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# Effects of depression and cognitive impairment on increased risks of incident dementia: a prospective study from three elderly cohorts

Yushun Yan<sup>1,3</sup>, Hailin Xiang<sup>1,3</sup>, Min Wang<sup>1</sup>, Jinxue Wei<sup>1</sup>, Huanhuan Fan<sup>1</sup>, Yue Du<sup>1</sup>, Yuanmei Tao<sup>1</sup>, Yikai Dou<sup>1</sup> , Yangrui Ma<sup>2</sup>, Xiao Yang<sup>1</sup> and Xiaohong Ma<sup>1</sup>

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Depression is usually accompanied with cognitive impairment and increases risk of incident dementia. However, evidence has been limited on the effect size of depression with cognitive impairment and their synergistic effect on future dementia. To explore this, we examined three large cross-country population-based prospective cohorts. Depressive symptoms were assessed by epidemiologic scale, while cognitive impairment was defined by subjective cognitive tests. Dementia was ascertained by self-reported physician-diagnosed conditions. Cox proportional hazard models were employed to determine the hazard ratio (HR) and 95% confidence interval (95% CI), with adjustments of potential confounding variables. Addictive and multiplicative interactions were calculated to evaluate the synergistic effect. A total of 64,706 participants were included at baseline (mean age: 63.9, female: 55.2%), where 4197 (6.5%) individuals had depressive symptoms only, 28,175 (43.5%) individuals had cognitive impairment only, 11,564 (17.9%) individuals had both, and 20,770 (32.1%) individuals had neither. Compared with the neither group, all the other three groups had higher risks of subsequent dementia (depression only: HR 1.65, 95% CI 1.26–2.17; cognitive impairment only: HR 2.71, 95% CI 2.33–3.14; depression with cognitive impairment: HR 3.51, 95% CI 2.95–4.17). There was insignificant additive (RERI, 0.15, 95% CI –0.45–0.75; AP, 0.042, 95% CI –0.13–0.21; SI, 1.06, 95% CI 0.83–1.37) and multiplicative (0.78, 95% CI 0.58–1.06) interaction between depression and cognitive impairment on subsequent dementia. We found depression with cognitive impairment has higher risks of dementia than either condition alone and no significant synergistic effect exists between these two factors.

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## INTRODUCTION

Dementia significantly contributes to the burden of disability-adjusted life years among elderly individuals aged 75 and above worldwide [1]. As a neurodegenerative condition, effective interventions for curing or reversing dementia are currently lacking. The common practice now is to identify its modifiable risk factors or pre-clinical prodromal stages and implement primary prevention strategies accordingly.

Previous studies have demonstrated the association between depression and dementia. Comorbid depression is common among the dementia population, with a prevalence of depressive symptoms at 37% to 41% and major depressive disorder at 15.9% [2, 3]. On the other side, previous depression is believed to be correlated with subsequent dementia. Meta-analytic researches suggest that depression convincingly increases the risks of all-cause dementia [4, 5]. An exposure-wide association study consisting of 344,324 individuals in UK Biobank demonstrates that diagnosis with depression as a modifiable factor increases the risk of incident dementia [6]. Several large-sample studies also indicate that those who experienced major depressive episodes in middle age are at a higher risk of developing dementia in elder age during long-term follow-up period [7, 8].

The impact of depression on dementia may not be independent but influenced by other factors. The onset time of depression is the most discussed factor, that depression is served as a modifiable risk factor or prodromal symptom of neurodegeneration [9, 10]. Physical conditions are also in consideration. Diabetes is independently associated with an elevated risk of dementia, and its interaction with depression significantly increases this risk [11]. Cerebrovascular diseases present a substantial risk for progressing to dementia [12]. When combined with depression, the association of vascular factors with future dementia is significantly stronger than an additive effect alone [13]. A few pathological indicators are associated with dementia, such as A $\beta$ -amyloid plaques, pathologic tau and apolipoprotein E allele, and there may also be a synergistic effect between depression and these biomarkers [14, 15]. Specific symptoms in relation to depression may contribute to the depression-dementia association. Higher scores on specific domain of depression symptoms such as appetite and weight loss are associated with increased likelihood of dementia [16]. Cognitive impairment may also be an accompanying symptom of depression [17]. Besides, cognitive impairment is considered as the core symptom of dementia, and individuals often experience progressive cognitive decline even

<sup>1</sup>Mental Health Center and Institute of Psychiatry, West China Hospital, Sichuan University, Chengdu, China. <sup>2</sup>School of Arts and Sciences, Brandeis University, Waltham, MA 02453, USA. <sup>3</sup>These authors contributed equally: Yushun Yan, Hailin Xiang. ✉email: [yangxiao@wchscu.cn](mailto:yangxiao@wchscu.cn); [maxiaohong@scu.edu.cn](mailto:maxiaohong@scu.edu.cn)

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before being diagnosed with dementia [18, 19]. Thus, we speculate that cognitive impairment is a critical factor in the relationship between depression and dementia. However, few studies have quantified either the effect size of early pre-dementia cognitive impairment or the interaction between cognitive impairment and depression on the risk of future dementia.

In the current study, we have conducted a secondary analysis upon three prospective cohorts of Health and Retirement Study (HRS), English Longitudinal Study of Ageing (ELSA), and Survey of Health, Ageing and Retirement in Europe (SHARE). Our primary objectives are to (1) explore the association between depression with cognitive impairment and subsequent dementia; and (2) exam the additive and multiplicative interactions of depression and cognitive impairment on future dementia.

## METHODS

### Study design and population

The HRS, ELSA, and SHARE were prospective, longitudinal cohort recruiting senior individuals in the USA, UK, and Europe, respectively. More than 42,000 participants in HRS, 19,000 in ELSA, and 139,000 in SHARE were included and followed up every two years. For each participant, the first wave after reaching the age of 50 was considered as the baseline. Moreover, participants were excluded if they reported a diagnosis with any memory-related disorders (i.e., Alzheimer's disease, dementia, organic brain senility, or any other serious memory condition) or somatic neurological diseases (i.e., stroke or/and Parkinson's disease) at a younger age. Endpoints were identified as the subsequent follow-up wave when participants initially reported a diagnosis with all-cause dementia, stroke, or Parkinson's disease at the follow-up phases. For those who never had a diagnosis of any memory or somatic neurological disorders throughout the entire follow-up period, the last wave they responded was considered as endpoints. At the endpoint, participants who reported a diagnosis of dementia and had not been diagnosed with stroke or Parkinson's disease were considered to have experienced an outcome event. Those who reported no diagnosis of dementia during follow-up, or who were diagnosed with stroke or Parkinson's before any dementia diagnosis, were considered censored.

### Depression assessment

Depressive symptoms were evaluated utilizing the Center for Epidemiologic Studies Depression Scale (CES-D) in HRS and ELSA, and European Depression scale (EURO-D) in SHARE, with items being dichotomized into 1 (yes) or 0 (no). The total scores of CES-D ranged from 0 to 8, while the total scores of EURO-D ranged from 0 to 12, with higher values indicating more severe depression. According to previous researches, participants with a CESD or SHARE score lower than 4 were considered to have no depressive symptoms, while those with a score equal to or higher than 4 were considered to have depressive symptoms (see Supplementary Method 2) [20–22].

### Cognition assessment

Objective cognitive performances were evaluated by calculating two summary scores: total cognitive scores and scores of verbal fluency test. Total cognitive scores summarized total word recall scores and mental status scores which consisted of a series of simplex ordinary cognitive tests (see Supplementary Method 1). In total word recall test, the participant was given with 10 words and was then asked to recall them immediately and later in the survey again (total score ranging from 0 to 20). The construction of mental status tests varied across different databases, depending on the completeness of the items reported at each follow-up visit. The tests battery contained serial 7's, backwards counting from 20, as well as object, date, and president/vice-president naming tasks in HRS (scores ranging from 0 to 15), date naming task only in ELSA (scores ranging 0 to 4); and serial 7's, simple computation, and date naming tasks in SHARE (scores ranging from 1 to 14). In the verbal fluency test, participants were asked to name as many animals as possible within one minute, and the count of all acceptable names served as the final score (ranging 0 to 100). Higher scores on these tests indicated better cognitive function.

To define cognitive impairment, a normative cognitive framework should be established to quantify age-dependent cognitive decline as well as cognitive deviations related to gender and education. A subset of baseline individuals was chosen if they (1) had never been diagnosed with any neurological diseases throughout the entire follow-up period, and (2) did not

display any depressive symptoms (i.e., CESD or EUROD score equal to zero). For each cohort, two regression models were constructed based on the subset, incorporating cognitive scores as response variables, and age, gender, and educational level as predictive variables. These two models were then employed to derive predictive values for total cognitive and verbal fluency scores across all participants at baseline. Those whose actual cognitive scores were both lower than the predictive values were categorized as having cognitive impairment, while those whose scores both exceeded the predictive values were considered to have cognitive preservation. Individuals with only one predictive score decline were considered as unrobust marginal threshold and removed from subsequent analysis (see Supplementary Method 2).

### Covariates

The covariates included age, gender, education, marital status, physical health conditions and health behaviors (see Supplementary Method 2). Age was recorded as the actual number of years at baseline, while gender was determined based on the first non-missing report. Education was categorized into three levels: (1) less than upper secondary, (2) upper secondary and vocational, and (3) tertiary. Marital status was classified into three categories: (1) married or partnered, (2) separated, divorced or widowed, and (3) never married nor partnered. Physical health conditions encompassed whether participants had been previously diagnosed with hypertension, diabetes, cancers, lung diseases, heart problems, or arthritis before the baseline assessment. Health behaviors comprised body mass index (BMI), drinking and smoking habit, and frequency of physical activity. Due to incomplete BMI records for participants in ELSA across all follow-up waves, we assumed minimal BMI fluctuations for each participant across waves and used the mean value to represent their BMI status at each follow-up point. For the same reason, drinking habit was defined as the consumption of any alcohol within the past seven days or weekly in HRS and SHARE, and as having ever consumed any alcohol in ELSA. Smoking habit was defined as smoking currently or not. Physical activity assessed the frequency of vigorous, moderate, and mild physical activities, which were categorized into (1) vigorous, (2) moderate, and (3) inactive, according to a previous study [23].

### Statistical analyses

For descriptive statistics, continuous variables were presented as mean accompanied [standard deviation (SD)], and categorical variables were denoted by count [percentage]. To assess the risks of incident dementia within subgroups, Cox proportional hazard regression was utilized to compute the hazard ratio (HR) and its corresponding 95% confidence interval (CI) (R package "survival" version 3.6). Basic model (Model 1) was adjusted by baseline age, gender, education, and marital status were considered as covariates, while expanded model (Model 2) incorporated physical health conditions and health behaviors. Missing covariates were imputed utilizing multiple imputations (R package "mice" version 3.16.0). Furthermore, pairwise comparison between groups and multiple comparison correlation were administrated (R package "multicomp" version 1.4-25).

The synergetic effects of depression and cognitive impairment on substantial dementia were quantified (R package "epiR" version 2.0.75) [24]. To assess additive interaction, we calculated the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (SI) to determine if the combined risk of both factors exceeded the sum of their individual risks. In addition, multiplicative interaction was assessed to evaluate whether the combined risk of both factors is greater than the product of their individual risks.

Sensitivity analyses were conducted to assess the robustness of main results, excluding (1) individuals under the age of 65; (2) participants with follow-up period no more than 1 year, in an attempt to mitigate the potential effects of reverse causality; and (3) participants with missing covariates instead of using multiple imputation.

Statistical analyses were conducted using R software version 4.2.1. We employed two-tailed tests for all *P*-values, with statistical significance defined as *P* < 0.05.

## RESULTS

The analysis consisted of Wave 10–15 of HRS, wave 1–9 of ELSA, and wave 4–8 of SHARE, from which data of 11,160 (17.25%) participants in HRS, 9719 (15.02%) in ELSA, and 43,827 (67.73%) in SHARE were included, respectively. Among these 64,706 participants, the mean age was 63.9 years (SD, 10.2 years) and 35,714 (55.2%) were woman (see Table 1). Also of these participants, 4197

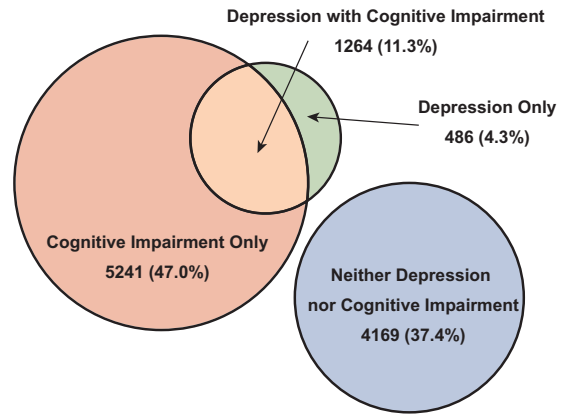
**Table 1.** Baseline characteristics of participants combining three databases.

	Neither depression nor cognitive impairment	Depression only	Cognitive impairment only	Depression with cognitive impairment	Overall
Sample size, <i>n</i> (%)	20,770 (32.1%)	4197 (6.5%)	28,175 (43.5%)	11,564 (17.9%)	64,706 (100%)
Age, year (SD)	63.4 (9.53)	63.4 (9.88)	63.8 (10.4)	65.2 (10.9)	63.9 (10.2)
Gender, <i>n</i> (%)					
Man	9910 (47.7%)	1341 (32.0%)	13,908 (49.4%)	3833 (33.1%)	28,992 (44.8%)
Woman	10,860 (52.3%)	2856 (68.0%)	14,267 (50.6%)	7731 (66.9%)	35,714 (55.2%)
Education, <i>n</i> (%)					
Less than upper secondary	6139 (29.6%)	1662 (39.6%)	8874 (31.5%)	5491 (47.5%)	22,166 (34.3%)
Upper secondary and vocational	9626 (46.3%)	1746 (41.6%)	12,964 (46.0%)	4505 (39.0%)	28,841 (44.6%)
Tertiary	5005 (24.1%)	789 (18.8%)	6337 (22.5%)	1568 (13.6%)	13,699 (21.2%)
Married status, <i>n</i> (%)					
Married/Partnered	16,184 (77.9%)	2859 (68.1%)	20,866 (74.1%)	7141 (61.8%)	47,050 (72.7%)
Separated/Divorced/Widowed	3758 (18.1%)	1090 (26.0%)	5694 (20.2%)	3694 (31.9%)	14,236 (22.0%)
Never married	825 (4.0%)	247 (5.9%)	1607 (5.7%)	726 (6.3%)	3405 (5.3%)
Body mass index, kg/m <sup>2</sup> (SD)	27.3 (4.94)	27.7 (5.66)	27.4 (4.94)	27.8 (5.59)	27.5 (5.12)
Having drinking habit, <i>n</i> (%)					
No	8632 (41.6%)	2207 (52.6%)	13,799 (49.0%)	7156 (61.9%)	31,794 (49.1%)
Yes	11,953 (57.5%)	1958 (46.7%)	13,985 (49.6%)	4248 (36.7%)	32,144 (49.7%)
Having smoking habit, <i>n</i> (%)					
No	17,427 (83.9%)	3320 (79.1%)	22,855 (81.1%)	8967 (77.5%)	52,569 (81.2%)
Yes	3305 (15.9%)	871 (20.8%)	5257 (18.7%)	2564 (22.2%)	11,997 (18.5%)
Frequency of physical activity, <i>n</i> (%)					
Vigorous	8181 (39.4%)	1297 (30.9%)	8618 (30.6%)	2391 (20.7%)	20,487 (31.7%)
Moderate	7770 (37.4%)	1562 (37.2%)	9677 (34.3%)	3643 (31.5%)	22,652 (35.0%)
Inactive	4789 (23.1%)	1327 (31.6%)	9804 (34.8%)	5493 (47.5%)	21,413 (33.1%)
Ever diagnosed hypertension, <i>n</i> (%)					
No	12,998 (62.6%)	2353 (56.1%)	16,919 (60.0%)	5771 (49.9%)	38,041 (58.8%)
Yes	7772 (37.4%)	1844 (43.9%)	11,256 (40.0%)	5793 (50.1%)	26,665 (41.2%)
Ever diagnosed diabetes, <i>n</i> (%)					
No	18,744 (90.2%)	3635 (86.6%)	24,535 (87.1%)	9444 (81.7%)	56,358 (87.1%)
Yes	2026 (9.8%)	562 (13.4%)	3640 (12.9%)	2120 (18.3%)	8348 (12.9%)
Ever diagnosed cancers, <i>n</i> (%)					
No	19,124 (92.1%)	3762 (89.6%)	26,388 (93.7%)	10,507 (90.9%)	59,781 (92.4%)
Yes	1646 (7.9%)	435 (10.4%)	1787 (6.3%)	1057 (9.1%)	4925 (7.6%)
Ever diagnosed lung diseases, <i>n</i> (%)					
No	19,773 (95.2%)	3787 (90.2%)	26,757 (95.0%)	10,347 (89.5%)	60,664 (93.8%)
Yes	997 (4.8%)	410 (9.8%)	1418 (5.0%)	1217 (10.5%)	4042 (6.2%)

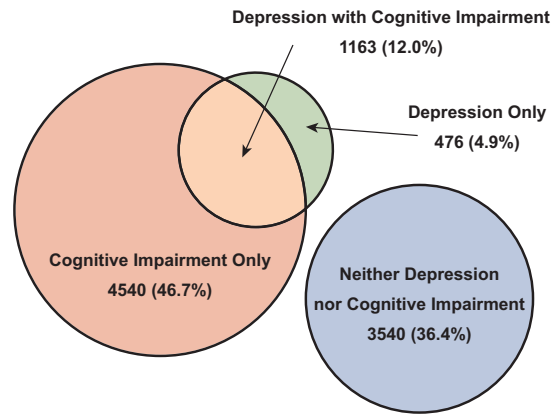
Table 1. continued

	Neither depression nor cognitive impairment	Depression only	Cognitive impairment only	Depression with cognitive impairment	Overall
Ever diagnosed heart problems, <i>n</i> (%)					
No	18,311 (88.2%)	3507 (83.6%)	24,723 (87.7%)	9375 (81.1%)	55,916 (86.4%)
Yes	2459 (11.8%)	690 (16.4%)	3452 (12.3%)	2189 (18.9%)	8790 (13.6%)
Ever diagnosed arthritis, <i>n</i> (%)					
No	15,516 (74.7%)	2602 (62.0%)	21,258 (75.4%)	7000 (60.5%)	46,376 (71.7%)
Yes	5254 (25.3%)	1595 (38.0%)	6917 (24.6%)	4564 (39.5%)	18,330 (28.3%)

A. The composition of subgroups in HRS



B. The composition of subgroups in ELSA



C. The composition of subgroups in SHARE

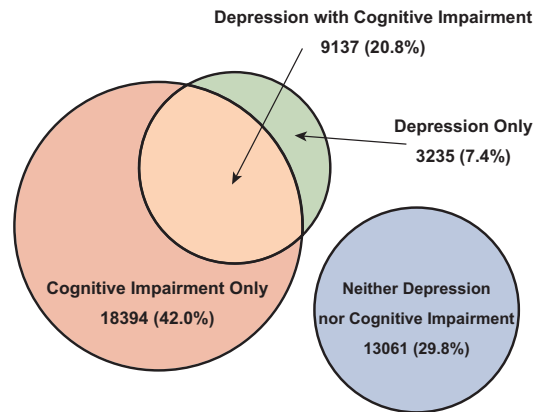


Fig. 1 Proportional Venn diagrams of subgroups division by cohorts. The distribution of sample size across different subgroups in cohort: **A** Health and Retirement Study (HRS), **B** English Longitudinal Study of Ageing (ELSA), and **C** Survey of health, Ageing and Retirement (SHARE). The size of the circles represents the proportion corresponding to each subgroup.

(6.5%) had depressive symptoms only, 28,175 (43.5%) had cognitive impairment only, 11,564 (17.9%) had both, and 20,770 (32.1%) had neither (see Fig. 1). In addition, any missing data in the following variables were addressed through multiple imputations: married status (<0.1%), BMI (6.7%), drinking habit (1.2%), smoking habit (0.2%), and frequency of physical activity (0.2%) (see Supplementary Table 1).

The mean follow-up periods were 4.53 years (SD, 4.04 years; range, 0–22 years). In the follow-up phases, 1437 participants developed incident dementia (533 in HRS, 238 in ELSA, and 666 in SHARE), and 2477 were censored for incident stroke or Parkinson’s disease (591 in HRS, 413 in ELSA, and 1473 in SHARE). After multiple comparison corrections, all three groups had higher risks of incident dementia using Model 1 than the neither group (depression only, HR 1.77, 95% CI 1.35–2.31; cognitive impairment only, HR 2.95, 95% CI 2.55–3.41; depression with cognitive impairment, HR 4.04, 95% CI 3.42–4.77). Moreover, when adjusting for physical conditions and health behaviors as potential covariates in Model 2, the results were similar (depression only, HR 1.65, 95% CI 1.26–2.17; cognitive impairment only, HR 2.71, 95% CI 2.33–3.14; depression with cognitive impairment, HR 3.51, 95% CI 2.95–4.17). Furthermore, compared with the depression only group, participants with cognitive impairment showed higher risks of incident dementia in both Model 1 (cognitive impairment

only, HR 1.67, 95% CI 1.31–2.14; depression with cognitive impairment only, HR 2.29, 95% CI 1.77–2.95) and Model 2 (cognitive impairment only, HR 1.64, 95% CI 1.27–2.11; depression with cognitive impairment, HR 2.12, 95% CI 1.63–2.76). Similarly, in comparison with the cognitive impairment only group, the depression with cognitive impairment group also exhibited a greater risk of developing dementia, as indicated by both Model 1 (HR 1.37, 95% CI 1.20–1.56) and Model 2 (HR 1.30, 95% CI 1.13–1.49) (see Figs. 2 and 3).

In the analysis of synergistic effects (see Table 2), statistically insignificant additive (RERI, 0.32, 95% CI –0.32–0.96; AP, 0.079, 95% CI –0.074–0.23; SI, 1.12, 95% CI 0.89–1.40) or multiplicative interactions (0.77, 95% CI 0.58–1.04) were observed between depression and cognitive impairment using Model 1. Upon adjusting for additional covariates in Model 2, both additive (RERI, 0.15, 95% CI –0.45–0.75; AP, 0.042, 95% CI –0.13–0.21; SI, 1.06, 95% CI 0.83–1.37) and multiplicative (0.78, 95% CI 0.58–1.06) interactions remained similar.

In the sensitivity analysis exploring the relationship between either depression or cognitive impairment and dementia, the findings remained consistent after excluding participants under the age of 65 (see Supplementary Tables 2, 3 and Supplementary Fig. 1). Similarly, the results were unchanged when excluding participants with follow-up period no more than one year

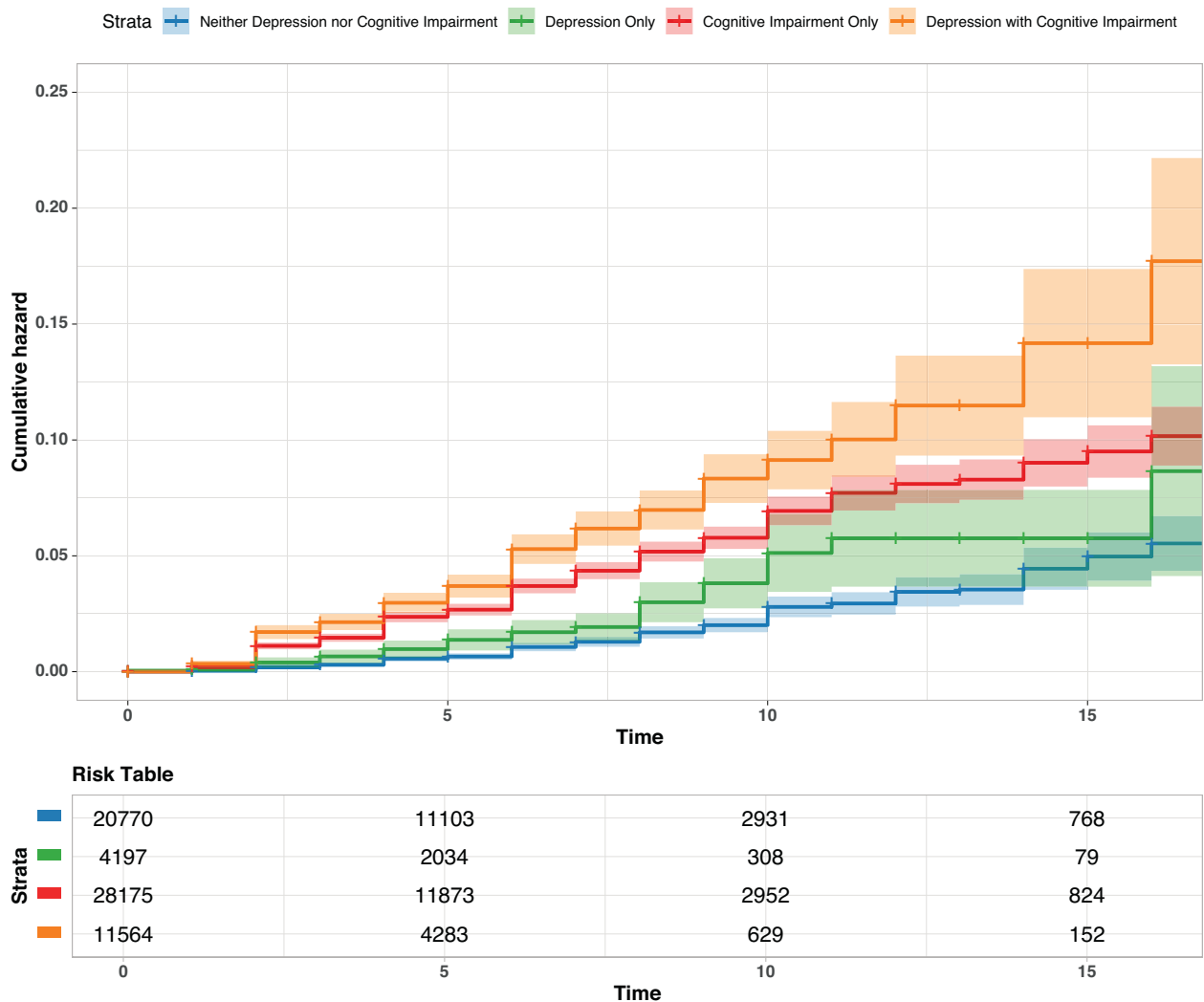
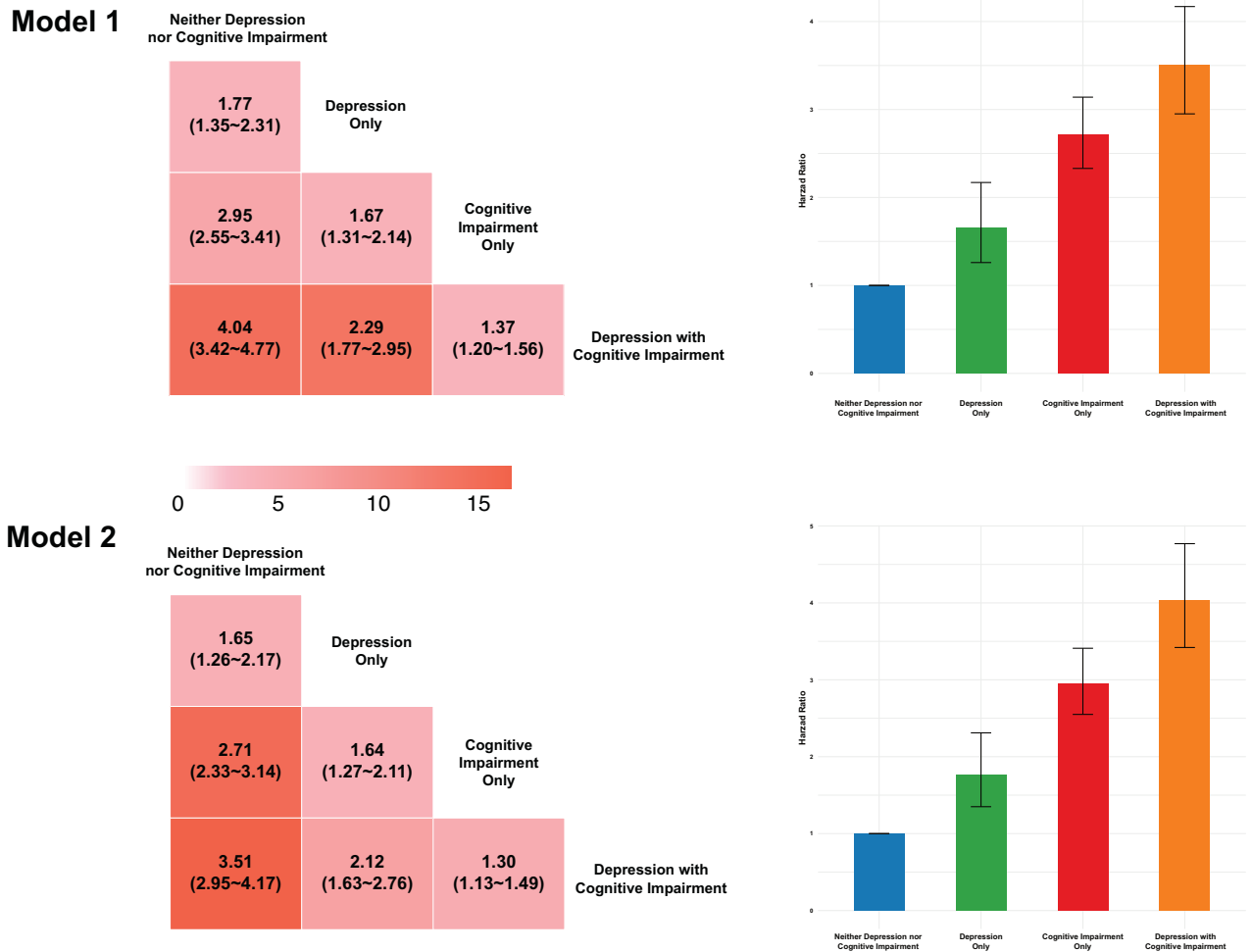


Fig. 2 Cumulative probability and risk table of dementia survival curve across subgroups.



**Fig. 3 Effect of depression and cognitive impairment on hazard risks of incident dementia.** Left tabular figures are pairwise comparisons among subgroups. The numbers in each cell represent the HR (Hazard ratio) and its 95% confidence interval for the corresponding row compared to the column, while the colors indicate Z-value after multiple comparison correction. Statistical significance:  $Z > 1.96$ ,  $P < 0.05$ ;  $Z > 2.58$ ,  $P < 0.01$ ;  $Z > 3.29$ ,  $P < 0.001$ . Right bar graphs represent the point estimates adjusted for covariates in each model, and the error bars represent the 95% confidence intervals.

(Supplementary Tables 5, 6 and Supplementary Fig. 2). In addition, the outcomes did not vary significantly when missing values were excluded instead of using multiple imputation (Supplementary Table 8 and Supplementary Fig. 3). In analyzing the synergistic effects, no statistically significant additive interactions between depression and cognitive impairment in relation to dementia were observed using three different approaches. The multiplicative interaction remained similar with the main analysis (Supplementary Tables 4, 7, and 9).

## DISCUSSION

In the current analysis of 64,706 individuals aged over 50 years, we quantified the effect of depression and cognitive impairment in promoting all-cause dementia progression. After adjusting for potential covariates, individuals with depression only had approximately a 1-fold increased risk, those with cognitive impairment only had a 2-fold increased risk, and those with both depression and cognitive impairment had a 3-fold increased risk of developing future dementia compared to those without depressive symptoms or cognitive impairment.

Our findings support the current perspective that individuals with depression are more susceptible to develop dementia. By utilizing three cross-country population-based cohorts, we

replicated previous results and provided further evidence on this topic. Previous findings have suggested that the effect size of depression is 1-to-2-fold increased risk on future dementia, which is similar to our findings [4–6]. We further quantified the effect size of cognitive function deviations on progressing dementia. Previous studies have demonstrated that individuals with poor education have higher risks of future dementia [25, 26]. Another study has suggested that lower cognitive reserve is independently significantly associated with a higher risk of dementia [27]. However, these measures are only partial or indirect indicators as mirror of cognitive function. In our study, we focused on cognitive test scores across multiple dimensions, which serve as direct indicators of cognitive function.

Our analysis did not detect significantly additive or robust multiplicative interactions between depression and cognitive impairment. Previous studies have also suggested inconsistent conclusions about the additive interaction between depression and cognitive impairment. A study has demonstrated that depression increases future dementia risks significantly in poor-educated but not well-educated individuals [26]. However, this conclusion was valid only for mid-life depression and could not be generalized to late-life or lifelong depression [26]. Depression and cognitive reserve have exhibited a significant attributable proportion [27]. However, the probability of

**Table 2.** Synergistic effect between depression and cognitive impairment on increased risk of future dementia.

Type of interaction	Model 1 <sup>a</sup>					Model 2 <sup>b</sup>						
	Estimate	SE	Lower	Upper	Z	P	Estimate	SE	Lower	Upper	Z	P
Addictive interaction	RERI 0.319	0.324	-0.316	0.955	0.986	0.324	0.149	0.307	-0.452	0.750	0.486	0.627
	AP 0.079	0.078	-0.074	0.232	1.011	0.312	0.042	0.086	-0.127	0.212	0.492	0.623
	SI 1.117	0.115	0.891	1.401	0.958	0.338	1.063	0.128	0.828	1.366	0.478	0.632
Multiplicative interaction	0.774	0.150	0.577	1.039	-1.707	0.088	0.784	0.154	0.580	1.060	-1.582	0.114

Null hypothesis for additive interaction: AP = 0, RERI = 0, SI = 1; multiplicative interaction = 1.

RERI relative excess risk due to interaction, AP attributable proportion due to interaction, SI synergy index.

<sup>a</sup>Adjusted for baseline age, gender, education, and marital status.

<sup>b</sup>Adjusted for baseline age, gender, education, marital status, physical health conditions and health behaviors.

statistical inference was close to the significance level (i.e.,  $P = 0.04$ ), indicating a possible likelihood of a Type I error. Therefore, the interpretation of the results requires caution. Another study has found that individuals with varying educational levels exhibit a similar depression-dementia association, suggesting possible absence of significant additive interaction between depression and cognition on dementia [25]. This finding is consistent with our results. Furthermore, we assessed the multiplicative interaction between depression and cognition on dementia, although some perspectives suggest that multiplicative interactions are less significant for public health than additive interactions [28, 29]. In our study, no significant or robust multiplicative interaction between depression and cognition was observed, which is similar to previous findings [25–27].

Although no significant interaction between depression and cognitive impairment was observed in our study, the risk of dementia was still higher when both factors were present than that with the presence of a single factor only. The comorbidity of depressive symptoms in individuals with mild cognitive impairment is prevalent, with the proportion ranging from 27 to 37% [30]. Another research has confirmed that mild cognitive impairment exacerbates the risk of developing depressive symptoms in the future [31]. On the other side, meta-analytic researches have indicated that individuals with major depressive disorder have worse performance in multiple cognitive domains than healthy controls [32–35]. Longitudinal studies have further indicated that elderly populations exhibiting depressive symptoms have an increased risk of subsequent cognitive impairment [36, 37]. Therefore, when either depression or cognitive impairment occurs alone, clinicians should be vigilant about the patient's future risk of developing dementia and provide timely preventive interventions. Furthermore, special attention should still be given to individuals with depression accompanied by cognitive impairment.

Despite the findings aforementioned, the current study had some limitations. First, the covariates lacked common dementia-related pathological changes during the analysis, such as A $\beta$ , tau, and APOE  $\epsilon$ 4 genotype. Our research can only predict the higher risk of dementia from a symptomatologic perspective. Second, the outcome measure determined in this study was all-cause dementia. Although we considered possible organic neurological disorders during the analysis and excluded dementia possibly caused by them, the remaining dementia was still unable to be further subtyped. Third, depression and cognitive impairment in this study was assessed based on survey screening scales and several cognitive tests, respectively. In addition, the scales used are self-report scales instead of clinician-administered ones such as Hamilton Depression Rating Scale or Montgomery-Åsberg Depression Rating Scale; the cognitive tests employed are not the commonly used Mini-Mental State Examination or Auditory Verbal Learning Test. No clear evidence indicated whether participants were diagnosed with major depressive disorder or mild cognitive impairment. Finally, depression and cognitive impairment are state indicators, but our study only considered baseline conditions and did not account for the longitudinal changes in depression and cognition.

## CONCLUSIONS

With three cross-country population-based prospective cohorts, individuals who had depression accompanied with cognitive impairment had higher risks of incident dementia than those with either depression or cognitive impairment only. The risk of dementia associated with cognitive impairment was higher than that associated with depression, and no significant additive or multiplicative interactions existed between these two factors.

## DATA AVAILABILITY

The original data of Health and Retirement Study (HRS) is available from <https://hrsdata.isr.umich.edu/>; English Longitudinal Study of Ageing (ELSA) is available from <https://beta.ukdataservice.ac.uk/>; and Survey of Health, Ageing and Retirement in Europe (SHARE) is available from <https://releases.sharedatportal.eu/>. These data were harmonized in <https://g2aging.org/>.

## REFERENCES

- GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396:1204–22.
- Leung DKY, Chan WC, Spector A, Wong GHY. Prevalence of depression, anxiety, and apathy symptoms across dementia stages: a systematic review and meta-analysis. *Int J Geriatr Psychiatry*. 2021;36:1330–44.
- Asmer MS, Kirkham J, Newton H, Ismail Z, Elbayoumi H, Leung RH, et al. Meta-analysis of the prevalence of major depressive disorder among older adults with dementia. *J Clin Psychiatry*. 2018;79:17r11772.
- Bellou V, Belbasis L, Tzoulaki I, Middleton LT, Ioannidis JPA, Evangelou E. Systematic evaluation of the associations between environmental risk factors and dementia: an umbrella review of systematic reviews and meta-analyses. *Alzheimer's Dement*. 2017;13:406–18.
- Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2015;86:1299–306.
- Zhang Y, Chen SD, Deng YT, You J, He XY, Wu XR, et al. Identifying modifiable factors and their joint effect on dementia risk in the UK Biobank. *Nat Hum Behav*. 2023;7:1185–95.
- Liou YJ, Tsai SJ, Bai YM, Chen TJ, Chen MH. Dementia risk in middle-aged patients with schizophrenia, bipolar disorder, and major depressive disorder: a cohort study of 84,824 subjects. *Eur Arch Psychiatry Clin Neurosci*. 2023;273:219–27.
- Larsen EN, Sloth MM, Osler M, Wiium-Andersen IK, Jørgensen TSH. Depression in adulthood and risk of dementia later in life: a Danish register-based cohort study of 595,828 men. *J Affect Disord*. 2022;302:25–32.
- Holmquist S, Nordström A, Nordström P. The association of depression with subsequent dementia diagnosis: a Swedish nationwide cohort study from 1964 to 2016. *PLoS Med*. 2020;17:e1003016.
- Singh-Manoux A, Dugravot A, Fournier A, Abell J, Ebmeier K, Kivimäki M, et al. Trajectories of depressive symptoms before diagnosis of dementia: a 28-year follow-up study. *JAMA Psychiatry*. 2017;74:712.
- Katon W, Pedersen HS, Ribe AR, Fenger-Grøn M, Davydov D, Waldorff FB, et al. Effect of depression and diabetes mellitus on the risk for dementia: a national population-based cohort study. *JAMA Psychiatry*. 2015;72:612.
- Köhler S, Buntinx F, Palmer K, Van Den Akker M. Depression, vascular factors, and risk of dementia in primary care: a retrospective cohort study. *J Am Geriatr Soc*. 2015;63:692–8.
- Jang YJ, Kang C, Myung W, Lim SW, Moon YK, Kim H, et al. Additive interaction of mid- to late-life depression and cerebrovascular disease on the risk of dementia: a nationwide population-based cohort study. *Alzheimer's Res Ther*. 2021;13:61.
- Kim JM, Stewart R, Kim SY, Kim SW, Bae KY, Yang SJ, et al. Synergistic associations of depression and apolipoprotein E genotype with incidence of dementia. *Int J Geriatr Psychiatry*. 2011;26:893–8.
- Marquíe M, García-Gutiérrez F, Orellana A, Montreal L, Rojas I, García-González P, et al. The synergic effect of AT(N) profiles and depression on the risk of conversion to dementia in patients with mild cognitive impairment. *IJMS*. 2023;24:1371.
- Saha S, Hatch DJ, Hayden KM, Steffens DC, Potter GG. Appetite and weight loss symptoms in late-life depression predict dementia outcomes. *Am J Geriatr Psychiatry*. 2016;24:870–8.
- Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: classification and criteria changes. *World Psychiatry*. 2013;12:92–98.
- Petersen RC, Knopman DS, Boeve BF, Geda YS, Ivnik RJ, Smith GE, et al. Mild cognitive impairment: ten years later. *Arch Neurol*. 2009;66:1447–55.
- Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *J Intern Med*. 2014;275:214–28.
- Conde-Sala JL, Garre-Olmo J, Calvó-Pexas L, Turró-Garriga O, Vilalta-Franch J. Course of depressive symptoms and associated factors in people aged 65+ in Europe: a two-year follow-up. *J Affect Disord*. 2019;245:440–50.
- Souza-Teodoro LH, De Oliveira C, Walters K, Carvalho LA. Higher serum dehydroepiandrosterone sulfate protects against the onset of depression in the elderly: findings from the English Longitudinal Study of Ageing (ELSA). *Psychoneuroendocrinology*. 2016;64:40–46.
- Kozlov E, Dong X, Kelley AS, Ankuda CK. The epidemiology of depressive symptoms in the last year of life. *J Am Geriatr Soc*. 2020;68:321–8.
- He D, Wang ZP, Li J, Yu KX, He YS, He XY, et al. Changes in frailty and incident cardiovascular disease in three prospective cohorts. *Eur Heart J*. 2024;45:1058–68.
- VanderWeele TJ, Knol MJ. A tutorial on interaction. *Epidemiol Methods*. 2014;3:162–93.
- Korhonen K, Tarkiainen L, Leinonen T, Einiö E, Martikainen P. Association between a history of clinical depression and dementia, and the role of sociodemographic factors: population-based cohort study. *Br J Psychiatry*. 2022;221:410–6.
- Yang WZ, Li XR, Pan KY, Yang RR, Song RX, Qi XY, et al. Association of life-course depression with the risk of dementia in late life: a nationwide twin study. *Alzheimer's Dement*. 2021;17:1383–90.
- Jia F, Wang J, Wei N, Sun D, Cao F. Depression, cognitive reserve markers, and dementia risk in the general population. *Aging Ment Health*. 2022;26:2006–13.
- Knol MJ, VanderWeele TJ, Groenwold RHH, Klungel OH, Rovers MM, DE Grobbee. Estimating measures of interaction on an additive scale for preventive exposures. *Eur J Epidemiol*. 2011;26:433–8.
- VanderWeele TJ. The interaction continuum. *Epidemiology*. 2019;30:648–58.
- Ismail Z, Elbayoumi H, Fischer CE, Hogan DB, Millikin CP, Schweizer T, et al. Prevalence of depression in patients with mild cognitive impairment: a systematic review and meta-analysis. *JAMA Psychiatry*. 2017;74:58.
- Mirza SS, Ikrama MA, Bos D, Mihaescua R, Hofman A, Tiemeier H. Mild cognitive impairment and risk of depression and anxiety: a population-based study. *Alzheimer's Dement*. 2017;13:130–9.
- Semkowska M, Quinlivan L, O'Grady T, Johnson R, Collins A, O'Connor J, et al. Cognitive function following a major depressive episode: a systematic review and meta-analysis. *Lancet Psychiatry*. 2019;6:851–61.
- Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med* 2014;44:2029–40.
- Hack LM, Tozzi L, Zenteno S, Olmsted AM, Hilton R, Jubeir J, et al. A cognitive biotype of depression linking symptoms, behavior measures, neural circuits, and differential treatment outcomes: a Prespecified secondary analysis of a randomized clinical trial. *JAMA Netw Open*. 2023;6:e2318411.
- Bora E, Harrison BJ, Yücel M, Pantelis C. Cognitive impairment in euthymic major depressive disorder: a meta-analysis. *Psychol Med* 2013;43:2017–26.
- Zahodne LB, Stern Y, Manly JJ. Depressive symptoms precede memory decline, but not vice versa, in non-demented older adults. *J Am Geriatr Soc*. 2014;62:130–4.
- Singh-Manoux A, Akbaraly TN, Ferrie JE. Persistent depressive symptoms and cognitive function in late midlife: the Whitehall II study. *J Clin Psychiatry*. 2010;71:1379–85.

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## AUTHOR CONTRIBUTIONS

Conceptualization: XHM and YSY. Literature review: HLX and YRM. Database application: YSY. Data extraction and cleaning: MW and HHF. Statistical analysis and visualization: YSY, HLX, JXW, YD, and YMT. Manuscript drafting and editing: YSY, HLX, XY, and YKD. Response to reviewer comments and manuscript revision: YSY, YKD, XY, and XHM. Project administration and supervision: XHM and XY.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

HRS was approved by the Ethics Review Committee of the University of Michigan, ELSA by the Ethics Review Committee of London Multi-Centre Research, and SHARE by the Institutional Review Board at the University of Pittsburgh Medical Center. Informed consent was obtained from each participant in these three cohorts. The current research constituted a secondary analysis conducted on the three openly

accessible datasets. As the data used for analysis were anonymized, ethical approval for the current research was unnecessary.

### ADDITIONAL INFORMATION

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**Correspondence** and requests for materials should be addressed to Xiao Yang or Xiaohong Ma.

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