% CI: -0.15, 0.03; wave 6 MD = -0.02, 95% CI: -0.12, 0.07; units: log(3MSE errors)) and higher SEVLT score (wave 4 MD = 0.33, 95% CI: 0.06, 0.61; wave 6 MD = 0.08, 95% CI: -0.27, 0.42; units: number of words) and thus better cognitive function in both wave 4 and wave 6 after accounting for age, sex, and education level, individual income, occupation grouping for main lifetime job and marital status, ADL and IADL difficulties. Living with a child, living with family and daily contact with the closest contact at baseline were associated with better cognitive function for 3MSE and SEVLT in wave 4 and wave 6. However, the results showed that participants living with spouses at baseline or always meeting or talking to family or friends at baseline tended to have decreased cognitive function at follow-up (Table 2).

The pure direct and total indirect effect through inflammation of family support and local ties measures on cognitive function adjusting for confounders included in GLM model 3 are shown in Table 3 and Table 4. The results of the estimates of the association of elevated inflammatory biomarkers' level and cognitive function are shown in Table S2. adjusted covariates for mediation analysis are age, sex education level, individual income, occupation grouping for main lifetime job, marital status, ADL, and IADL difficulties. The results of mediation through inflammation are further illustrated with results of other decompositions of the total effect (Figures S2 and S3). The estimated indirect effects through most of the inflammatory biomarkers were very small and null. Applying the G-computation algorithm, we estimated that only a small fraction of the total effect of family support on wave 4 3MSE log error was mediated through the tested inflammatory biomarkers: HsCRP (3%), IL-6 (0.33%), and TNF-α (-1.22%). For wave 4 SEVLT, the proportion of the total effect of family support mediated through the biomarkers was 1.62% for HsCRP, 0.44% for IL-6, 1.93% for TNF-α. For wave 6 cognitive function measures, -9.91% of the total effect of family support on 3MSE log error was mediated through HsCRP, IL-6 (1.80%), TNF-α (4.95%) while 3.46% of the total effect on SEVLT was mediated through HsCRP, IL-6 (0.36%), TNF-α (6.32%). The proportion of the estimated effect of local ties (Table 3) on wave 4 and wave 6 cognitive measures was smaller than that of family support (Table 4).

# Discussion

In our study, we estimated the effect of baseline family support, always meeting with family/friends, and having daily contact with the closest contact on the cognitive function score in wave 4 (after approximately 5-7 years) and wave 6 (after approximately 7-9 years) of the SALSA study. The direct and indirect effects of having family support and local ties on the cognitive function scores measured in wave 4 and wave 6 of the SALSA study through hsCRP, IL-6, and TNF-α inflammatory biomarkers were also assessed by conducting a causal mediation analysis using g-computation.

Overall, our study suggests that family support and local ties might be beneficial for cognitive function among older Mexican Americans, which is consistent with prior studies[50–53]. For both 3MSE and SEVLT scores, the effects on wave 4 (5-7 years after baseline) had tighter confidence intervals than on wave 6 (7-9 years after baseline) due to the larger sample size we had for Wave 4 cognitive measures. The magnitude of the wave 4 effect was also larger than of wave 6 suggesting that there might be a difference in the effect of family support and social activities as time passed. A prior study analyzing data from Mexico, Study on Global Ageing (SAGE) study provides evidence that social support is positively associated with the cognitive function of Mexican adults aged 71 to 80 and that this association was not observed in the 80+ age group. Social support in this prior study was defined using social connection indices like marital status, connection with friends, socializing with colleagues, etc.[50] Another study using the prospective multicenter cohort study AgeCoDe indicated the influence of family support is limited for those aged 80 and over[14]. This suggests that the contribution of family support and local ties to cognitive function may shrink in older age. The mean baseline age of our study sample was 70 years old. Evidence has shown that cognitive decline was already affected for the older group[52,54].

The effect of different components of family support and local ties were also tested in our study. Living with children and living with family members other than spouse and children showed effects consistent with the combined measure: having family support or not. They had negative associations with cognitive function and the magnitude of the effects were larger in wave 4 than in wave 6. However, living with a spouse was associated with reduced cognitive function in our sample (Table 2). Evidence showed the relationship between living with family members and cognitive function may depend on the starting level of cognitive function. An unexpected detrimental role of living with a spouse was found among older people with low baseline cognitive level[55]. Another study using nationally representative panel data from American's Changing Lives Survey suggests that the relationship with their children affected cognitive function. Also, there is a potential gender gap in cognitive function among aging parents experiencing high levels of strain with their children. Higher levels of strain with their children were positively linked with cognitive function for fathers but not for mothers[56]. Daily contact with the closest contact appeared to be a protective factor to cognitive function while always meeting or talking with family/friends showed the opposite association (Table 3). The discordance between the response of these two measures potentially suggests the presence of measurement error. There were around 45% of participants who reported that they interacted daily with the closest contact and who reported that they didn't always meet or talk to family/friends and vice versa.

To the best of our knowledge, this is the first study to investigate whether inflammation mediated the effect of family support and local ties on cognitive function. Though the total effects shown in this study are compatible with the protective effects of family support and local ties on cognitive function scores, our mediation results should be interpreted with caution. The 95% CI for the indirect effects of family support or local ties on cognitive scores through hsCRP, IL-6, and TNF-$\alpha$ were null in this study sample (Table 3 & 4).

Though the baseline measures for the inflammatory biomarkers were used in this study, having family support or having local ties might predict inflammation more immediately. Thus, the proportion of the total effect mediated by the inflammatory biomarkers might be limited.

One of the major strengths of this study is that the analysis is based on a population-based cohort study of older Mexican Americans followed for up to 10 years with up to 7 interviews. Moreover, we conducted a rigorous causal mediation analysis based on the potential outcomes framework to assess the direct and indirect effects[49]. However, there are several limitations of the study which should be noted. Similar to other analyses of observational studies, we made several assumptions. First, positivity, consistency, and no other unmeasured confounders were assumed[57–59]. To identify the decomposition of the total effect, we also assumed that the confounder set was the same for exposure-mediator, mediator-outcome, and exposure-outcome paths. Since the natural effects were assessed in the study, we further assumed none of the mediator-outcome confounders are affected by exposure[49].

To obtain the analysis sample, participants without family support and local ties information were dropped. There was more missingness for the family support among those participants with lower education levels which implies missing at random mechanism. For the difference between effects on wave 4 and wave 6 cognitive function score measures, many participants had an event (death, loss to follow up, or dementia or CIND) before the wave 6 interview. Participants might have a very different interpretation of the questions asked for family support and local ties. For instance, as mentioned above, there are a lot of discordant responses to the questions: how often they contact daily with the closest contact and how often did they meet or talk to family/friends. The type of contacts is defined vaguely in the questionnaire that participants might not have family members or friends as their closest contact or they did not consider the closest contact as their friends

suggesting it is not a good measure for social relationship and local ties. Another weakness worth noting is that due to the limited availability of the data, we only assessed the effect for the baseline measures of family support and local ties. We are not able to observe the effect of family support trajectories of older Mexican Americans. The effect of different types of family support such as emotional and physical support can be further studied as shown in the previous studies that emotional support has a positive association with cognitive functioning[60].

In conclusion, our findings for the total effect of family support and local ties are compatible with a protective effect on the indicators of cognitive functioning. Based on our estimates, it is very unlikely that this effect was mediated through inflammatory biomarkers within this study sample. The mediation analysis in this study was for a small set of biomarkers. Future studies should look at more inflammatory biomarkers, start the follow-up earlier at the time when support can be more beneficial and have a better and more detailed measurement of family support and also look at such effects for participants by different birth country or time in the US since immigration.

**Tables and Figures**
**Table 1 Baseline characteristics of the study population stratified by family support and local ties, Sacramento Area Latino Study on Aging, 1998-2007.**

| | Overall, N = 1,374 | Family support* | | Local ties* | |
|---|---|---|---|---|---|
| | | No, N = 289 | Yes, N = 1,085 | No, N = 149 | Yes, N = 1,119 |
| Baseline Age | 69.97 (6.59) | 71.22 (6.81) | 69.63 (6.50) | 70.75 (6.53) | 69.94 (6.60) |
| Female | 576 (41.92%) | 80 (27.68%) | 496 (45.71%) | 57 (38.26%) | 480 (42.90%) |
| Education level: >= 12 years | 431 (31.37%) | 105 (36.33%) | 326 (30.05%) | 37 (24.83%) | 362 (32.35%) |
| Individual gross income (monthly) | 882.15 (584.16) | 1,028.90 (725.95) | 843.06 (533.79) | 761.62 (531.92) | 898.37 (584.33) |
| Occupation attainment: high professional level | 171 (12.45%) | 47 (16.26%) | 124 (11.43%) | 12 (8.05%) | 144 (12.87%) |
| Language | | | | | |
|   English | 627 (45.63%) | 151 (52.25%) | 476 (43.87%) | 43 (28.86%) | 537 (47.99%) |
|   Spanish | 747 (54.37%) | 138 (47.75%) | 609 (56.13%) | 106 (71.14%) | 582 (52.01%) |
| Self Reported Health | | | | | |
|   Excellent | 97 (7.09%) | 29 (10.07%) | 68 (6.29%) | 8 (5.37%) | 81 (7.27%) |
|   Very Good | 183 (13.37%) | 40 (13.89%) | 143 (13.23%) | 15 (10.07%) | 154 (13.82%) |
|   Good | 440 (32.14%) | 87 (30.21%) | 353 (32.65%) | 47 (31.54%) | 363 (32.59%) |
|   Fair | 522 (38.13%) | 101 (35.07%) | 421 (38.95%) | 57 (38.26%) | 421 (37.79%) |
|   Poor | 127 (9.28%) | 31 (10.76%) | 96 (8.88%) | 22 (14.77%) | 95 (8.53%) |
| ADL difficulty | 144 (10.48%) | 47 (16.26%) | 97 (8.94%) | 20 (13.42%) | 107 (9.56%) |

| | | | | | |
|---|---|---|---|---|---|
| IADL difficulty | 771 (56.11%) | 165 (57.09%) | 606 (55.85%) | 95 (63.76%) | 607 (54.24%) |
| Diabetes | 380 (27.66%) | 85 (29.41%) | 295 (27.19%) | 47 (31.54%) | 302 (26.99%) |
| Marital status: Married | 818 (59.53%) | 11 (3.81%) | 807 (74.38%) | 70 (46.98%) | 700 (62.56%) |
| High Sensitive CRP level: high | 1,100 (80.12%) | 231 (79.93%) | 869 (80.17%) | 121 (81.21%) | 894 (79.96%) |
| IL-6 level: high | 1,224 (89.47%) | 259 (89.62%) | 965 (89.43%) | 136 (91.28%) | 1,000 (89.77%) |
| TNF Alpha level: high | 50 (3.83%) | 9 (3.27%) | 41 (3.98%) | 4 (2.78%) | 40 (3.78%) |
| Baseline 3MSE score | 86.75 (10.20) | 87.07 (9.79) | 86.66 (10.30) | 84.05 (10.41) | 87.16 (10.00) |
| Baseline CES-D | 9.62 (10.40) | 11.55 (11.11) | 9.11 (10.15) | 12.46 (12.02) | 9.16 (10.07) |
| Dementia/CIND | 127 (9.24%) | 27 (9.34%) | 100 (9.22%) | 15 (10.07%) | 102 (9.12%) |
| Wave 4 log 3MSE error | 2.17 (1.05) | 2.13 (1.00) | 2.18 (1.06) | 2.44 (1.06) | 2.15 (1.04) |
| Wave 6 log 3MSE error | 2.61 (0.89) | 2.51 (0.91) | 2.63 (0.88) | 2.57 (1.01) | 2.62 (0.87) |
| Wave 4 SEVLT | 8.79 (2.99) | 8.70 (3.22) | 8.81 (2.92) | 8.30 (2.52) | 8.80 (3.03) |
| Wave 6 SEVLT | 8.72 (3.09) | 9.00 (3.06) | 8.66 (3.09) | 9.02 (2.99) | 8.64 (3.04) |

Mean(SD) for continuous variables; n(%) for categorical variables

* Stratified by having family support or not and having local ties or not

**Table 2 Mean difference of family support as well as local ties and cognitive function, Sacramento Area Latino Study on Aging, 1998 - 2007**

| | 3MSE log error | | | | | | SEVLT | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Wave 4 | | | Wave 6 | | | Wave 4 | | | Wave 6 | | |
| | Estimate | 95% CI | | Estimate | 95% CI | | Estimate | 95% CI | | Estimate | 95% CI | |
| **Having family support** | | | | | | | | | | | | |
| Crude | 0.0242 | -0.0601 | 0.1085 | 0.0318 | -0.0467 | 0.1102 | 0.2129 | -0.0405 | 0.4664 | -0.0642 | -0.3747 | 0.2464 |
| Model 1 | 0.0286 | -0.0484 | 0.1056 | 0.0318 | -0.046 | 0.1096 | 0.1663 | -0.069 | 0.4016 | -0.1151 | -0.4038 | 0.1736 |
| Model 2 | -0.0772 | -0.1687 | 0.0143 | -0.0298 | -0.1246 | 0.0649 | 0.3382 | 0.0546 | 0.6218 | 0.1 | -0.2454 | 0.4455 |
| Model 3 | -0.0611 | -0.1508 | 0.0286 | -0.0218 | -0.1157 | 0.072 | 0.3348 | 0.0555 | 0.6142 | 0.0781 | -0.2657 | 0.422 |
| **Living with spouse** | | | | | | | | | | | | |
| Crude | -0.1703 | -0.3156 | -0.0249 | -0.0103 | -0.1493 | 0.1287 | 0.1147 | -0.3235 | 0.5529 | -0.181 | -0.7308 | 0.3688 |
| Model 1 | -0.0167 | -0.154 | 0.1206 | 0.0069 | -0.1363 | 0.15 | 0.0343 | -0.3852 | 0.4538 | -0.0521 | -0.5823 | 0.478 |
| Model 2 | 0.0623 | -0.2448 | 0.3694 | 0.0878 | -0.2441 | 0.4197 | -0.5614 | -1.4959 | 0.3731 | -0.4237 | -1.5954 | 0.748 |
| Model 3 | 0.0736 | -0.2275 | 0.3746 | 0.0878 | -0.2411 | 0.4167 | -0.4827 | -1.404 | 0.4387 | -0.3853 | -1.5514 | 0.7808 |
| **Living with Children** | | | | | | | | | | | | |
| Crude | 0.1328 | -0.0146 | 0.2803 | 0.0689 | -0.0701 | 0.2079 | 0.1418 | -0.3052 | 0.5888 | -0.203 | -0.7514 | 0.3454 |
| Model 1 | 0.0261 | -0.1069 | 0.1591 | 0.0174 | -0.1183 | 0.153 | 0.138 | -0.2696 | 0.5457 | -0.141 | -0.6405 | 0.3586 |
| Model 2 | -0.1434 | -0.282 | -0.0048 | -0.0907 | -0.2358 | 0.0543 | 0.3717 | -0.059 | 0.8024 | 0.2292 | -0.2958 | 0.7542 |
| Model 3 | -0.1219 | -0.2576 | 0.0138 | -0.0882 | -0.2318 | 0.0553 | 0.355 | -0.0688 | 0.7788 | 0.2116 | -0.3102 | 0.7334 |
| **Living with other family members** | | | | | | | | | | | | |
| Crude | 0.1565 | -0.0143 | 0.3274 | 0.0495 | -0.1133 | 0.2124 | 0.5575 | 0.0452 | 1.0699 | 0.3138 | -0.3281 | 0.9558 |
| Model 1 | 0.0947 | -0.0586 | 0.2479 | 0.0923 | -0.0668 | 0.2513 | 0.4598 | -0.0065 | 0.9262 | -0.1687 | -0.7573 | 0.4199 |
| Model 2 | -0.0601 | -0.2172 | 0.097 | 0.005 | -0.1602 | 0.1703 | 0.7152 | 0.2342 | 1.1961 | 0.1746 | -0.4293 | 0.7786 |
| Model 3 | -0.0461 | -0.2 | 0.1077 | 0.0244 | -0.1395 | 0.1882 | 0.7212 | 0.2475 | 1.1949 | 0.1269 | -0.4753 | 0.7292 |
| **Having local ties** | | | | | | | | | | | | |
| Crude | -0.0629 | -0.1713 | 0.0456 | -0.0019 | -0.107 | 0.1033 | 0.2758 | -0.0532 | 0.6049 | -0.0211 | -0.4333 | 0.3912 |
| Model 1 | -0.072 | -0.1679 | 0.0239 | -0.0197 | -0.1203 | 0.0808 | 0.3792 | 0.0854 | 0.6729 | 0.1018 | -0.2655 | 0.4691 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Model 2** | -0.0657 | -0.1595 | 0.0282 | -0.0238 | -0.1235 | 0.076 | 0.3592 | 0.0675 | 0.651 | 0.1425 | -0.2197 | 0.5047 |
| **Model 3** | -0.048 | -0.1405 | 0.0444 | -0.0233 | -0.1224 | 0.0759 | 0.3156 | 0.0261 | 0.6051 | 0.1151 | -0.2459 | 0.476 |
| **Always meet to or talk to family/friends** | | | | | | | | | | | | |
| **Crude** | -0.2204 | -0.4245 | -0.0163 | 0.1144 | -0.0838 | 0.3126 | 0.3299 | -0.292 | 0.9518 | -0.5146 | -1.2968 | 0.2677 |
| **Model 1** | -0.1529 | -0.3339 | 0.0281 | 0.1147 | -0.0747 | 0.3041 | 0.4363 | -0.1213 | 0.9938 | -0.3016 | -1.0016 | 0.3985 |
| **Model 2** | -0.125 | -0.3033 | 0.0533 | 0.1156 | -0.0729 | 0.3042 | 0.3473 | -0.2096 | 0.9043 | -0.3364 | -1.0262 | 0.3535 |
| **Model 3** | -0.0778 | -0.2541 | 0.0985 | 0.1437 | -0.0439 | 0.3313 | 0.256 | -0.2984 | 0.8103 | -0.4569 | -1.1475 | 0.2337 |
| **Daily contact with the closest contact** | | | | | | | | | | | | |
| **Crude** | 0.002 | -0.1463 | 0.1504 | -0.084 | -0.2221 | 0.0541 | 0.3222 | -0.1252 | 0.7696 | 0.2506 | -0.2947 | 0.7959 |
| **Model 1** | -0.0555 | -0.1869 | 0.0758 | -0.1157 | -0.2477 | 0.0163 | 0.4514 | 0.052 | 0.8508 | 0.3597 | -0.127 | 0.8463 |
| **Model 2** | -0.0619 | -0.1903 | 0.0665 | -0.1252 | -0.2563 | 0.0059 | 0.4673 | 0.0712 | 0.8633 | 0.4527 | -0.0277 | 0.9332 |
| **Model 3** | -0.0526 | -0.1789 | 0.0737 | -0.1373 | -0.2677 | -0.007 | 0.4306 | 0.0387 | 0.8226 | 0.4637 | -0.0154 | 0.9427 |

3MSE: Modified Mini Mental State Exam, SEVLT: Spanish and English Verbal Learning Test

Variables adjusted in the models:

Model 1: sex, and education level

Model 2: + individual income, occupational main lifetime job category, and marital

Model 3: + ADL and IADL difficulties

**Table 3 Direct and Indirect (Through Different Mediators as shown in the table) Effects of family support (any v.s. 0) on the cognitive function (Mean Difference scale), Sacramento Area Latino Study on Aging, 1998 - 2007**

| | Total Effect | | | Direct Effect | | | Indirect Effect | | | % |
|---|---|---|---|---|---|---|---|---|---|---|
| | MD | 95% CI | | MD | 95% CI | | MD | 95% CI | | Mediated |
| **Outcome: Wave 4 3MSE log error** | | | | | | | | | | |
| **Mediators** | | | | | | | | | | |
| HsCRP | | | | -0.0885 | -0.2916 | 0.1047 | -0.0027 | -0.0781 | 0.0742 | 2.98% |
| IL-6 | -0.0905 | -0.2835 | 0.1024 | -0.0824 | -0.2741 | 0.1397 | -3e-04 | -0.0688 | 0.0753 | 0.33% |
| TNF-α | | | | -0.0797 | -0.2791 | 0.1331 | 0.0011 | -0.0763 | 0.077 | -1.22% |
| **Outcome: Wave 4 SEVLT** | | | | | | | | | | |
| **Mediators** | | | | | | | | | | |
| HsCRP | | | | 0.4132 | -0.2623 | 1.12 | 0.0067 | -0.2057 | 0.2178 | 1.62% |
| IL-6 | 0.4136 | -0.1918 | 1.0189 | 0.4157 | -0.2732 | 1.1066 | 0.0018 | -0.203 | 0.2097 | 0.44% |
| TNF-α | | | | 0.4065 | -0.3057 | 1.1051 | 0.008 | -0.1967 | 0.2135 | 1.93% |
| **Outcome: Wave 6 3MSE log error** | | | | | | | | | | |
| **Mediators** | | | | | | | | | | |
| HsCRP | | | | 0.0218 | -0.2165 | 0.236 | -0.0022 | -0.0507 | 0.0453 | -9.91% |
| IL-6 | 0.0222 | -0.1829 | 0.2274 | 0.0222 | -0.1982 | 0.2402 | 4e-04 | -0.0479 | 0.0441 | 1.80% |
| TNF-α | | | | -0.0039 | -0.2208 | 0.2153 | 0.0011 | -0.0438 | 0.0497 | 4.95% |
| **Outcome: Wave 6 SEVLT** | | | | | | | | | | |
| **Mediators** | | | | | | | | | | |
| HsCRP | | | | 0.2244 | -0.6133 | 1.1144 | 0.0076 | -0.2164 | 0.2308 | 3.46% |
| IL-6 | 0.2199 | -0.539 | 0.9788 | 0.2509 | -0.6396 | 1.1364 | 8e-04 | -0.2224 | 0.2348 | 0.36% |
| TNF-α | | | | 0.2461 | -0.5891 | 1.2092 | 0.0139 | -0.2167 | 0.2465 | 6.32% |

CI: confidence interval; HsCRP: high-sensitivity C-reactive protein, IL-6: Interleukin 6, TNF-α: tumor necrosis factor alpha

**Table 4 Direct and Indirect (Through Different Mediators as shown in the table) Effects of local ties (any v.s. 0) on the cognitive function (Mean Difference scale), Sacramento Area Latino Study on Aging, 1998 - 2007**

| | Total Effect | | | Direct Effect | | | Indirect Effect | | | % |
|---|---|---|---|---|---|---|---|---|---|---|
| | MD | 95% CI | | MD | 95% CI | | MD | 95% CI | | Mediated |
| **Outcome: Wave 4 3MSE log error** | | | | | | | | | | |
| **Mediators** | | | | | | | | | | |
| HsCRP | | | | -0.1814 | -0.4218 | 0.0484 | -2e-04 | -0.107 | 0.1098 | 0.12% |
| IL-6 | -0.1619 | -0.3634 | 0.0396 | -0.1672 | -0.3856 | 0.0638 | -0.0011 | -0.1017 | 0.1053 | 0.68% |
| TNF-α | | | | -0.1633 | -0.392 | 0.0491 | -2e-04 | -0.1016 | 0.1095 | 0.12% |
| **Outcome: Wave 4 SEVLT** | | | | | | | | | | |
| **Mediators** | | | | | | | | | | |
| HsCRP | | | | 0.3954 | -0.3028 | 1.0778 | -0.0038 | -0.2596 | 0.2584 | -1.22% |
| IL-6 | 0.3108 | -0.3338 | 0.9554 | 0.3147 | -0.3695 | 1.0204 | 0.0031 | -0.2838 | 0.2599 | 1.00% |
| TNF-α | | | | 0.2696 | -0.4278 | 0.9734 | 0.0043 | -0.2778 | 0.296 | 1.38% |
| **Outcome: Wave 6 3MSE log error** | | | | | | | | | | |
| **Mediators** | | | | | | | | | | |
| HsCRP | | | | 0.029 | -0.2434 | 0.2856 | -0.0018 | -0.0616 | 0.059 | -4.30% |
| IL-6 | 0.0419 | -0.1875 | 0.2714 | 0.0469 | -0.1924 | 0.3208 | -0.001 | -0.0639 | 0.0539 | -2.39% |
| TNF-α | | | | -0.0102 | -0.2762 | 0.2644 | 0 | -0.0581 | 0.0555 | 0.00% |
| **Outcome: Wave 6 SEVLT** | | | | | | | | | | |
| **Mediators** | | | | | | | | | | |
| HsCRP | | | | -0.2951 | -1.1274 | 0.5681 | -0.0011 | -0.2832 | 0.2805 | 0.28% |
| IL-6 | -0.3865 | -1.2317 | 0.4587 | -0.3366 | -1.184 | 0.4896 | 0.0023 | -0.2902 | 0.2996 | -0.60% |
| TNF-α | | | | -0.3001 | -1.1859 | 0.6119 | 0.0031 | -0.2761 | 0.2696 | -0.80% |

CI: confidence interval; HsCRP: high-sensitivity C-reactive protein, IL-6: Interleukin 6, TNF-α: tumor necrosis factor alpha

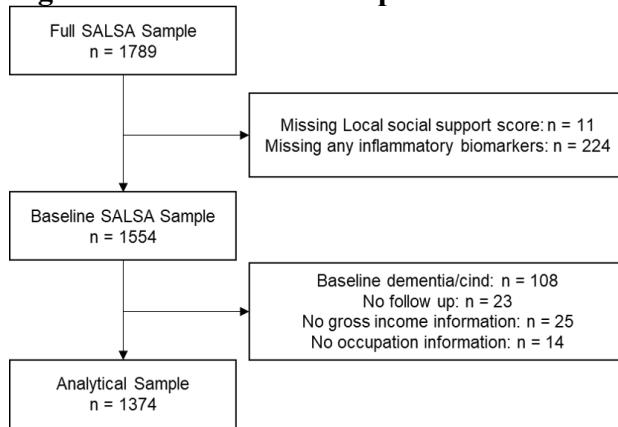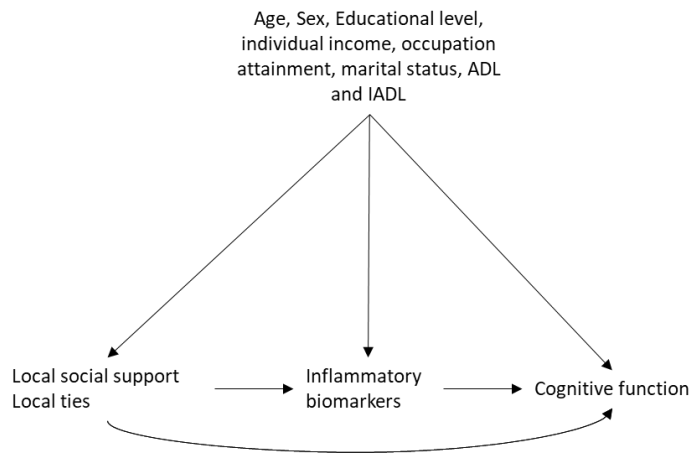**Figure 1 Flow chart of sample size determination.**



**Figure 2 Assumed causal structure of the relationship of family support/ local ties (exposure), inflammatory markers (mediators) and cognitive function (outcome) with confounders: Age, Sex, Educational level,  individual income, occupation attainment, marital status, ADL and IADL.**

# APPENDIX

**Table S1 Causal quantities, empirical analogues and equations used to simulate potential mediators and outcomes.**

| Effect | Causal quantities | Empirical analogues | Equations |
|---|---|---|---|
| PDE | $E(Y_{xM_{x^*}})$ $- E(Y_{x^*M_{x^*}})$ | $\sum_C \sum_m E(Y\|x, m, c)P(m\|x^*, c)P(c) -$ $\sum_C \sum_m E(Y\|x^*, m, c)P(m\|x^*, c)P(c)$ | $Y_{PDE} = \theta_0 + \theta_1 do(x) + \theta_2 m_{do(x=0)} + \theta_3 do(x)m_{do(x=0)} + \theta_4 c$ |
| TIE | $E(Y_{xM_x}) - E(Y_{xM_{x^*}})$ | $\sum_C \sum_m E(Y\|x, m, c)P(m\|x, c)P(c) -$ $\sum_C \sum_m E(Y\|x, m, c)P(m\|x^*, c)P(c)$ | $Y_{TIE} = \theta_0 + \theta_1 do(x = 1) + \theta_2 m_{do(x)} + \theta_3 do(x = 1)m_{do(x)} + \theta_4 c$ |
| TDE | $E(Y_{xM_x}) - E(Y_{x^*M_x})$ | $\sum_C \sum_m E(Y\|x, m, c)P(m\|x, c)P(c) -$ $\sum_C \sum_m E(Y\|x^*, m, c)P(m\|x, c)P(c)$ | $Y_{TDE} = \theta_0 + \theta_1 do(x) + \theta_2 m_{do(x=1)} + \theta_3 do(x)m_{do(x=1)} + \theta_4 c$ |
| PIE | $E(Y_{x^*M_x})$ $- E(Y_{x^*M_{x^*}})$ | $\sum_C \sum_m E(Y\|x^*, m, c)P(m\|x, c)P(c) -$ $\sum_C \sum_m E(Y\|x^*, m, c)P(m\|x^*, c)P(c)$ | $Y_{TIE} = \theta_0 + \theta_1 do(x = 0) + \theta_2 m_{do(x)} + \theta_3 do(x = 0)m_{do(x)} + \theta_4 c$ |
| CDEref | $E(Y_{xm^*}) - E(Y_{x^*m^*})$ | $\sum_C \sum_m E(Y\|x, m^*, c)P(m^*)P(c) -$ $\sum_C \sum_m E(Y\|x^*, m^*, c)P(m^*)P(c)$ | $Y_{CDE_{ref}} = \theta_0 + \theta_1 do(x) + \theta_2 do(m = 0) + \theta_3 do(x)do(m = 0) + \theta_4 c$ |
| CDEind | $E(Y_{xm}) - E(Y_{x^*m})$ | $\sum_C \sum_m E(Y\|x, m, c)P(m)P(c) -$ $\sum_C \sum_m E(Y\|x^*, m, c)P(m)P(c)$ | $Y_{CDE_{ind}} = \theta_0 + \theta_1 do(x) + \theta_2 do(m = 1) + \theta_3 do(x)do(m = 1) + \theta_4 c$ |
| CDEsto | $E(Y_{xM'}) - E(Y_{x^*M'})$ | $\sum_C \sum_m E(Y\|x, m, c)P(M')P(c) -$ $\sum_C \sum_m E(Y\|x^*, m, c)P(M')P(c)$ | $Y_{CDE_{ind}} = \theta_0 + \theta_1 do(x) + \theta_2 do(m) + \theta_3 do(x)do(m) + \theta_4 c$ |

**Table S2. Mean difference of elevated level of inflammatory biomarkers and cognitive function, Sacramento Area Latino Study on Aging, 1998 - 2007**

| | 3MSE log error | | | | | | SEVLT | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Wave 4 | | | Wave 6 | | | Wave 4 | | | Wave 6 | | |
| | Estimate | 95% CI | | Estimate | 95% CI | | Estimate | 95% CI | | Estimate | 95% CI | |
| High Sensitive CRP level: high | | | | | | | | | | | | |
| Crude | -0.0183 | -0.1936 | 0.1571 | -0.1024 | -0.2664 | 0.0615 | 0.3357 | -0.2013 | 0.8727 | 0.8753 | 0.2382 | 1.5125 |
| Model 1 | -0.0527 | -0.2112 | 0.1059 | -0.0672 | -0.2296 | 0.0953 | 0.0485 | -0.4455 | 0.5424 | 0.357 | -0.2433 | 0.9573 |
| Model 2 | -0.0888 | -0.2439 | 0.0663 | -0.078 | -0.2388 | 0.0829 | 0.0547 | -0.436 | 0.5455 | 0.3845 | -0.2077 | 0.9768 |
| Model 3 | -0.1368 | -0.2889 | 0.0153 | -0.108 | -0.2678 | 0.0519 | 0.1879 | -0.2973 | 0.6731 | 0.4814 | -0.1095 | 1.0723 |
| IL-6 level: high | | | | | | | | | | | | |
| Crude | 0.1375 | -0.0843 | 0.3594 | 0.1369 | -0.0686 | 0.3424 | -0.5903 | -1.2699 | 0.0892 | 0.0804 | -0.7186 | 0.8794 |
| Model 1 | 0.0509 | -0.1464 | 0.2482 | 0.059 | -0.1404 | 0.2585 | -0.1774 | -0.7916 | 0.4369 | 0.476 | -0.2545 | 1.2066 |
| Model 2 | 0.0165 | -0.1765 | 0.2096 | 0.0275 | -0.1704 | 0.2254 | -0.2088 | -0.8197 | 0.4022 | 0.5485 | -0.1756 | 1.2725 |
| Model 3 | -0.0029 | -0.1921 | 0.1863 | 0.0225 | -0.1733 | 0.2184 | -0.11 | -0.7141 | 0.494 | 0.5621 | -0.1569 | 1.2811 |
| TNF Alpha level: high | | | | | | | | | | | | |
| Crude | 0.0145 | -0.4094 | 0.4384 | 0.0926 | -0.302 | 0.4872 | -0.1309 | -1.4188 | 1.1569 | 0.5215 | -1.2043 | 2.2473 |
| Model 1 | 0.0025 | -0.3701 | 0.3752 | 0.0496 | -0.3308 | 0.43 | 0.182 | -0.9742 | 1.3382 | 1.1244 | -0.4431 | 2.6919 |
| Model 2 | 0.0264 | -0.338 | 0.3909 | 0.0549 | -0.3223 | 0.4321 | 0.1094 | -1.04 | 1.2588 | 0.9324 | -0.6239 | 2.4888 |
| Model 3 | 0.0581 | -0.2995 | 0.4156 | 0.0622 | -0.3116 | 0.4361 | 0.08 | -1.051 | 1.2111 | 1.0338 | -0.5155 | 2.5831 |

**Figure S1. The total effect of family support and local ties as well as its components on cognitive function (wave 4 and wave 6 3MSE log error and SEVLT)**
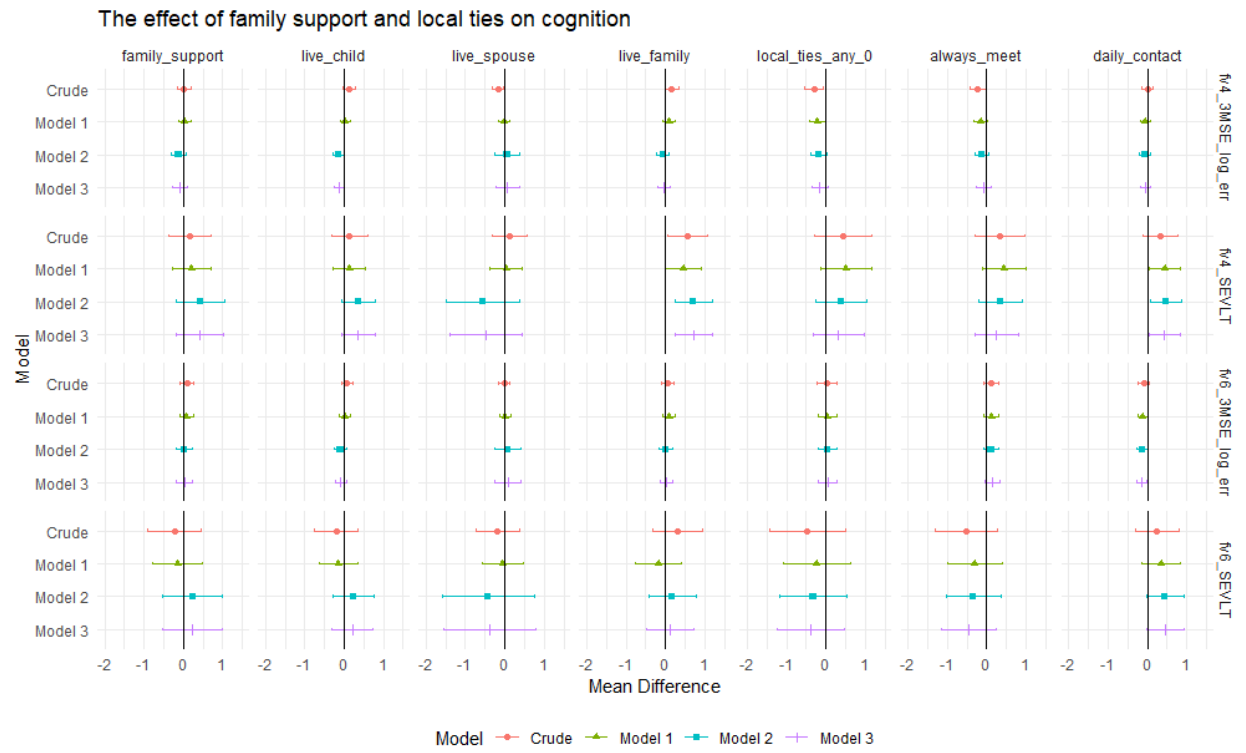
**Figure S2. The decompositions of the total effects of family support (any v.s. 0) on cognitive function (wave 4 and wave 6 3MSE log error and SEVLT)**



The Direct and indirect effect of local social ties (any v.s. 0) on cognition
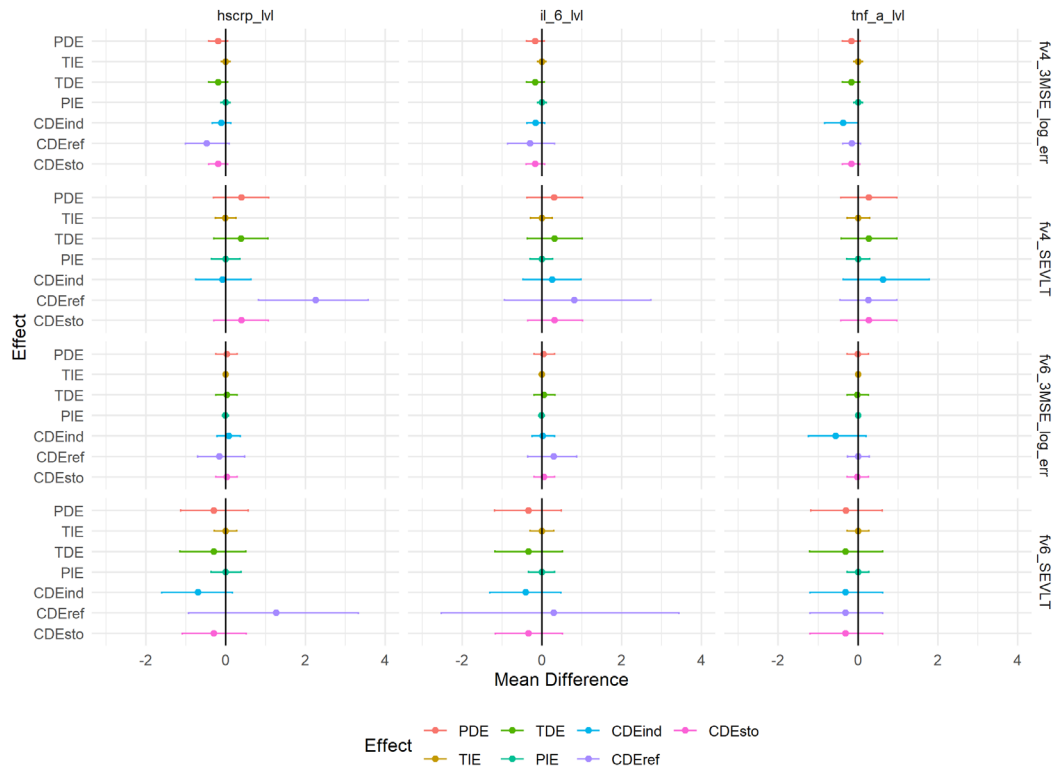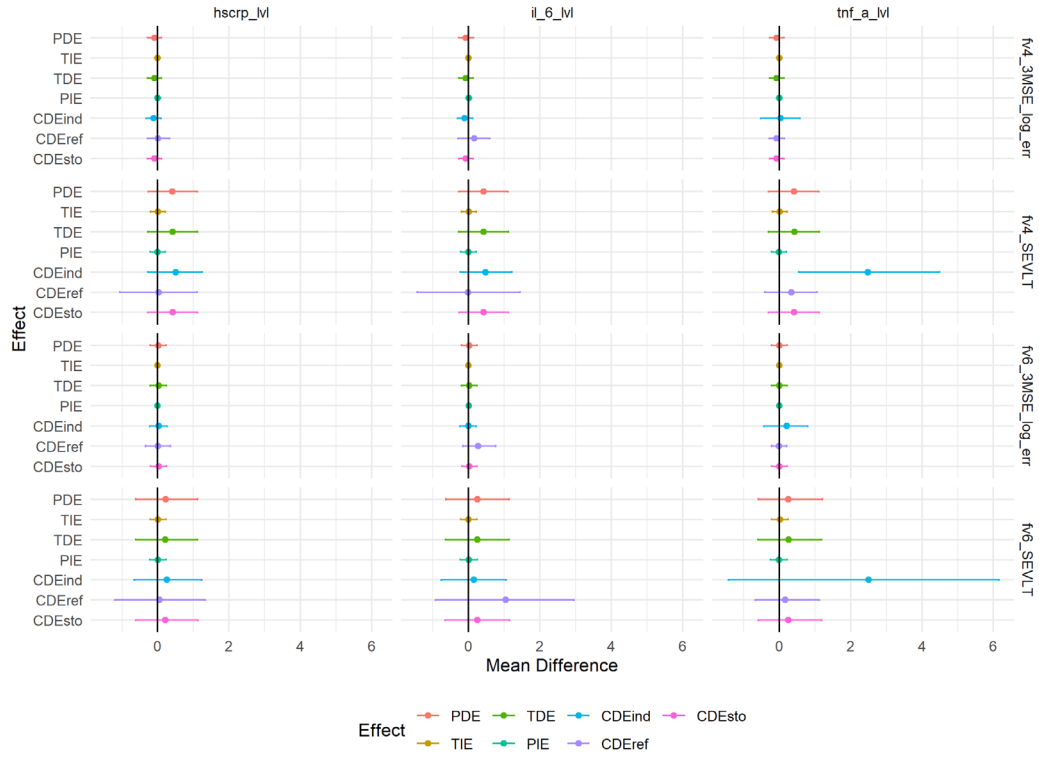
**Figure S3. The decompositions of the total effects of local ties (any v.s. 0) on cognitive function (wave 4 and wave 6 3MSE log error and SEVLT)**



The Direct and indirect effect of local social support (any v.s. 0) on cognition

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