Research Square

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Synergistic Interactions of Midlife Multimorbidity on Dementia： A Stratified Analysis by Neuropsychiatric Subtypes

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Abstract

Background

This study examined whether individual chronic conditions, disease combinations, and disease-disease interactions were associated with suspected dementia and its neuropsychiatric symptom profiles.

Methods

This cross-section study included adults aged 60 years or older from three districts in Nantong, China. Suspected dementia was identified using the Revised Hasegawa Dementia Scale. Six somatic comorbidities were assessed from reported medical history, and neuropsychiatric symptoms were evaluated using the Neuropsychiatric Inventory Questionnaire. Multiple imputation was used for missing covariate data. Logistic regression and Firth penalized logistic regression were used to estimate associations for single diseases, two- and three disease combinations, and interaction terms. Latent class analysis was performed among participants with suspected dementia and complete neuropsychiatric symptom data.

Results

Among 2,597 participants, 591 were classified as having suspected dementia. After full adjustment, multimorbidity patterns showed stronger associations than individual diseases. The leading two-disease combinations were diabetes with oral disease (aOR = 4.28), osteoporosis with ear disease (aOR = 3.13), ear disease with oral disease (aOR = 2.88), and diabetes with osteoporosis (aOR = 2.50). The strongest three-disease patterns were diabetes with eye disease and oral disease (aOR = 4.22), diabetes with ear disease and oral disease (aOR = 3.51), and hypertension with diabetes and oral disease (aOR = 3.09). Latent class analysis identified minimal-symptom, sleep appetite disturbance, and agitated-irritable profiles; multimorbidity was most strongly associated with the agitated–irritable class.

Conclusion

Specific disease clusters involving diabetes, oral disease, sensory impairment, and osteoporosis were associated with suspected dementia and neuropsychiatric heterogeneity, supporting integrated multimorbidity-oriented screening and care.

Trial registration:

This study was registered with the Chinese Clinical Trial Registry (ChiCTR1900020923).

Background

Dementia is one of the major public health challenges associated with population ageing. An estimated 57.4 million people were living with dementia worldwide in 2019, and this number is projected to reach 152.8 million by 2050 [1]. Its impact extends well beyond cognitive impairment. Dementia is a leading cause of disability and dependency in later life and generates substantial costs for families, health-care systems, and long-term care services. Global societal costs attributable to dementia were estimated at US$1.3 trillion in 2019[2]. Although dementia is usually diagnosed in older age, the processes that contribute to its development often begin much earlier. This has shifted attention towards midlife as a critical period for dementia prevention.

The 2024 Lancet Standing Commission identified 14 potentially modifiable risk factors for dementia across the life course, including hypertension, diabetes, hearing loss, and visual impairment [3]. These factors are particularly relevant because many chronic diseases emerge or become established during midlife, long before dementia becomes clinically apparent. Evidence from longitudinal studies supports the importance of cardiometabolic disease. In the Whitehall II cohort, diabetes diagnosed more than 10 years before the age of 70 was associated with a more than twofold higher risk of subsequent dementia compared with no diabetes at that age (hazard ratio [HR] 2.12, 95% confidence interval [CI] 1.50 to 3.00) [4]. Sustained hypertension from midlife to later life was also associated with incident dementia (HR 1.41, 95% CI 1.17 to 1.71) [5]. A meta-analysis of 144 prospective studies similarly showed that diabetes was associated with increased risks of cognitive impairment and dementia[6].

Evidence has also accumulated for sensory, skeletal, and oral health conditions. A recent meta-analysis found that hearing loss was associated with a 32% higher risk of incident dementia [7] In two prospective cohorts, moderate-to-severe visual impairment was associated with approximately twice the risk of incident dementia, while a meta-analysis of prospective studies reported an overall relative risk of 1.38 for visual impairment [8]. Low bone mineral density has also been associated with incident dementia in prospective studies [9]. For oral health, a systematic review and meta-analysis of longitudinal studies reported that poor periodontal health was associated with dementia (HR 1.21, 95% CI 1.07 to 1.38), and an updated meta-analysis of cohort studies found that tooth loss was associated with a 15% higher risk of dementia [10, 11]. These findings suggest that diabetes, hypertension, osteoporosis, ear disease, eye disease, and oral disease may represent clinically relevant components of the chronic disease burden that precedes dementia.

However, chronic diseases do not usually occur in isolation. Midlife multimorbidity is common, and its relevance to dementia may not be adequately captured by studying one condition at a time. In the Whitehall II study, multimorbidity at age 55 was associated with a higher incidence of dementia over 30 years of follow-up (HR 2.44, 95% CI 1.82 to 3.26), while the presence of three or more chronic conditions at age 55 was associated with an even greater risk (HR 4.96, 95% CI 2.54 to 9.67) [12]. Consistent findings were reported in the UK Biobank, where multimorbidity was associated with a 63% higher risk of incident dementia, and cardiometabolic disease clusters containing hypertension and diabetes were

associated with approximately twofold higher dementia risk [13]. More recent life-course analyses further indicate that the timing and composition of multimorbidity matter, with cardiometabolic disease accumulation before midlife showing a particularly strong association with later dementia risk [14].

Despite this progress, important gaps remain. Most previous studies have used simple disease counts or data-driven disease clusters. These approaches are useful for describing multimorbidity, but they do not clarify whether particular disease combinations exert joint effects beyond those expected from each condition alone. In particular, little is known about additive and multiplicative interactions between specific chronic diseases, or whether the coexistence of two or three chronic conditions is associated with progressively greater odds of dementia. Addressing these questions may help identify clinically actionable combinations of chronic disease during midlife.

Dementia is also heterogeneous in its clinical presentation. Behavioural and psychological symptoms of dementia, including depression, apathy, agitation, irritability, psychotic symptoms, and sleep disturbance, are common and are associated with greater caregiver distress, poorer quality of life, and more complex care needs [15]. These symptoms tend to occur in recognisable patterns rather than as isolated manifestations. Latent class analyses of Neuropsychiatric Inventory data have identified distinct neuropsychiatric profiles, including depressive, irritable, and complex symptom patterns, which differ in clinical characteristics and outcomes [16, 17]. Recent multi-regional evidence further suggests that cardiometabolic multimorbidity may be particularly associated with affective neuropsychiatric symptoms in older adults [18]. Whether a broader history of midlife multimorbidity is differentially associated with neuropsychiatric symptom phenotypes among people with suspected dementia remains unclear.

Therefore, this study aimed to investigate the associations between retrospectively reported midlife histories of six chronic conditions—diabetes, hypertension, osteoporosis, ear disease, eye disease, and oral disease—and late-life suspected dementia among community-dwelling older adults. Specifically, (1) we examined the independent effects of each condition, the joint effects of selected disease combinations, potential additive and multiplicative interactions, and whether increasing numbers of coexisting conditions were associated with higher odds of suspected dementia; (2) among participants with suspected dementia, we used the Neuropsychiatric Inventory Questionnaire to identify latent neuropsychiatric symptom phenotypes and explored whether multimorbidity was differentially associated with these phenotypes.

Methods

Ethical Approval and Informed Consent

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Nantong University (2018-K042) and was registered with the Chinese Clinical Trial Registry (ChiCTR1900020923). Prior to enrollment and data collection, written informed consent was obtained from all participants or

their legally authorized representatives. Participants were fully informed of the study's objectives, procedures, and their unconditional right to withdraw at any time.

Study Design and Participants

Data were derived from a population-based cross-sectional epidemiological survey conducted in Nantong, China. Details of the study protocol, including the two-stage sampling procedure implemented between February and June 2019, have been described elsewhere[19].

Briefly, we recruited community-dwelling adults aged 60 and above from three districts (Chongchuan, Gangzha, and Kaifa). Eligible participants required normal hearing and communication abilities. To avoid intra-household bias, enrollment was limited to one person per family. We excluded individuals with a prior diagnosis of dementia (DSM-IV), aphasia, or severe sensory deficits.

Study Design and Participants

This was a secondary analysis of a population-based cross-sectional survey conducted in Nantong, Jiangsu Province, China, from February to June 2019. Details of the original study design have been reported previously[19, 20]. Briefly, a two-stage sampling procedure was used to recruit community-dwelling older adults from Chongchuan, Gangzha, and Kaifa districts. One community was selected from each district, and eligible residents were identified through Community Health Service Center registration records and invited by telephone.

Eligibility Criteria

Participants were eligible if they were aged 60 years or older, resided in the selected communities, and were able to complete a face-to-face interview and cognitive assessment. Only one participant was recruited from each household. Individuals with a documented diagnosis of dementia according to DSM-IV criteria before the survey, aphasia, severe hearing or visual impairment, or other conditions preventing completion of the assessment were excluded.

Data Collection

Trained investigators conducted face-to-face interviews. Demographic characteristics and medical history were obtained from Community Health Service Center records and verified during the interview. Information on smoking, alcohol use, social activity, living arrangements, and household responsibilities was collected by self-report. Medical history was further verified with family members, usually an adult child or spouse. For participants living alone, information was checked with relatives by telephone whenever possible.

Participants with available HDS-R data were included in the present analysis. Missing exposure and covariate data were handled using multiple imputation by chained equations, and estimates across five imputed datasets were combined using Rubin’s rules.

Ethical Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Hospital of Nantong University (No. 2018-K042). The study was registered with the Chinese Clinical Trial Registry (ChiCTR1900020923). Written informed consent was obtained from all participants or their legally authorised representatives before data collection.

Data Collection and Assessments

Data were derived from the first wave of a population-based epidemiological survey conducted in Nantong, China. Demographic information was initially obtained from registration records held by local Community Health Service Centers and was further verified during the field survey. Trained investigators conducted face-to-face interviews and administered the Revised Hasegawa Dementia Scale (HDS-R) to assess cognitive function.

A structured questionnaire was used to collect information on sociodemographic characteristics, physical functioning, lifestyle factors, medical history, social participation, memory-related concerns, and neuropsychiatric symptoms. For most questionnaire items, information was obtained from family members or relatives who were familiar with the participant's daily life. For participants living in institutions, information was collected from facility staff with the participant's consent where appropriate. If the participant lived alone or if key information was incomplete, the investigators cross-checked the responses through telephone interviews with children or other relatives. Selected symptom items were asked directly to the participants themselves.

Dementia

Cognitive function was assessed using the Revised Hasegawa Dementia Scale (HDS-R), a 30-point screening instrument widely used to identify cognitive impairment and possible dementia in Asian older adults[21, 22]. The HDS-R assesses orientation, immediate and delayed recall, attention and calculation, backward digit span, object memory, and verbal fluency, with lower scores indicating poorer cognitive performance. Consistent with the established cut-off, participants with an HDS-R score of 20 or lower were classified as HDS-R-positive and defined as having suspected dementia, whereas those scoring 21 or higher were classified as screen-negative. At this threshold, the HDS-R has demonstrated a sensitivity of 0.90 and a specificity of 0.82 for differentiating dementia from normal cognition [23]. As the HDS-R is a screening rather than a diagnostic instrument, the outcome was referred to as suspected dementia throughout this study.

Chronic comorbidities

Six chronic conditions were included based on their prevalence greater than 5% and their relevance to cognitive health. All were coded as binary variables, with "yes" indicating a self- or family-reported physician diagnosis after age 40.

Diabetes, hypertension, and osteoporosis were defined by reported physician diagnosis. Eye diseases included 1) glaucoma, cataracts, and retinopathy; and 2) ear disease, which refers to hearing loss. Dental/oral diseases included denture use, periodontitis, periapical periodontitis, residual roots, and tooth loss (excluding denture installation).

The number of conditions was summed (0-6) and categorised as 0, 1, 2, or ≥3. Multimorbidity was defined as ≥2 conditions. For each disease pair, participants were classified into four groups (neither, A only, B only, both) to assess joint associations with suspected dementia and potential interactions.

Behavioral and Psychological Symptoms

Among participants with suspected dementia, behavioral and psychological symptoms of dementia were assessed for the preceding month using the informant-rated Neuropsychiatric Inventory Questionnaire (NPI-Q) [24]. The NPI-Q evaluates 12 symptom domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, nighttime behaviour disturbances, and appetite/eating abnormalities. Behavioral and psychological symptoms of dementia were defined as the presence of at least one domain.

The NPI-Q is a brief informant-based version of the Neuropsychiatric Inventory and has shown strong convergent validity with the standard NPI, with correlations of 0.91 for total symptom scores and 0.92 for caregiver distress scores in the original validation study. Subsequent validation studies have also reported acceptable internal consistency and good to excellent short-term test-retest reliability, with multiple studies demonstrating high correlations with the original NPI ($r = 0.80$-0.95), internal consistency coefficients (Cronbach's α) ranging from 0.75 to 0.85, and test-retest reliability (intraclass correlation coefficient, ICC) ranging from 0.70 to 0.90 [25, 26].

Covariates

Potential confounders included sociodemographic characteristics, lifestyle factors, and social engagement variables, including age, gender, educational level, family composition, income-generating work, fixed family responsibilities, participation in group activities, smoking status, and alcohol consumption.

Analyze

Categorical variables were presented as frequencies and percentages, and continuous variables were expressed as means with standard deviations (SDs). Missing data were handled using multiple imputation by chained equations (MICE), generating five imputed datasets. Estimates obtained from the imputed datasets were combined according to Rubin's rules.

Baseline characteristics were summarized using standard descriptive statistics. Differences between groups were examined using chi-square tests or Fisher's exact tests for categorical variables, and

Student's t tests or Mann-Whitney U tests for continuous variables, as appropriate.

To examine the associations between six age-related chronic conditions, namely diabetes, hypertension, osteoporosis, eye disease, ear disease, and oral or dental disease, and dementia, multivariable logistic regression analyses were performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs). Conventional multivariable logistic regression was used when model convergence was stable and cell counts were sufficient. Firth's penalized logistic regression was applied when the target comorbidity group contained fewer than five participants, when any exposure-outcome cell contained fewer than five participants, or when conventional logistic regression showed non-convergence or complete/quasi-complete separation.

Both multiplicative and additive interactions between comorbid conditions were assessed. Multiplicative interaction was evaluated by including cross-product terms in the logistic regression models. Additive interaction was quantified using the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (S), to determine whether the joint association of two conditions exceeded the sum of their independent associations.

Among participants classified as having dementia, latent class analysis (LCA) was applied to neuropsychiatric symptom indicators to identify unobserved behavioral and psychological symptom phenotypes. The optimal number of latent classes was determined by comparing the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), sample-size adjusted BIC (aBIC), entropy, class size, and clinical interpretability.

All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

Results

Following multiple imputation, the final analytical sample comprised 2,597 older adults, including 1,170 men (45.1%) and 1,425 women (54.9%). Based on the HDS-R,591 individuals (22.8%) were identified with suspected dementia. Within this suspected dementia cohort, hypertension was the most prevalent comorbidity, affecting 292 patients (49.4%). Other frequently observed conditions included diabetes (n = 132, 22.3%), osteoarthritis (n = 83, 14.0%), oral diseases (n = 82, 13.9%), eye diseases (n = 65, 11.0%), and ear diseases (n = 53, 9.0%) (Figure S2). The most frequent two-disease combination was hypertension and diabetes (n = 85, 14.4%), followed by hypertension and osteoporosis (n = 49, 8.3%), hypertension and oral disease (n = 43, 7.3%), and hypertension and eye disease (n = 42, 7.1%). Among three-disease patterns, hypertension, diabetes, and oral disease was the most common combination (n = 22, 3.7%), followed by hypertension, diabetes, and osteoporosis (n = 21, 3.6%) and hypertension, ear disease, and eye disease (n = 19, 3.2%). (Table 1, Fig. 1).

Table 1
Baseline characteristics

	Total number N(%)	No suspected dementia N(%)	Suspected dementia N(%)	p
	2597	**2006**	**591**	
Age(mean)	75.56 (7.89)	73.76 (6.83)	77.42 (8.51)	**< 0.001**
Gender				
male	1170 (45.1)	899 (44.8)	271 (45.9)	0.69
female	1425 (54.9)	1107 (55.2)	320 (54.1)	
Education				
Primary School	1261 (60.8)	1199 (59.8)	378 (64.0)	0.095
Junior High School	279 (13.5)	287 (14.3)	66 (11.2)	
Senior High School	401 (19.3)	401 (20.0)	106 (17.9)	
University	133 (6.4)	119 (5.9)	41 (6.9)	
Living status				
Living alone	328 (12.9)	251 (12.5)	89 (15.1)	0.123
Living with others	2213 (87.1)	1755 (87.5)	502 (84.9)	
Paid employment				
No	2163 (83.4)	1637 (81.6)	527 (89.2)	**< 0.001**
Yes	432 (16.6)	369 (18.4)	64 (10.8)	
Regular family role and duty				
No	1421 (54.8)	1014 (50.5)	407 (68.9)	**< 0.001**
Yes	1174 (45.2)	992 (49.5)	184 (31.1)	
Group activity participation				
No	2038 (78.5)	1537 (76.6)	502 (84.9)	**< 0.001**
Yes	557 (21.5)	469 (23.4)	89 (15.1)	
Smoke				
No	2248 (86.6)	1722 (85.8)	528 (89.3)	**0.033**

	Total number N(%)	No suspected dementia N(%)	Suspected dementia N(%)	p
	2597	**2006**	**591**	
Yes	347 (13.4)	284 (14.2)	63 (10.7)	
Drink				
No	2066 (79.6)	1574 (78.5)	493 (83.4)	**0.01**
Yes	529 (20.4)	432 (21.5)	98 (16.6)	
Hyperlipidemia				
No	2310 (89.0)	1795 (89.5)	517 (87.5)	0.196
Yes	285 (11.0)	211 (10.5)	74 (12.5)	
Depression				
No	2547 (99.1)	1992 (99.3)	582 (98.5)	0.103
Yes	22 (0.9)	14 (0.7)	9 (1.5)	
Stroke				
No	2381 (91.8)	1860 (92.7)	523 (88.5)	**0.001**
Yes	214 (8.2)	146 (7.3)	68 (11.5)	
Coronary heart disease				
No	2425 (94.4)	1894 (94.4)	558 (94.4)	1
Yes	144 (5.6)	112 (5.6)	33 (5.6)	
Rheumatoid arthritis				
No	2279 (88.7)	1787 (89.1)	517 (87.5)	0.313
Yes	290 (11.3)	219 (10.9)	74 (12.5)	
Hypertension				
No	1307 (50.9)	1028 (51.2)	299 (50.6)	0.816
Yes	1262 (49.1)	978 (48.8)	292 (49.4)	
Diabetes mellitus				
No	2123 (81.8)	1666 (83.1)	459 (77.7)	**0.003**
Yes	472 (18.2)	340 (16.9)	132 (22.3)	
Osteoporosis				

	Total number N(%)	No suspected dementia N(%)	Suspected dementia N(%)	p
	2597	**2006**	**591**	
No	2261 (88.0)	1777 (88.6)	508 (86.0)	0.098
Yes	308 (12.0)	229 (11.4)	83 (14.0)	
Ear diseases				
No	2448 (94.3)	1912 (95.3)	538 (91.0)	**< 0.001**
Yes	147 (5.7)	94 (4.7)	53 (9.0)	
Eye diseases				
No	2347 (90.4)	1823 (90.9)	526 (89.0)	0.199
Yes	248 (9.6)	183 (9.1)	65 (11.0)	
Oral diseases				
No	2323 (89.5)	1816 (90.5)	509 (86.1)	**0.003**
Yes	272 (10.5)	190 (9.5)	82 (13.9)	
Hypertension + Diabetes				
No	2290 (88.2)	1784 (88.9)	506 (85.6)	0.034
Yes	307 (11.8)	222 (11.1)	85 (14.4)	
Hypertension + Osteoporosis				
No	2409 (92.8)	1867 (93.1)	542 (91.7)	0.302
Yes	188 (7.2)	139 (6.9)	49 (8.3)	
Hypertension + Ear disease				
No	2520 (97.0)	1960 (97.7)	560 (94.8)	**< 0.001**
Yes	77 (3.0)	46 (2.3)	31 (5.2)	
Hypertension + Eye disease				
No	2464 (94.9)	1915 (95.5)	549 (92.9)	**0.017**
Yes	133 (5.1)	91 (4.5)	42 (7.1)	
Hypertension + Oral disease				
No	2450 (94.3)	1902 (94.8)	548 (92.7)	0.067

	Total number N(%)	No suspected dementia N(%)	Suspected dementia N(%)	p
	2597	**2006**	**591**	
Yes	147 (5.7)	104 (5.2)	43 (7.3)	
Diabetes + Osteoporosis				
No	2512 (96.7)	1950 (97.2)	562 (95.1)	0.016
Yes	85 (3.3)	56 (2.8)	29 (4.9)	
Diabetes + Ear disease				
No	2560 (98.6)	1986 (99.0)	574 (97.1)	**0.001**
Yes	37 (1.4)	20 (1.0)	17 (2.9)	
Diabetes + Eye disease				
No	2545 (98.0)	1975 (98.5)	570 (96.4)	**0.004**
Yes	52 (2.0)	31 (1.5)	21 (3.6)	
Diabetes + Oral disease				
No	2538 (97.7)	1973 (98.4)	565 (95.6)	**< 0.001**
Yes	59 (2.3)	33 (1.6)	26 (4.4)	
Osteoporosis + Ear disease				
No	2555 (98.4)	1980 (98.7)	575 (97.3)	**0.027**
Yes	42 (1.6)	26 (1.3)	16 (2.7)	
Osteoporosis + Eye disease				
No	2547 (98.1)	1974 (98.4)	573 (97.0)	**0.037**
Yes	50 (1.9)	32 (1.6)	18 (3.0)	
Osteoporosis + Oral disease				
No	2536 (97.7)	1964 (97.9)	572 (96.8)	0.154
Yes	61 (2.3)	42 (2.1)	19 (3.2)	
Ear disease + Eye disease				
No	2527 (97.3)	1960 (97.7)	567 (95.9)	**0.029**
Yes	70 (2.7)	46 (2.3)	24 (4.1)	
Ear disease + Oral disease				

	Total number N(%)	No suspected dementia N(%)	Suspected dementia N(%)	p
	2597	**2006**	**591**	
No	2552 (98.3)	1981 (98.8)	571 (96.6)	**0.001**
Yes	45 (1.7)	25 (1.2)	20 (3.4)	
Eye disease + Oral disease				
No	2544 (98.0)	1975 (98.5)	569 (96.3)	**0.002**
Yes	53 (2.0)	31 (1.5)	22 (3.7)	
Hypertension + Diabetes + Osteoporosis				
No	2532 (97.5)	1962 (97.8)	570 (96.4)	0.087
Yes	65 (2.5)	44 (2.2)	21 (3.6)	
Hypertension + Diabetes + Ear disease				
No	2572 (99.0)	1995 (99.5)	577 (97.6)	**< 0.001**
Yes	25 (1.0)	11 (0.5)	14 (2.4)	
Hypertension + Diabetes + Eye disease				
No	2559 (98.5)	1985 (99.0)	574 (97.1)	**0.002**
Yes	38 (1.5)	21 (1.0)	17 (2.9)	
Hypertension + Diabetes + Oral disease				
No	2550 (98.2)	1981 (98.8)	569 (96.3)	**< 0.001**
Yes	47 (1.8)	25 (1.2)	22 (3.7)	
Hypertension + Osteoporosis + Ear disease				
No	2567 (98.8)	1988 (99.1)	579 (98.0)	0.041
Yes	30 (1.2)	18 (0.9)	12 (2.0)	
Hypertension + Osteoporosis + Eye disease				
No	2566 (98.8)	1986 (99.0)	580 (98.1)	0.138

	Total number N(%)	No suspected dementia N(%)	Suspected dementia N(%)	p
	2597	**2006**	**591**	
Yes	31 (1.2)	20 (1.0)	11 (1.9)	
Hypertension + Osteoporosis + Oral disease				
No	2556 (98.4)	1975 (98.5)	581 (98.3)	0.949
Yes	41 (1.6)	31 (1.5)	10 (1.7)	
Hypertension + Ear disease + Eye disease				
No	2549 (98.2)	1977 (98.6)	572 (96.8)	**0.008**
Yes	48 (1.8)	29 (1.4)	19 (3.2)	
Hypertension + Ear disease + Oral disease				
No	2571 (99.0)	1992 (99.3)	579 (98.0)	**0.009**
Yes	26 (1.0)	14 (0.7)	12 (2.0)	
Hypertension + Eye disease + Oral disease				
No	2563 (98.7)	1987 (99.1)	576 (97.5)	**0.005**
Yes	34 (1.3)	19 (0.9)	15 (2.5)	
Diabetes + Osteoporosis + Ear disease				
No	2583 (99.5)	2000 (99.7)	583 (98.6)	**0.006**
Yes	14 (0.5)	6 (0.3)	8 (1.4)	
Diabetes + Osteoporosis + Eye disease				
No	2584 (99.5)	1999 (99.7)	585 (99.0)	0.092
Yes	13 (0.5)	7 (0.3)	6 (1.0)	
Diabetes + Osteoporosis + Oral disease				
No	2578 (99.3)	1994 (99.4)	584 (98.8)	0.232
Yes	19 (0.7)	12 (0.6)	7 (1.2)	

	Total number N(%)	No suspected dementia N(%)	Suspected dementia N(%)	p
	2597	**2006**	**591**	
Diabetes + Ear disease + Eye disease				
No	2577 (99.2)	1995 (99.5)	582 (98.5)	**0.035**
Yes	20 (0.8)	11 (0.5)	9 (1.5)	
Diabetes + Ear disease + Oral disease				
No	2583 (99.5)	2000 (99.7)	583 (98.6)	**0.006**
Yes	14 (0.5)	6 (0.3)	8 (1.4)	
Diabetes + Eye disease + Oral disease				
No	2585 (99.5)	2002 (99.8)	583 (98.6)	**0.001**
Yes	12 (0.5)	4 (0.2)	8 (1.4)	
Osteoporosis + Ear disease + Eye disease				
No	2569 (98.9)	1988 (99.1)	581 (98.3)	0.156
Yes	28 (1.1)	18 (0.9)	10 (1.7)	
Osteoporosis + Ear disease + Oral disease				
No	2581 (99.4)	1996 (99.5)	585 (99.0)	0.266
Yes	16 (0.6)	10 (0.5)	6 (1.0)	
Osteoporosis + Eye disease + Oral disease				
No	2581 (99.4)	1998 (99.6)	583 (98.6)	**0.021**
Yes	16 (0.6)	8 (0.4)	8 (1.4)	
Ear disease + Eye disease + Oral disease				
No	2574 (99.1)	1995 (99.5)	579 (98.0)	**0.002**
Yes	23 (0.9)	11 (0.5)	12 (2.0)	
Diabetes + Eye disease + Oral disease				

	Total number N(%)	No suspected dementia N(%)	Suspected dementia N(%)	p
	2597	**2006**	**591**	
No	2585 (99.5)	2002 (99.8)	583 (98.6)	**0.001**
Yes	12 (0.5)	4 (0.2)	8 (1.4)	
Osteoporosis + Ear disease + Eye disease				
No	2569 (98.9)	1988 (99.1)	581 (98.3)	0.156
Yes	28 (1.1)	18 (0.9)	10 (1.7)	
Osteoporosis + Ear disease + Oral disease				
No	2581 (99.4)	1996 (99.5)	585 (99.0)	0.266
Yes	16 (0.6)	10 (0.5)	6 (1.0)	
Osteoporosis + Eye disease + Oral disease				
No	2581 (99.4)	1998 (99.6)	583 (98.6)	**0.021**
Yes	16 (0.6)	8 (0.4)	8 (1.4)	
Ear disease + Eye disease + Oral disease				
No	2574 (99.1)	1995 (99.5)	579 (98.0)	**0.002**
Yes	23 (0.9)	11 (0.5)	12 (2.0)	
Yes	28 (1.1)	18 (0.9)	10 (1.7)	
Osteoporosis + Ear disease + Oral disease				
No	2581 (99.4)	1996 (99.5)	585 (99.0)	0.266
Yes	16 (0.6)	10 (0.5)	6 (1.0)	
Osteoporosis + Eye disease + Oral disease				
No	2581 (99.4)	1998 (99.6)	583 (98.6)	**0.021**
Yes	16 (0.6)	8 (0.4)	8 (1.4)	
Ear disease + Eye disease + Oral disease				
No	2574 (99.1)	1995 (99.5)	579 (98.0)	**0.002**

	Total number N(%)	No suspected dementia N(%)	Suspected dementia N(%)	p
	2597	**2006**	**591**	
Yes	23 (0.9)	11 (0.5)	12 (2.0)	

For individual chronic conditions, diabetes, ear disease, osteoporosis, and oral disease were significantly associated with suspected dementia in the fully adjusted model. The strongest association was observed for ear disease (OR = 1.64, 95% CI: 1.08–2.50, P = 0.020), followed by oral disease (OR = 1.59, 95% CI: 1.17–2.14, P = 0.003), diabetes (OR = 1.50, 95% CI: 1.16 1.94, P = 0.002), and osteoporosis (OR = 1.40, 95% CI: 1.04–1.87, P = 0.027). Eye disease and hypertension were not significantly associated with suspected dementia after full adjustment (Table 2).

Table 2
Single diease between dementia and six diseases (Diabetes, Ear, Eye, Hypertension, Osteoporosis, Oral). Model 1: unadjusted. Model 2: adjusted for age, gender, and education. Model 3: adjusted for age, gender, education, paid work, household role, group activity, smoking, drinking, hyperlipidemia, depression, stroke, angina/myocardial infarction, and rheumatoid arthritis.

Disease	Model 1		Model 2		Model 3	
	OR	P_value	OR	P_value	OR	P_value
Single disease						
Diabetes	1.50 (1.19–1.88)	0.0005	1.46 (1.15–1.85)	0.002	1.50 (1.16–1.94)	**0.002**
Ear	1.78 (1.22–2.58)	0.0027	1.56 (1.06–2.29)	0.023	1.64 (1.08–2.50)	**0.020**
Eye	1.33 (1.00-1.76)	0.0523	1.17 (0.87–1.58)	0.291	1.20 (0.88–1.64)	0.247
Hypertension	1.16 (0.97–1.38)	0.1047	1.10 (0.92–1.32)	0.290	1.11 (0.92–1.33)	0.282
Osteoporosis	1.45 (1.11–1.88)	0.0062	1.30 (0.99–1.71)	0.059	1.40 (1.04–1.87)	**0.027**
Oral	1.49 (1.13–1.95)	0.0047	1.46 (1.10–1.94)	0.009	1.59 (1.17–2.14)	**0.003**

Associations of Comorbidities with Dementia

Two-disease comorbidity patterns showed stronger associations with suspected dementia than those observed for individual conditions. In the fully adjusted model, the largest odds were observed for diabetes combined with oral disease (OR = 4.28, 95% CI: 2.18–8.39), followed by osteoporosis with ear disease (OR = 3.13, 95% CI: 1.44–6.79), ear disease with oral disease (OR = 2.88, 95% CI: 1.36–6.08), and diabetes with osteoporosis (OR = 2.50, 95% CI: 1.46–4.29). Several other two-disease combinations also

remained significant, including diabetes with eye disease (OR = 1.96, 95% CI: 1.00-3.83), ear disease with eye disease (OR = 1.84, 95% CI: 1.01–3.36), eye disease with oral disease (OR = 2.10, 95% CI: 1.11–3.98), hypertension with diabetes (OR = 1.61, 95% CI: 1.19–2.16), hypertension with osteoporosis (OR = 1.48, 95% CI: 1.03–2.13), hypertension with oral disease (OR = 1.62, 95% CI: 1.09–2.40), and osteoporosis with oral disease (OR = 2.01, 95% CI: 1.07–3.76) (Table 3, Figure S2).

Table 3
Multiple comorbidities between dementia and six diseases (Diabetes, Ear, Eye, Hypertension, Osteoporosis, Oral).

Disease	Model 1		Model 2		Model 3	
	OR	P_value	OR	P_value	OR	P_value
Two comorbidities						
Diabetes + Ear	1.96 (0.96–3.98)	0.0632	1.66 (0.79–3.49)	0.177	2.09 (0.90–4.83)	0.085
Diabetes + Eye	1.94 (1.07–3.52)	0.0281	1.69 (0.91–3.12)	0.097	1.96 (1.00-3.83)	**0.049**
Diabetes+Osteoporosis	2.46 (1.54–3.94)	0.0002	2.20 (1.35–3.60)	0.002	2.50 (1.46–4.29)	**0.001**
Diabetes+Oral	3.31 (1.83–5.99)	0.0001	3.34 (1.80–6.18)	0.000	4.28 (2.18–8.39)	**< 0.001**
Ear + eye	1.96 (1.17–3.27)	0.0101	1.60 (0.94–2.74)	0.082	1.84 (1.01–3.36)	**0.047**
Ear+oral	2.77 (1.44–5.32)	0.0023	2.44 (1.23–4.83)	0.011	2.88 (1.36–6.08)	**0.006**
Eye+oral	2.24 (1.25–4.02)	0.0067	1.92 (1.04–3.52)	0.036	2.10 (1.11–3.98)	**0.023**
Hypertension+diab	1.62 (1.25–2.11)	0.0003	1.52 (1.16-2.00)	0.003	1.61 (1.19–2.16)	**0.002**
Hypertension + ear	1.76 (1.07–2.89)	0.0267	1.49 (0.89–2.48)	0.127	1.70 (0.94–3.10)	0.081
Hypertension + eye	1.50 (1.03–2.17)	0.0342	1.32 (0.90–1.95)	0.160	1.42 (0.93–2.16)	0.105
Hypertension + oa	1.52 (1.10–2.11)	0.0113	1.36 (0.97–1.91)	0.073	1.48 (1.03–2.13)	**0.034**

Model 1: unadjusted. Model 2: adjusted for age, gender, and education. Model 3: adjusted for age, gender, education, paid work, household role, group activity, smoking, drinking, hyperlipidemia, depression, stroke, angina/myocardial infarction, and rheumatoid arthritis.

Disease	Model 1		Model 2		Model 3	
	OR	P_value	OR	P_value	OR	P_value
Two comorbidities						
Hypertension+oral	1.53 (1.08–2.18)	0.0182	1.50 (1.04–2.16)	0.030	1.62 (1.09–2.40)	**0.017**
Osteoporosis + ear	2.84 (1.46–5.56)	0.0022	2.47 (1.24–4.94)	0.011	3.13 (1.44–6.79)	**0.004**
Osteoporosis + eye	1.85 (1.02–3.34)	0.0416	1.49 (0.80–2.76)	0.204	1.77 (0.90–3.48)	0.099
Osteoporosis+oral	1.91 (1.12–3.28)	0.0185	1.61 (0.92–2.82)	0.095	2.01 (1.07–3.76)	**0.029**

Model 1: unadjusted. Model 2: adjusted for age, gender, and education. Model 3: adjusted for age, gender, education, paid work, household role, group activity, smoking, drinking, hyperlipidemia, depression, stroke, angina/myocardial infarction, and rheumatoid arthritis.

A similar pattern was observed for three-disease combinations, with several profiles showing even higher odds of suspected dementia. The strongest associations were observed for diabetes, eye disease, and oral disease (OR = 4.22, 95% CI: 1.61–11.07), followed by diabetes, ear disease, and oral disease (OR = 3.51, 95% CI: 1.39–8.86), hypertension, diabetes, and oral disease (OR = 3.09, 95% CI: 1.63–5.88), hypertension, diabetes, and ear disease (OR = 2.80, 95% CI: 1.13–6.94), ear disease, eye disease, and oral disease (OR = 2.59, 95% CI: 1.07–6.25), and hypertension, ear disease, and oral disease (OR = 2.35, 95% CI: 1.02–5.41), (Table 4). Overall, the associations tended to become stronger as multiple somatic conditions co-occurred, particularly when diabetes, oral disease, or sensory impairments were included in the comorbidity pattern (Table 4, Fig. 2).

Table 4
Associations between neuropsychiatric symptom subtypes of dementia and each of the six chronic diseases.

	C1: Minimal-symptom class		C2: Sleep-appetite disturbance class		C3: Agitated-irritable class	
	OR	**p**	**OR**	**p**	**OR**	**p**
Diabetes	0.74 (0.49–1.11)	0.145	1.79 (1.33–2.42)	**< 0.001**	2.07 (1.05–4.08)	**0.035**
Ear disease	0.62 (0.29–1.35)	0.230	2.11 (1.35–3.31)	**0.001**	2.78 (1.20–6.43)	**0.017**
Eye disease	0.66 (0.38–1.13)	0.131	1.11 (0.74–1.67)	0.614	2.84 (1.40–5.74)	**0.004**
Hypertension	0.91 (0.69–1.22)	0.543	0.96 (0.74–1.25)	0.749	1.42 (0.73–2.78)	0.302
Oral disease	0.64 (0.36–1.14)	0.129	2.36 (1.66–3.34)	**< 0.001**	2.94 (1.40–6.18)	**0.005**
Osteoporosis	0.62 (0.37–1.05)	0.078	1.44 (1.01–2.06)	**0.042**	2.13 (1.04–4.38)	**0.039**

Table 4
Associations of three comorbid conditions with dementia. Model 1: unadjusted. Model 2: adjusted for age, gender, and education. Model 3: adjusted for age, gender, education, paid work, household role, group activity, smoking, drinking, hyperlipidemia, depression, stroke, angina/myocardial infarction, and rheumatoid arthritis.

Disease	Model 1		Model 2		Model 3	
	OR	P_value	OR	P_value	OR	P_value
Three or more comorbidities						
Diabetes + Ear disease + Eye disease	2.46 (0.97–6.21)	0.0569	1.46 (0.52–4.08)	0.4693	1.40 (0.56–3.47)	0.4688
Diabetes + Ear disease + Oral disease	4.54 (1.57–13.14)	0.0052	4.07 (1.49–11.09)	0.0060	3.51 (1.39–8.86)	**0.0079**
Diabetes + Eye disease + Oral disease	6.44 (2.05–20.26)	0.0015	5.24 (1.72–15.89)	0.0035	4.22 (1.61–11.07)	**0.0035**
Diabetes + Osteoporosis + Ear disease	4.54 (1.57–13.14)	0.0052	2.66 (0.95–7.43)	0.0624	2.27 (0.90–5.74)	0.0822
Diabetes + Osteoporosis + Eye disease	2.91 (0.97–8.69)	0.0559	1.71 (0.60–4.93)	0.3172	1.73 (0.66–4.52)	0.2614
Diabetes + Osteoporosis + Oral disease	1.98 (0.78–5.05)	0.1536	1.63 (0.60–4.41)	0.3334	1.59 (0.67–3.75)	0.2951
Ear disease + Eye disease + Oral disease	3.73 (1.64–8.50)	0.0017	3.01 (1.25–7.23)	0.0137	2.59 (1.07–6.25)	**0.0349**
Hypertension + Diabetes + Ear disease	3.96 (1.75–8.95)	< 0.001	2.92 (1.21–7.02)	0.0169	2.80 (1.13–6.94)	**0.0265**
Hypertension + Diabetes + Eye disease	2.60 (1.34–5.04)	0.0046	2.11 (1.05–4.27)	0.0372	2.06 (1.00-4.26)	0.0502
Hypertension + Diabetes + Osteoporosis	1.62 (0.96–2.75)	0.0725	1.32 (0.75–2.32)	0.3367	1.27 (0.71–2.27)	0.4138
Hypertension + Diabetes + Oral disease	3.15 (1.75–5.67)	< 0.001	3.07 (1.64–5.71)	< 0.001	3.09 (1.63–5.88)	**< 0.001**
Hypertension + Ear disease + Eye disease	2.13 (1.17–3.88)	0.0133	1.51 (0.79–2.87)	0.2088	1.37 (0.70–2.66)	0.3595

Disease	Model 1		Model 2		Model 3	
	OR	P_value	OR	P_value	OR	P_value
Three or more comorbidities						
Hypertension + Ear disease + Oral disease	2.93 (1.35–6.37)	0.0067	2.63 (1.16–5.97)	0.0211	2.35 (1.02–5.41)	**0.0436**
Hypertension + Eye disease + Oral disease	2.51 (1.24–5.07)	0.0102	2.25 (1.07–4.71)	0.0324	1.87 (0.88–3.99)	0.1036
Hypertension + Osteoporosis + Ear disease	2.27 (1.09–4.75)	0.0289	2.02 (0.93–4.40)	0.0764	1.67 (0.75–3.72)	0.2085
Hypertension + Osteoporosis + Eye disease	1.71 (0.79–3.71)	0.1722	1.35 (0.59–3.07)	0.4732	1.18 (0.51–2.76)	0.6979
Hypertension + Osteoporosis + Oral disease	1.00 (0.47–2.13)	0.9970	0.91 (0.41-2.00)	0.8142	0.86 (0.39–1.93)	0.7216
Osteoporosis + Ear disease + Eye disease	1.89 (0.87–4.11)	0.1098	1.30 (0.56-3.00)	0.5402	1.12 (0.47–2.69)	0.7941
Osteoporosis + Ear disease + Oral disease	2.03 (0.74–5.62)	0.1713	1.56 (0.58–4.18)	0.3794	1.46 (0.60–3.59)	0.4068
Osteoporosis + Eye disease + Oral disease	2.92 (1.04–8.22)	0.0421	1.88 (0.61–5.74)	0.2705	1.69 (0.67–4.26)	0.2660

Subgroup Analysis

In age-stratified analyses, the association patterns varied across age groups. Among participants aged 60–74 years, diabetes showed a clear association with suspected dementia (OR = 1.79, 95% CI: 1.21–2.66), and several diabetes-related comorbidity patterns showed stronger effects, including diabetes with osteoporosis (OR = 2.82, 95% CI: 1.36–5.83), diabetes with ear disease (OR = 3.67, 95% CI: 1.29–10.46), diabetes with eye disease (OR = 4.00, 95% CI: 1.58–10.15), and diabetes with oral disease (OR = 2.82, 95% CI: 1.21–6.59). In the 75-89-year group, oral disease was significantly associated with suspected dementia (OR = 1.94, 95% CI: 1.28–2.93), and stronger associations were observed for several multimorbidity patterns, such as hypertension with ear disease (OR = 2.07, 95% CI: 1.06–4.04), diabetes with oral disease (OR = 2.36, 95% CI: 1.16–4.79), ear disease with oral disease (OR = 2.48, 95% CI: 1.21–5.06), hypertension with diabetes and oral disease (OR = 2.42, 95% CI: 1.08–5.41), and diabetes with eye disease and oral disease (OR = 3.49, 95% CI: 1.04–11.73). In the oldest age group (≥ 90 years), few

disease or comorbidity patterns were significantly associated with suspected dementia (Table S2, Figure S4).

Gender-stratified analyses showed that multimorbidity associations were generally more pronounced in men. Among men, ear disease (OR = 1.96, 95% CI: 1.10–3.48) and oral disease (OR = 2.35, 95% CI: 1.54–3.60) were individually associated with suspected dementia. Stronger associations were observed when these conditions co-occurred with other chronic diseases, including diabetes with oral disease (OR = 4.53, 95% CI: 2.15–9.54), ear disease with oral disease (OR = 4.40, 95% CI: 2.00-9.71), hypertension with diabetes and oral disease (OR = 5.51, 95% CI: 2.42–12.55), hypertension with ear disease and oral disease (OR = 7.10, 95% CI: 2.61–19.32), and diabetes with ear disease and oral disease (OR = 6.88, 95% CI: 2.16–21.94). In women, fewer associations reached statistical significance; diabetes alone was associated with suspected dementia (OR = 1.46, 95% CI: 1.04–2.06), while the strongest multimorbidity signal was observed for diabetes, eye disease, and oral disease (OR = 5.95, 95% CI: 1.39–25.53). Overall, these subgroup findings suggest that the burden of combined somatic conditions, particularly diabetes-related and oral/sensory disease-related patterns, was more strongly associated with suspected dementia than individual diseases alone.

Interaction Analysis

Overall, no clear evidence of statistically significant multiplicative interaction was observed between pairs of chronic diseases. Nevertheless, diabetes combined with oral disease showed the strongest positive interaction tendency, with RERI = 1.567 (95% CI: −0.281 to 3.414), AP = 0.500 (95% CI: 0.170 to 0.829), S = 3.807, and a borderline multiplicative interaction (OR = 1.91, 95% CI: 0.95–3.84, P = 0.0699), suggesting a potentially meaningful joint effect that warrants further investigation (Table S1, Figure S3).

Latent Class Analysis of BPSD Phenotypes

Based on the fit indices and clinical interpretability, the three-class model was selected for the LCA (Table S3, Figure S5-6). Although the two-class model had the lowest BIC, the three-class solution had the lowest adjusted BIC and provided more distinguishable symptom profiles. C1 was labelled as the minimal-symptom class (38.0%), with near-zero probabilities across most NPI-Q domains. C2, the largest class, was labelled as the sleep-appetite disturbance class (53.4%), mainly characterized by depression, appetite disturbance, sleep disturbance, anxiety, and apathy. C3 was labelled as the agitated-irritable class (8.6%), with high probabilities of depression, anxiety, irritability, apathy, agitation, and sleep disturbance (Table S4).

Somatic disease burden differed across the three classes. The prevalence of diabetes increased from 13.4% in C1 to 28.4% in C2 and 35.7% in C3. Similar gradients were observed for oral disease, eye disease, ear disease, and osteoporosis. Hypertension was numerically more common in C3 but did not differ significantly across classes. Age and gender were comparable among the three groups (Fig. 3).

In adjusted regression analyses, no single disease was significantly associated with the minimal-symptom class (C1). In contrast, the sleep-appetite disturbance class (C2) was associated with diabetes

(aOR = 1.79, 95% CI: 1.33–2.42), ear disease (aOR = 2.11, 95% CI: 1.35–3.31), oral disease (aOR = 2.36, 95% CI: 1.66–3.34), and osteoporosis (aOR = 1.44, 95% CI: 1.01–2.06). The agitated-irritable class (C3) showed broader and stronger associations, including diabetes (aOR = 2.07, 95% CI: 1.05–4.08), ear disease (aOR = 2.78, 95% CI: 1.20–6.43), eye disease (aOR = 2.84, 95% CI: 1.40–5.74), oral disease (aOR = 2.94, 95% CI: 1.40–6.18), and osteoporosis (aOR = 2.13, 95% CI: 1.04–4.38) (Table 4).

Pairwise comorbidity analyses showed stronger associations than those observed for individual diseases, particularly in the two symptomatic classes. In C2, the largest associations were observed for diabetes with oral disease (aOR = 4.36, 95% CI: 2.39–7.94), ear disease with oral disease (aOR = 3.63, 95% CI: 1.94–6.79), diabetes with ear disease (aOR = 3.26, 95% CI: 1.59–6.64), and hypertension with ear disease (aOR = 2.37, 95% CI: 1.34–4.18). In C3, the strongest associations were found for diabetes with oral disease (aOR = 7.00, 95% CI: 2.60-18.87), eye disease with oral disease (aOR = 6.47, 95% CI: 2.61–16.08), diabetes with eye disease (aOR = 6.14, 95% CI: 2.40-15.71), and osteoporosis with eye disease (aOR = 5.59, 95% CI: 2.28–13.71). These findings suggest that multimorbidity was more closely related to symptomatic neuropsychiatric profiles than to the minimal-symptom profile (Table 5).

Table 5
Associations between pairwise chronic disease comorbidities and neuropsychiatric symptom subtypes of dementia patients.

	C1: Minimal-symptom class		C2: Sleep-appetite disturbance class		C3: Agitated-irritable class	
	aOR*	p	aOR*	p	aOR*	p
Diabetes + Ear disease	0.77 (0.19–3.03)	0.706	3.26 (1.59–6.64)	**0.001**	2.39 (0.60–9.43)	0.214
Diabetes + Eye disease	1.04 (0.38–2.83)	0.940	1.87 (0.93–3.78)	0.081	6.14 (2.40-15.71)	**< 0.001**
Diabetes + Oral disease	0.44 (0.09–2.11)	0.301	4.36 (2.39–7.94)	**< 0.001**	7.00 (2.60-18.87)	**< 0.001**
Diabetes + Osteoporosis	0.66 (0.26–1.64)	0.366	2.13 (1.25–3.64)	**0.005**	1.94 (0.67–5.66)	0.224
Ear disease + Eye disease	0.35 (0.11–1.13)	0.080	1.60 (0.87–2.93)	0.128	2.25 (0.83–6.10)	0.111
Ear disease + Oral disease	0.14 (0.01–1.99)	0.147	3.63 (1.94–6.79)	**< 0.001**	2.89 (0.88–9.43)	0.079
Eye disease + Oral disease	0.80 (0.27–2.37)	0.684	1.89 (0.95–3.77)	0.072	6.47 (2.61–16.08)	**< 0.001**
Hypertension + Diabetes	0.62 (0.37–1.04)	0.072	1.59 (1.12–2.26)	**0.010**	2.15 (1.03–4.47)	**0.041**
Hypertension + Ear disease	0.64 (0.23–1.79)	0.393	2.37 (1.34–4.18)	**0.003**	3.82 (1.53–9.54)	**0.004**
Hypertension + Eye disease	1.03 (0.53–1.97)	0.938	1.24 (0.74–2.10)	0.416	2.74 (1.16–6.45)	**0.021**
Hypertension + Oral disease	0.60 (0.27–1.33)	0.211	1.88 (1.17–3.02)	**0.010**	3.00 (1.26–7.12)	**0.013**
Hypertension + Osteoporosis	0.69 (0.37–1.30)	0.255	1.25 (0.79–1.98)	0.345	2.27 (1.00-5.14)	0.050
Osteoporosis + Ear disease	0.22 (0.04–1.32)	0.098	2.03 (1.01–4.07)	**0.047**	3.18 (1.08–9.38)	**0.036**
Osteoporosis + Eye disease	0.40 (0.10–1.54)	0.182	1.23 (0.58–2.60)	0.588	5.59 (2.28–13.71)	**< 0.001**
Diabetes + Ear disease	0.77 (0.19–3.03)	0.706	3.26 (1.59–6.64)	**0.001**	2.39 (0.60–9.43)	0.214

*All models were adjusted for age, gender, educational level, family composition, income-generating work, fixed family responsibilities, participation in group activities, smoking status, and alcohol consumption.

Interaction analyses identified only a few significant multiplicative interactions, and these differed by symptom class. In C1, hypertension and eye disease showed a positive interaction (OR = 3.576, 95% CI: 1.115–11.469, P = 0.032). In C2, osteoporosis and oral disease showed an inverse interaction (OR = 0.354, 95% CI: 0.148–0.850, P = 0.020). In C3, inverse interactions were observed for osteoporosis with oral disease (OR = 0.185, 95% CI: 0.038–0.899, P = 0.036) and ear disease with eye disease (OR = 0.143, 95% CI: 0.027–0.754, P = 0.022). Other disease pairs did not show statistically significant multiplicative interactions (Table S5).

Discussion

Our findings suggest that suspected dementia was more strongly associated with specific multimorbidity patterns than with isolated chronic diseases. In the fully adjusted models, single diseases showed only modest associations, whereas selected two- and three-disease combinations showed larger effect estimates. The most prominent two-disease patterns were diabetes with oral disease, osteoporosis with ear disease, ear disease with oral disease, and diabetes with osteoporosis. Among three-disease patterns, diabetes with eye disease and oral disease, diabetes with ear disease and oral disease, and hypertension with diabetes and oral disease showed the clearest associations. These findings are consistent with growing evidence that dementia risk is shaped by multimorbidity burden and disease clustering rather than by single conditions alone [3, 13, 27–29].

Several shared biological pathways may explain these associations. Diabetes, hypertension, sensory impairment, oral disease, and osteoporosis may converge through chronic inflammation, endothelial dysfunction, cerebral small-vessel injury, oxidative stress, frailty, impaired nutrition, and reduced sensory stimulation [3, 30, 31]. Diabetes may promote cognitive decline through insulin resistance, hyperglycemia-related vascular damage, impaired neuronal insulin signaling, and neuroinflammation[30, 31]. Oral disease may add systemic inflammatory and nutritional burden through periodontitis, tooth loss, impaired mastication, and altered oral microbiota [10, 32–34]. Sensory impairment may further reduce environmental stimulation and social engagement, while osteoporosis may reflect frailty, reduced mobility, and shared aging-related pathways between bone and brain health[27, 35–39].

The relatively weak independent association of hypertension in our study should be interpreted cautiously. Hypertension is a well-established vascular risk factor, but its association with dementia becomes more complex in late life. Blood pressure may decline in advanced age because of frailty, weight loss, autonomic dysfunction, neurodegeneration, antihypertensive treatment, or competing mortality, which may attenuate cross-sectional associations [18, 19]. In this context, hypertension may be more informative when considered as part of broader multimorbidity patterns, especially when combined with diabetes, oral disease, or sensory impairment[40, 41].

Subgroup analyses further supported the heterogeneity of these associations. Multimorbidity patterns were generally more evident in men than in women, particularly combinations involving diabetes, oral disease, ear disease, and hypertension. In women, fewer combinations reached statistical significance,

although diabetes alone and diabetes with eye disease and oral disease remained notable. Age-stratified analyses showed clearer associations in the 60–74 and 75–89 year groups, whereas fewer significant findings were observed among participants aged ≥ 90 years. This may partly reflect survival selection: older adults with severe metabolic, vascular, or systemic disease burden may be less likely to survive into very advanced age, leaving a relatively healthier and more resilient oldest-old subgrou[40, 42].

The LCA results further suggest that somatic multimorbidity may be linked not only to suspected dementia, but also to neuropsychiatric symptom profiles. The minimal-symptom class showed little association with chronic disease patterns, whereas the sleep-appetite disturbance and agitated-irritable classes carried heavier somatic burdens. Diabetes, ear disease, oral disease, and osteoporosis were associated with the sleep-appetite disturbance class, while the agitated-irritable class showed broader and stronger associations involving diabetes, ear disease, eye disease, oral disease, and osteoporosis. Clinically, this suggests that sleep disturbance, appetite change, apathy, agitation, or irritability in suspected dementia should prompt attention to underlying metabolic dysfunction, oral disease, sensory impairment, pain, frailty, and nutritional problems. These conditions may contribute to behavioral symptoms through inflammation, vascular injury, discomfort, reduced sensory input, impaired sleep, and nutritional compromise[43–45].

This study has several strengths. First, it examined specific disease combinations rather than only counting the number of chronic diseases, which provides more clinically interpretable information. Second, the analysis combined overall models, subgroup analyses, LCA-based symptom profiling, and interaction testing, allowing dementia heterogeneity to be examined from multiple perspectives. Third, Firth penalized logistic regression was used for sparse disease patterns, improving model stability in rare comorbidity combinations. Multiple imputation was also applied to reduce information loss due to missing covariates. However, several limitations should be acknowledged. The cross-sectional design precludes causal inference. Disease history and neuropsychiatric symptoms may be affected by reporting bias. Some subgroup and interaction estimates were based on small cells, and the LCA-derived classes require validation in independent cohorts.

From a clinical and nursing perspective, these findings support a shift from single-disease management to integrated multimorbidity-oriented dementia care. Older adults with diabetes combined with oral disease, sensory impairment, osteoporosis, or hypertension may require closer cognitive and behavioral monitoring. Routine oral assessment, glycemic control, blood pressure management, hearing and vision screening, fall-risk assessment, nutritional evaluation, and symptom-based behavioral care could be incorporated into community and geriatric nursing practice. For patients with sleep-appetite disturbance or agitated-irritable symptoms, targeted assessment of oral discomfort, sensory loss, metabolic instability, and frailty may help identify modifiable contributors to behavioral deterioration.

In summary, suspected dementia was associated with distinct multimorbidity patterns, and these patterns differed by gender, age group, and neuropsychiatric symptom profile. These findings highlight the need to understand dementia through an integrated somatic-cognitive-behavioral framework. Future

longitudinal studies should clarify temporal relationships and determine whether early management of metabolic, oral, sensory, vascular, and skeletal conditions can reduce dementia risk or modify neuropsychiatric symptom trajectories.

Conclusion

Suspected dementia was associated with specific multimorbidity patterns rather than individual chronic diseases alone. Combinations involving diabetes, oral disease, sensory impairment, osteoporosis, and hypertension showed stronger associations with suspected dementia and were differentially related to neuropsychiatric symptom profiles, especially the sleep-appetite disturbance and agitated-irritable classes. These findings support integrated screening and management of somatic disease clusters in older adults to improve dementia risk identification and targeted care. Future longitudinal studies are needed to clarify causal pathways and evaluate whether early multimorbidity management can reduce cognitive and behavioral decline.

List of abbreviation

THN, hypertension; DM, diabetes mellitus; OA, osteoporosis; HDS-R, the Revised Hasegawa Dementia Scale; NPI-Q, the Neuropsychiatric Inventory Questionnaire; RERI, Relative excess risk due to interaction; AP, Attributable proportion due to interaction; S, synergy index; LCA, latent class analysis; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; aBIC, sample-size adjusted BIC; ORs, estimate odds ratios; aORs, adjust estimate odds ratios; CIs, 95% confidence intervals.

Abbreviations

THN, hypertension; DM, diabetes mellitus; OA, osteoporosis; HDS-R, the Revised Hasegawa Dementia Scale; NPI-Q , the Neuropsychiatric Inventory Questionnaire; RERI, Relative excess risk due to interaction; AP, Attributable proportion due to interaction; S, synergy index; LCA, latent class analysis; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; aBIC, sample-size adjusted BIC; ORs, estimate odds ratios; aORs, adjust estimate odds ratios; CIs, 95% confidence intervals.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Nantong University (2018-K042) and all participants signed the informed consent form.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

R.W. contributes to data analysis and write the entire text; Z.X. and J.N. are jointly responsible for the revision of the background section and the discussion section, as well as the verification of the literature; Y.C. and T.C. contribute to data collection and entrying; F.Z. and X.Z contribute to pprovide design, review articles and make revisions. All authors reviewed the manuscript and approve of the submission.

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Availability of data and materials

The deidentified data and R code (link) that support the findings of this study are available on the Open Science Framework.

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Figures

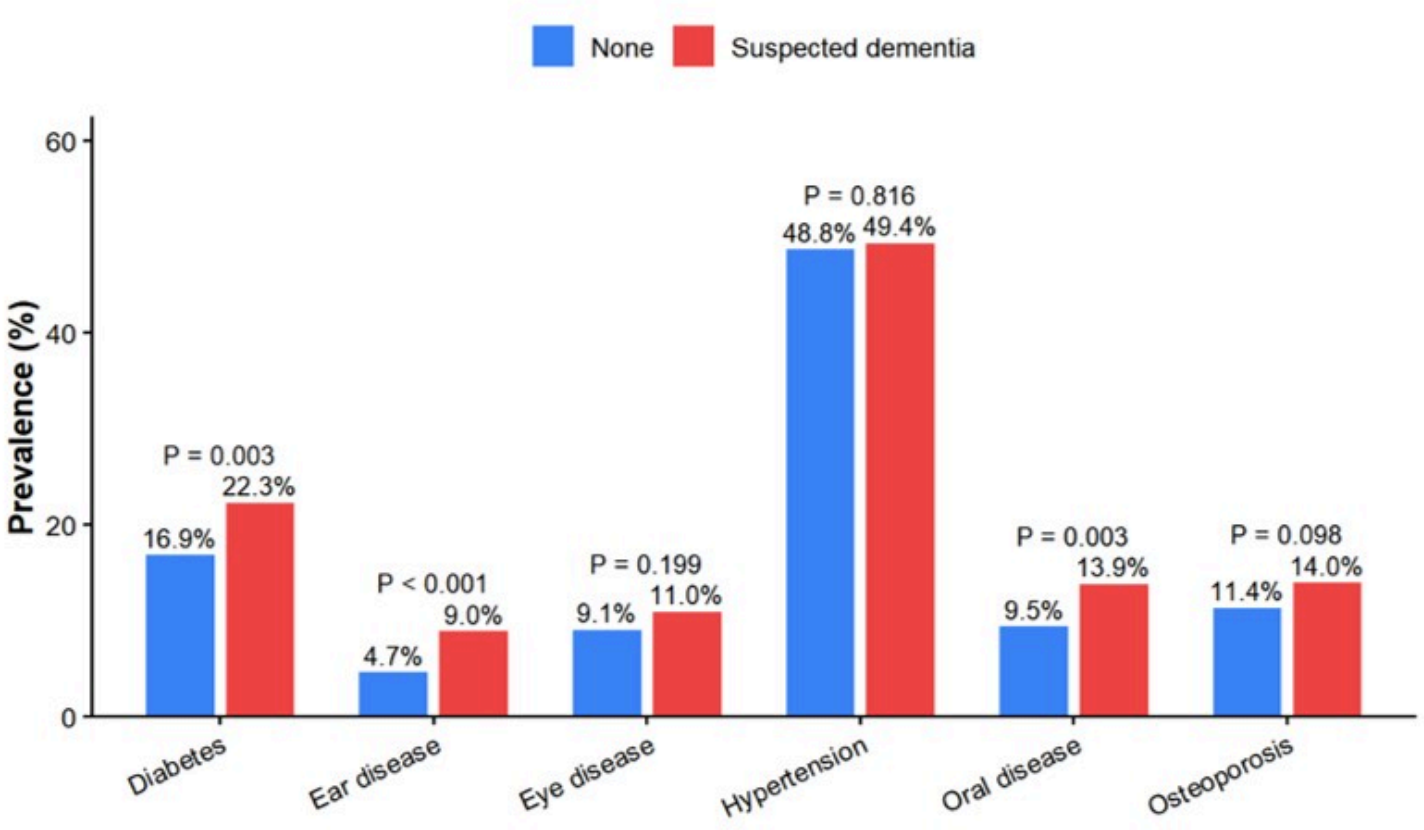


Figure 1

Prevalence of major somatic comorbidities by suspected dementia status.

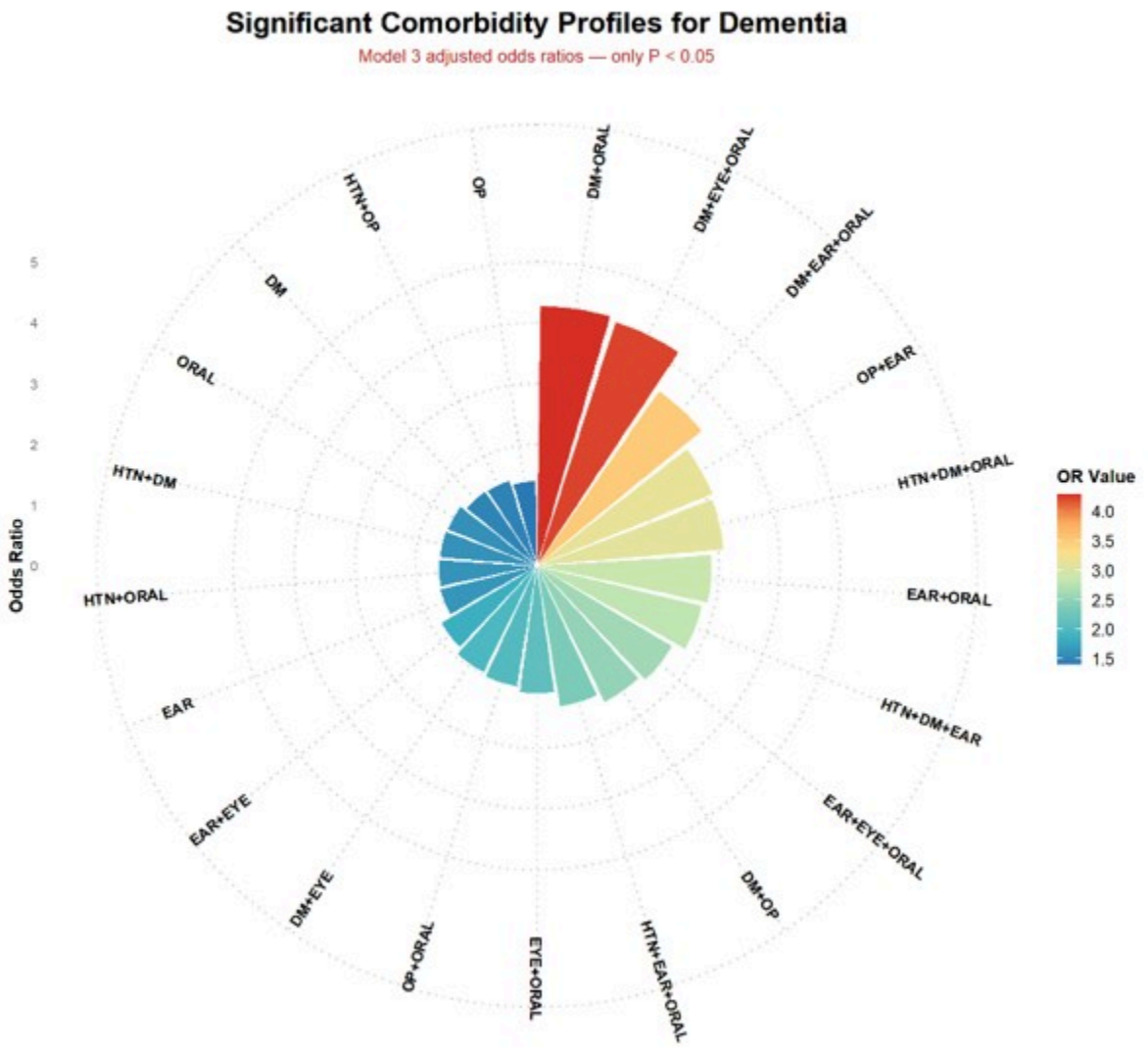


Figure 2

Significant comorbidity profiles for dementia: relative risk (odds ratio) compared to a healthy baseline (only P < 0.05).

The radial bar chart shows odds ratios (OR) for dementia associated with various single and multiple chronic disease comorbidities, compared to a healthy baseline group. Only associations with P < 0.05 are presented. Each segment represents a distinct comorbidity profile, with bar length and color intensity indicating the magnitude of the OR value (legend: blue = lower OR values, red = higher OR values). Abbreviations: DM, diabetes mellitus; HTN, hypertension; OP, osteoporosis; EAR, ear diseases; EYE, eye diseases; ORAL, oral diseases.

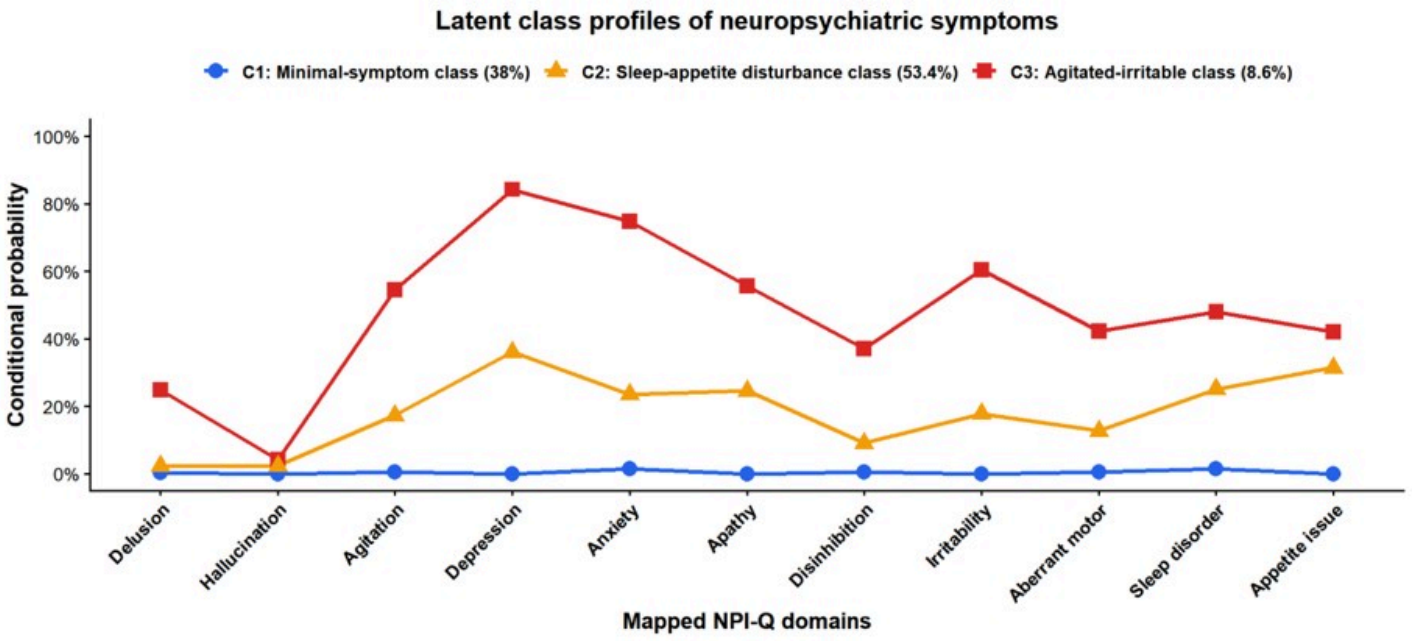


Figure 3

Latent class profiles of neuropsychiatric symptoms in patients with dementia.

Conditional probability plot of 12 Neuropsychiatric Inventory Questionnaire (NPI-Q) symptom domains across three latent classes. Symbols: triangles = asymptomatic class (44.8%), circles = depressive-apathetic class (47.6%), squares = agitated-delusional class (7.6%). The vertical axis shows conditional symptom probability.

Supplementary Files

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