

The Temporal Relationship Between Depressive Symptoms and Dementia

A Community-Based Prospective Study

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Background: The temporal relationship between the appearance of depressive symptoms and the clinical onset of dementia and Alzheimer disease was evaluated in a community sample.

Methods: An original sample of 1366 subjects aged 65 years or older, selected randomly from a rural Pennsylvania community, was cognitively screened at study entry and every 2 years thereafter. A subset of 954 survivors of this cohort without dementia was screened for depressive symptoms at the second and subsequent data-collection waves. A "depression cluster" was identified by the presence of 5 or more depressive symptoms, including depressed mood, at the time of screening. Cognitively impaired subjects and a sample of unimpaired controls underwent standardized clinical evaluation to determine the presence of incident dementia (by *DSM-III-R* criteria) and probable or possible Alzheimer disease (by criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) and to estimate the clinical onset of dementia symptoms.

Results: A highly increased probability of the depression cluster developing existed among subjects following the onset of dementia (15.4% [6/39]) and Alzheimer disease (17.6% [6/34]) compared with subjects without dementia (3.2% [23/712]). The odds ratios, after adjustment for age, sex, education level, and self-reported memory loss, for the development of depression were 6.5 (95% confidence interval, 2.2-19.1) in subjects with Alzheimer disease and 5.2 (95% confidence interval, 1.8-15.2) in subjects with overall dementia. Depressive symptoms did not confer a significantly increased relative risk of dementia (1.27; 95% confidence interval, 0.55-2.93) or Alzheimer disease (1.28; 95% confidence interval, 0.51-3.20).

Conclusion: Depressive symptoms appeared to be early manifestations, rather than predictors, of Alzheimer disease in this community sample.

Arch Gen Psychiatry. 1999;56:261-266

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DEPRESSION AND dementia (including Alzheimer disease [AD]) are among the most prevalent and disabling mental disorders among elders.^{1,2} Their frequent coexistence has stimulated speculation that complex associations exist between these 2 conditions.³⁻⁵

Despite the cross-sectional association between depression and dementia or AD,⁶⁻¹⁰ the temporal and causal nature of the relationship has yet to be determined. Some studies^{3,11-14} have suggested that depression is a prodrome of dementia or that it co-occurs with early AD or other dementias, whereas other studies¹⁵⁻¹⁷ did not find such relationships. Results have been inconsistent among studies examining depression as a risk factor for the development of dementia or AD. Two large prospective cohort studies^{6,18} found that depressive symptoms did not predict the onset of cognitive decline or

dementia within a few years. By contrast, pooled data¹⁹ from 4 case-control studies showed an association between a remote history of depression and a subsequent diagnosis of AD, and 2 cohort studies showed an elevated risk of dementia developing among those with depression²⁰ or depressed mood.²¹

The above-cited inconsistent results likely reflect methodological differences among studies, including study design, sample size, generalizability, measurements, diagnoses, and the selection of different time frames and end points. As Devanand et al²¹ suggested, a prediction of dementia by recent depression can imply that depression is either an early manifestation of dementia or a true risk factor for dementia.

We evaluated the temporal relationship between the appearance of depressive symptoms and the clinical onset of dementia or AD in a community-based prospective study. Specifically, we tested whether

SUBJECTS AND METHODS

SUBJECTS

The data reported here were derived from a community-based multiwave prospective study, the Monongahela Valley Independent Elders Survey (MoVIES).²²⁻²⁶ This survey is an ongoing project first established in 1987 as a model population-based registry for dementing disorders. At study entry (wave 1), the MoVIES cohort included 1366 subjects aged 65 years or older (97.0% white, 54.6% women, and 54.2% with at least a high school education). This cohort represented a 1:13 age-stratified sample selected randomly from the voter registration lists of 23 communities of the mid-Monongahela Valley, about 40 km south of Pittsburgh, Pa.²² The MoVIES cohort was then observed prospectively in a series of data-collection “waves” at, on average, 2-year intervals. Starting from wave 2, data on depressive symptoms were collected at each wave using a modified Center for Epidemiological Studies Depression Scale (mCES-D),^{23,24} described later. The data in this article were derived from completed waves 2, 3, and 4, representing 8 years of serial evaluation of this cohort.

COGNITIVE SCREENING AND RESCREENING

At each wave, after providing informed consent, subjects underwent in-home screening with the same cognitive tests carried out by bachelor's-degree-level research associates trained and supervised by the project neuropsychologist. The reliability of examinations was established by training and reestablished annually. Descriptions and population norms on the MoVIES cognitive test battery and test scores in subjects with and without dementia have been reported previously.^{25,26} The MoVIES battery incorporated the neuropsychological panel of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).²⁷ Briefly, the battery consisted of a general mental status test, the Mini-Mental State Examination (MMSE),²⁸ and a set of other tests of more specific cognitive domains (eg, memory, language, and constructional praxis) known to be impaired in dementia. Operational criteria for “cognitive impairment” were scores at or below the 10th percentile of

the MoVIES sample on the MMSE or on at least 1 memory test and 1 other cognitive test. At each wave, both for cognitive impairment and for cognitive decline, percentiles were calculated using each subject's raw scores (and change in scores) against raw scores (or change in scores) for the whole cohort at that wave. Sensitivity and specificity of these criteria for dementia have been reported previously.²² At each wave, a clinical evaluation (see below) was performed on 3 groups: those who were “cognitively impaired,” those who were “cognitively declined” (defined as a decline in scores since an earlier wave by an amount equal to or greater than the decline experienced by 95% of the sample), and a randomly selected subgroup of cognitively unimpaired controls at baseline.

IDENTIFICATION OF DEMENTIA

The standardized MoVIES procedures for clinical evaluation followed protocols of the University of Pittsburgh Alzheimer Disease Research Center and the CERAD, modified for use in the field and described in detail elsewhere.²² Briefly, subjects underwent a standardized general medical history and physical examination; detailed neurologic, psychiatric, and mental status examinations; blood tests for a hematologic, metabolic, and serologic workup; and neuroimaging when possible. Relevant medical records were obtained and abstracted. Clinical evaluations were performed by clinical research associates (registered nurse or equivalent) trained at our Alzheimer's Disease Research Center, supervised by a board-certified geriatric psychiatrist (M.G.), and blind to the screening scores. Final diagnoses were made by consensus, as per the Alzheimer's Disease Research Center protocol, among all evaluating clinicians and using all available data. Because the study started in 1987, the diagnoses of dementia were made according to *DSM-III-R* criteria.²⁹ Diagnoses of probable or possible AD were made according to criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).³⁰ Once selected for clinical evaluation, subjects were contacted annually for follow-up evaluations. Thus, diagnoses made in previous waves were validated by data obtained during later waves. Once a diagnosis of dementia or AD (probable or possible) was made, the date of the onset of dementia or AD was

depressive symptoms predict the clinical onset of dementia or AD and whether the appearance of depressive symptoms follows the clinical onset of dementia or AD.

RESULTS

SAMPLE

Of the original random sample of 1366 subjects at wave 1, there were 1040 surviving participants at wave 2; 954 of these 1040 did not have dementia and provided data for the present analyses. Of these, 803 completed a wave 3 screen and 634 completed wave 3 and 4 screens. The median length of time was 801 days from wave 2 to wave 3 and 854 days from wave 3 to wave 4. Those without data at wave 3 ($n = 151$) were considered lost to follow-up for these analyses because they were deceased

($n = 80$), refused ($n = 22$), relocated ($n = 6$), were untestable due to severe physical illnesses ($n = 2$), had incomplete mCES-D data ($n = 10$), or were temporarily unavailable ($n = 31$). The group lost to follow-up tended to include more men, to be older, and to have lower MMSE scores at wave 2 ($P < .001$) than those who were followed up (**Table 1**). The prevalence of depression at wave 2, however, was not significantly different ($P = .34$) between these 2 groups.

BASELINE (WAVE 2) DEPRESSIVE SYMPTOMS AS PREDICTORS OF ONSET OF DEMENTIA OR AD

Of 803 subjects without dementia who had completed at least 1 subsequent screening wave (waves 3 and 4) since wave 2, incident dementia subsequently developed in 78 (including 35 with probable AD and 29 with

estimated based on all available evidence as to the time of emergence of cognitive and functional decline.

MEASUREMENT OF DEPRESSIVE SYMPTOMS

During the screening interview, depressive symptoms were measured using the mCES-D,²³ an interviewer-administered version of the original CES-D.²⁴ In the mCES-D, subjects are asked whether or not they have experienced each symptom “most of the time,” defined as 3 or more days of the previous week, so as to ascertain the persistence of depressive symptoms. The questions thus allow a yes or no response, scored as 1 or 0, for a maximum possible score of 20. Thus, the total score represents the number of persistent depressive symptoms present during most of the preceding week, a higher score reflecting more depressive symptoms. Further details²³ have been reported previously.

Depressive symptoms were assessed at each of the waves (2, 3, and 4) reported here. Although a single “depressed mood” approach has shown good reliability and validity,²¹ in this study we have defined “depression” as a depressive symptom cluster at 1 or more wave, using a DSM-III-R–guided approach²⁹ requiring the presence of both depressed mood and other symptoms. Thus, the presence of a depressive symptom cluster in the current analyses is defined as a cluster of mCES-D items, including depressed mood (any 1 of “felt depressed,” “felt sad,” “[did not] feel happy,” and “could not shake off the blues”) and at least 4 other symptoms (“restless sleep,” “could not get going,” “had trouble keeping your mind on what you were doing,” “[did not] enjoy life,” “[did not] feel you were just as good as others,” “thought your life had been a failure,” “poor appetite,” “bothered by things that usually don’t bother you,” “felt everything you did was an effort,” “[did not] feel hopeful about the future,” “felt fearful,” “talked less than usual,” “felt lonely,” “people were unfriendly,” “had crying spells,” or “felt that people disliked you”). This community-screening approach aims to detect depressive symptoms, rather than to diagnose depressive disorders such as major depression. The depressive cluster defined by our approach, however, had a prevalence of 8.27% among 1040 subjects aged 65 years and older, comparable with the combined rate of depressive syndromes reported from another community study by Blazer et al.²

possible AD). The mean (SD) changes in MMSE scores from waves 1 to 4 were -0.9 (2.0) for the group without dementia and -5.2 (5.6) for the group with incident dementia. The prevalence of baseline depression (at wave 2) was 7.7% among those in whom incident dementia subsequently developed between waves 2 and 4 and 6.3% among those who remained without dementia. This difference was not statistically significant ($\chi^2_1=0.21$; $P=.65$). On the other hand, dementia subsequently developed in 11.5% of subjects with baseline depression and in 9.6% of subjects without depression. In the Cox proportional hazards models, depression at wave 2 did not significantly increase the relative risk (RR) of a subsequent onset of dementia (RR = 1.27, 95% CI = 0.55-2.93) or AD (RR = 1.28, 95% CI = 0.51-3.20) after adjusting for age, sex, and education level. Significantly increased risks of dementia developing

MEASUREMENT OF SUBJECTIVE MEMORY LOSS

Self-reported (subjective) memory loss was determined by asking the subject a series of questions, including “Do you feel you remember things less well than you did 2 years ago?” The response, coded as yes or no, was used to classify subjective memory status as “loss” vs “stable.” This variable was used to indicate insight (awareness of cognitive loss), which we hypothesized might be associated with both depressive symptoms and dementia, potentially confounding the relationship between depression and dementia or AD.

After a complete description of the study to the subjects, written informed consent was obtained. All data were collected according to procedures approved by the University of Pittsburgh institutional review board.

STATISTICAL METHODS

Data were analyzed using statistical software (SAS, Version 6).³¹ All tests were 2-tailed. Pearson χ^2 tests (or Fisher exact probability tests, when appropriate) were used to test differences between groups on categorical data. Student *t* tests were used to test the differences between groups on continuous variables. The 95% confidence intervals (CIs) for point estimates of rates were calculated based on the normal approximation to the binomial distribution.

An overview of the study design is presented in the **Figure**. To evaluate whether depression predicts the clinical onset of dementia, a Cox proportional hazards model³² was used to assess the relative risk for reaching the clinical onset of dementia or AD associated with baseline depression.

To evaluate the likelihood of the appearance of new depressive symptoms following the onset of dementia or AD, a logistic regression model was used to estimate the odds ratios (ORs) of the presence of incident depression associated with a recent onset of dementia and AD. Subjective memory loss was found cross-sectionally to be associated with both dementia ($P<.001$) and depression ($P=.01$) in our cohort. To adjust for potential confounding, the models were initially fit within each stratum of self-reported memory (loss vs stable). Because ORs across the strata were not significantly different using the Woolf test for homogeneity³³ (see the “Results” section), the common OR was estimated using the Mantel-Haenszel method across the strata. We also examined ORs from logistic regression models adjusted for age, sex, education, and subjective memory loss.

were associated with greater age (RR = 1.14, 95% CI = 1.10-1.19; $P<.001$) and less than high school education (RR = 1.91, 95% CI = 1.21-3.02; $P=.006$), but not female sex (RR = 0.81, 95% CI = 0.52-1.27; $P=.37$). The corresponding parameters for AD were age (RR = 1.15, 95% CI = 1.11-1.20; $P<.001$), lower education (RR = 1.73, 95% CI = 1.05-2.86; $P=.03$), and female sex (RR = 0.84, 95% CI = 0.51-1.34; $P=.49$). The results remained similar when using depression as a time-dependent variable.

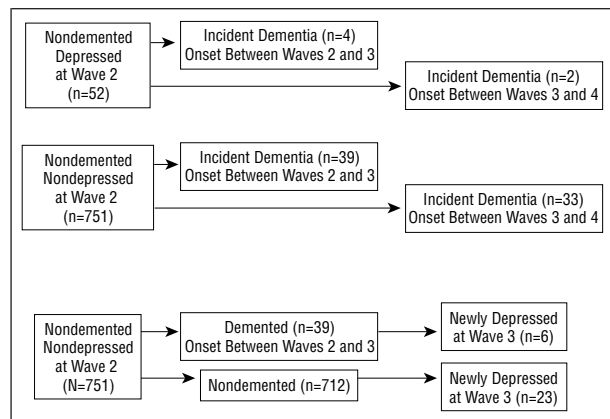
APPEARANCE OF DEPRESSIVE SYMPTOMS FOLLOWING RECENT ONSET OF DEMENTIA

Table 2 presents the likelihood of the appearance of depressive symptoms at wave 3 following a recent onset of dementia (between waves 2 and 3) compared with

that in subjects without dementia, stratified by self-reported memory. Subjects with depression at wave 2 were excluded from these analyses. Subjects with dementia include only those with a clinical onset between waves 2 and 3. Thus, the sample consists of 39 subjects with incident dementia (including 19 with probable AD and 15 with possible AD) and 712 without dementia. Within each stratum of subjective memory, the ORs of depression developing were higher among subjects with dementia and AD than among subjects without dementia. Age-, sex-, and education-adjusted ORs in each stratum showed similar patterns, although the lower bound of the 95% CI in the stable subjective memory stratum was just below 1 for dementia and AD. The ORs across strata were homogeneous ($P = .73$ for dementia vs nondementia and $P = .86$ for AD vs nondementia), ie, the associations were similar between dementia and depression regardless of subjective memory status. Therefore, common ORs (across strata) were estimated for dementia vs nondementia

(OR = 4.33) and for AD vs nondementia (OR = 5.26). The ORs adjusted for age, sex, education, and self-reported memory showed about a 5-fold increased risk of depression developing for those with dementia and about a 6-fold increased risk for those with AD compared with those without dementia.

For comparison with other studies, similar analyses were performed using depressed mood alone (rather than the depressive symptom cluster). Results show that the adjusted RR of dementia developing was 1.15 (95% CI = 0.63-2.08; $P = .66$) in those with depressed mood, and the adjusted OR of the appearance of a new depressed mood was 3.68 (95% CI = 1.54-8.80; $P = .003$) in those with dementia. In addition, results from analyses using 5 or more depressive symptoms on the mCES-D (comparable to a score of ≥ 16 on the original CES-D) were similar (data not shown) to that using the symptom cluster.



Design of longitudinal study on the temporal relationship of the appearance of depression to a recent onset of dementia or Alzheimer disease. The top half shows the baseline incidence of depression as a predictor of the subsequent onset of depression. The bottom half shows the appearance of depression following a recent onset of dementia.

Table 1. Distribution of Demographic and Clinical Characteristics at Wave 2 by Follow-up Status*

Variable at Wave 2	Followed up From Waves 2 to 3 (n=803)	Lost to Follow-up From Waves 2 to 3 (n=151)	χ^2 Test†	P
Female sex	60.0	43.7	13.84 (1)	.001
High school education	61.4	53.0	3.75 (1)	.05
Age, y				
65-74	61.5	54.3		
75-84	35.2	34.4		
≥ 85	3.2	11.3	19.26 (2)	.001
Mean \pm SD	73.7 \pm 5.0	75.5 \pm 6.2	3.28 (189)‡	.001
MMSE, mean \pm SD§	27.3 \pm 1.9	26.6 \pm 2.1	4.34 (948)‡	<.001
Depression	6.5	8.6	0.911 (1)	.34

*Data are given as percentage except where noted.

†Numbers in parentheses indicate degrees of freedom.

‡Student t test.

§Mini-Mental State Examination; 2 subjects had missing data.

Table 2. Risk of Depression Developing in Early Dementia and Alzheimer Disease (AD), Stratified by Self-reported Memory Loss and Combined Across Strata (N=751)*

Subjective Memory Status During Past 2 y	New Onset of Dementia Between Waves 2 and 3	New Onset of Depression at Wave 3, No.		Rates of Depression, %	Odd Ratios (95% CI)	Adjusted Odd Ratios (95% CI)†
		No	Yes			
Stable	Nondemented	498	12	2.35	1.00	1.00
	Demented	15	2	11.76	5.53 (1.14-26.93)‡	4.74 (0.89-25.24)
	AD	14	2	12.50	5.93 (1.21-29.02)§	4.96 (0.93-26.45)
Worse	Nondemented	191	11	5.4	1.00	1.00
	Demented	18	4	18.18	3.86 (1.11-13.36)‡	5.72 (1.33-24.62)
	AD	14	4	22.22	4.96 (1.40-17.60)§	8.33 (1.79-38.72)
Combined	Nondemented	689	23	3.23	1.00	1.00
	Demented	33	6	15.38	4.33 (1.61-11.62)	5.19 (1.78-15.15)
	AD	28	6	17.65	5.26 (1.94-14.29)	6.45 (2.18-19.14)

*CI indicates confidence interval.

†Adjusted odd ratios for each stratum were estimated from a logistic regression model after adjustment for age, sex, and education; adjusted odd ratios for the combined group were estimated from a logistic regression model after adjustment for age, sex, education, and self-reported memory loss.

‡Odds ratios in the 2 strata not significantly different using the Woolf test for homogeneity ($\chi^2=0.12$; $P = .73$).

§Odds ratios in the 2 strata not significantly different using the Woolf test for homogeneity ($\chi^2=0.03$; $P = .86$).

||Common odds ratios over strata were estimated using the Mantel-Haenszel method.

Within a randomly sampled community-based study cohort, this study examined the temporal relationship between the appearance of a depressive symptom cluster and the estimated onset of dementia and AD. Subjects in whom incident dementia and AD developed had a significantly higher likelihood of depressive symptoms also developing. The common clinical observation that depression may be an early sign of dementia and AD has been supported by some cross-sectional studies.^{12,21} Follow-up of “depressive pseudodementia” in clinical and in community settings has shown that subsequent irreversible dementia frequently develops in these subjects.^{3,11,34,35}

It is, of course, difficult to pinpoint the actual onset of most chronic diseases, including AD and depression. We used all available evidence to estimate the date of onset of cognitive and functional manifestations of dementia. This date represents the time during the brain disease when a clinically observable threshold was crossed, rather than the initiation of neurodegeneration. For our purposes, using the clinical onset of dementia, rather than the time when the diagnosis of dementia was made, provides a way to better clarify the temporal relationship between depressive symptoms and dementia. We do not, however, have data on the onset of depression beyond its minimum 1-week duration of the screening. Thus, the newly emerged depressive symptoms that some subjects reported at wave 3 might have begun before the onset of dementia and AD, although close to it because of the short 2-year interval between waves.

Depression in early AD could reflect either a biologically based clinical manifestation of brain disease, a psychological reaction of subjects to the awareness of their declining cognitive function, or both. We attempted to distinguish between those 2 possibilities by examining interactions with self-reported memory loss. As expected, we found an association between depression and the self-awareness of memory loss. Our subjects with a recent onset of dementia or AD, however, still were at a higher risk of depressive symptoms developing than subjects without dementia, independent of self-reported memory loss. The cross-sectional relationship between depression and dementia or AD may be at least partly due to depressive symptoms developing more commonly in the early course of dementia and AD than before its onset.

In our cohort, subjects with depressive symptoms at baseline did not have a significantly increased probability of the subsequent development of dementia and AD. The RR was greater than 1, however, and the CI was wide. This finding does not necessarily refute previous findings^{10,18} that major depression may be a risk factor for AD, because our analyses used a depressive symptom cluster rather than a clinical diagnosis of major depression. Our findings only suggest that depression preceding the onset of dementia by a few years is not a risk factor for dementia. The occurrence of depression several years earlier has not been studied in these analyses. Our negative finding may also be due to the relatively small number of depressed persons and the relatively mild depression seen in the community setting. Depressive symptoms in community samples may be qualitatively

or quantitatively different from those seen in clinical samples and may not be sufficient to demonstrate an effect on the onset of dementia or AD in the population at large. The requirement that depressed mood had to be endorsed by all subjects may have eliminated purely anhedonic depression (ie, without depressed mood) as a predictor of dementia and AD.

Although depression and dementia or AD occurred together significantly more often than by chance, their co-occurrence was seen only in a small subgroup of our subjects. It may be asked whether either condition nonspecifically unmasked or increased a susceptibility to the other. This subgroup may share a distinct subtype of disease; previous studies have suggested that the development of depression in dementia is associated with the degeneration of the locus ceruleus and substantia nigra.³⁶⁻³⁹ Also, 2 conditions may share common pathways through an interaction between the hippocampus and the hypothalamic-pituitary-adrenal axis.⁴⁰⁻⁴⁸ Clues may emerge from trials of the effects of antidementia drugs on mood or of the effects of antidepressant drugs on cognition: studies of trichlorfon (metrifonate) and tacrine hydrochloride in AD suggest that these agents can lessen anhedonia and other symptoms of depression.⁴⁹⁻⁵³

One concern regarding possible bias in interpreting our results is the effect of sample attrition, largely from death. Such a bias may exist, as suggested by differences in the mean MMSE score, age, and sex ratio between those observed and those lost to follow-up. This is not a large bias, however, and its effect would distort our results only slightly because we have a relatively low attrition rate (about 15%, including mortality), similar proportions of depressed subjects in those observed and those lost to follow-up, and fairly large ORs. The relatively small number of subjects with both depression and dementia, reflected by wide CIs, also prevented us from including other possible relevant variables in the analyses. We could not examine the relationships of depression with dementia other than AD because 82% of cases of dementia in this sample were diagnosed as probable or possible AD. Subjects with incident dementia may have misunderstood the self-report questions about depression and memory loss, but this would not have led systematically to either underreporting or overreporting. Furthermore, these subjects were only mildly cognitively impaired at the time of questioning (mean MMSE score, 24). Depressed subjects may also have introduced response bias by being more likely to report subjective memory loss, and some mCES-D symptoms could have been attributable to dementia rather than depression.

CONCLUSIONS

We have reported unique epidemiological data from a prospective, population-based study of a rural elderly population. In the population at large, the depressive symptoms associated with AD and overall dementia are prodromal or early manifestations of the dementia, rather than predictors of the subsequent development of dementia. Being community-based, these findings are at least generalizable to other rural, mainly white, populations and contribute to our broader understanding of the relationship between depression and dementia in the community.

Accepted for publication November 18, 1998.

This study was supported by grants AG00181, AG00312, AG06782, and AG07562 from the National Institute on Aging, National Institutes of Health (NIH), Bethesda, Md, and grants MH49786, MH52247, and MH01613 from the National Institute of Mental Health, NIH, Rockville, Md.

Presented in part at the 11th Annual Meeting of the American Association for Geriatric Psychiatry, San Diego, Calif, March 8-11, 1998.

We thank Steven Belle, PhD, Hiroko Dodge, PhD, and Jane Cauley, DrPH, for their valuable comments on previous drafts. We also thank the participants and staff of the Monongahela Valley Independent Elders Survey (MoVIES) project, without whom this work would not have been accomplished.

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