

Original Research Article

# A Longitudinal Study of Peripheral and Central Auditory Function in Alzheimer's Disease and in Mild Cognitive Impairment

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## Keywords

Central auditory processing · Dichotic digits test · Hearing loss · Alzheimer's disease · Dementia · Mild cognitive impairment

## Abstract

**Background/Aim:** Central auditory processing disorder (CAPD) might precede the onset of Alzheimer's disease (AD). A method of evaluating CAPD is the dichotic digits test (DDT). The aim was to address this in a longitudinal setting. **Methods:** A total of 136 individuals were assessed with peripheral and central hearing tests at baseline and at 5-year follow-up. **Results:** Subjects with AD showed a significant decline in DDT scores of the right ear from baseline to follow-up. The other groups retained high DDT scores. Peripheral auditory function declined as expected according to age. **Conclusions:** Our study indicates that DDT performance reflects an ongoing process resulting in dementia.

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## Introduction

Due to longer life expectancy, the number of elderly people will increase considerably in the future. This development is predicted to occur in high- as well as medium- and low-income countries. One important implication of this demographic trend is that the prevalence of patients with dementia will increase. It is estimated that 50 million people are living with

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dementia in 2018 and that this number will increase to 152 million in 2050 [1]. Different rehabilitation and treatment strategies are under development. These strategies depend on early diagnosis, including the identification of precursor stages of dementia. One of the most important challenges of the health and social services is the management of patients, in most cases elderly persons, with Alzheimer's disease (AD), accounting for an estimated 60–80% of all dementia cases [2].

Mild cognitive impairment (MCI) as defined by Petersen in 2004 [3] includes individuals who do not meet the requirements for dementia, but have subjective memory complaints (SMC) greater than expected for their age, combined with objective cognitive decline. The annual rate of progression from MCI to dementia is 6–10% in epidemiological studies and 10–15% in clinical materials [4]. Over a 3-year period 20% of MCI cases were diagnosed with dementia, of whom 78% were suffering from AD [5].

Apart from cognitive decline, hearing also tends to deteriorate with age, commonly known as presbycusis, or age-related hearing loss. In a systematic review, 30% of men and 20% of women by the age of 70 and 55% of men and 45% of women by the age of 80 were found to have mild to severe hearing loss [6]. The peripheral auditory system, i.e., the function of the middle ear, the cochlea, and the cochlear nerve, can be studied with pure-tone audiometry. Speech audiometry studies speech perception and monitors mainly the peripheral auditory system, but also, to some extent, the central auditory system. The central auditory system includes auditory centers and neural pathways from the brainstem to the cortex as well as the auditory cortex.

Dichotic hearing tests evaluate the central auditory function (primary, secondary, and tertiary auditory cortex) and, in part, the hemispheric lateralization of speech perception. Many elderly have adequate sensitivity to sound, but are poor at recognizing complex sounds in background noise or even in quiet conditions, indicating a central auditory processing disorder (CAPD). CAPD has been described in AD and has also been demonstrated in MCI [7, 8]. Gates et al. [9] showed that tests of central auditory function can be used to predict the development of incipient dementia. In their study, a cohort of elderly persons was tested on one occasion. Those who later developed AD had significantly reduced central auditory processing function compared with the others, taking into account that the central auditory processing function deteriorates with age [7].

To differentiate CAPD from other forms of age-related hearing loss, two main types of tests have been recommended: dichotic listening and speech-in-noise perception [10]. Dichotic listening measures the ability to identify conflicting auditory stimuli (most often speech, e.g., different number words) presented simultaneously to both ears. In experimental studies a right-ear advantage is normally observed, i.e., listeners report more accurately what they hear in their right ear – contralateral to the speech-specialized left brain hemisphere. Dichotic listening is valid as a hearing test because it resembles a real-life social situation where listeners hear multiple speakers talk at the same time, which is difficult for persons with CAPD. Speech-in-noise tests require listeners to recognize words presented against background noise, with either fixed or adaptive signal-to-noise ratios.

There is a need for a practical, clinical test for subjects who are at risk of developing dementia, a test that should be easily performed and not too time consuming. The dichotic digits test (DDT) possibly fulfils this demand [11, 12]. Before it can be recommended, it is of importance to demonstrate that the DDT has the ability to monitor an ongoing process resulting in dementia.

The aim of the present study was to study longitudinal changes in CAPD, as measured by DDT, in study groups consisting of patients with AD, MCI, and a reference group with SMC.

**Table 1.** Numbers and ages of the participants

	All	AD	MCI	SMC
Subjects at follow-up (female), <i>n</i>	47 (28)	8	12	27
Mean age at baseline, years	62.0	63.9	60.1	62.3
SD	0.9	2.4	6.1	5.9
Mean time baseline to follow-up, years	5.1	5.2	5.2	5.0

AD, Alzheimer's disease; MCI, mild cognitive impairment; SMC, subjective memory complaints.

## Subjects and Methods

### Design

This was a longitudinal study in which patients belonging to the three study groups were examined with peripheral and central auditory tests at baseline and 5–6 years later.

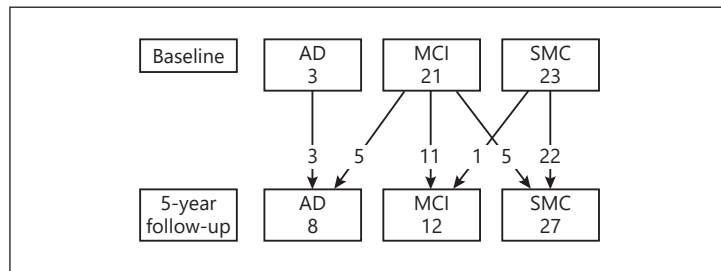
### Study Groups

A group of men and women aged 50–75 years with memory problems, originally referred to the Memory Clinic at the Karolinska University Hospital in Stockholm, was invited to participate in the baseline study. The Memory Clinic is a regional center mainly focused on persons with memory complaints before retirement age. The proposed participants were examined at baseline with a comprehensive assessment battery consisting of an interview with a specialist in geriatrics, a general physical and neurological investigation, a detailed neuropsychological assessment with tests from various cognitive domains (language skills, visuo-spatial functions, psychomotor speed, executive function, short-term memory, and verbal episodic memory), neuroimaging, and cerebrospinal fluid investigation for biochemical markers. Based on this examination they were classified as AD, MCI, or SMC. The latter group consisted of persons with SMC, but the test battery showed cognitive function within normal limits, and this group was included for reference purposes. Apart from belonging to one of the three above-mentioned groups, inclusion criteria were a pure-tone average across 0.5, 1, 2, and 4 kHz (PTA4) not exceeding 70 dB hearing loss. Exclusion criteria were abnormal otoscopy or tympanometry, conductive hearing loss, use of hearing aids, neurodegenerative diseases other than AD, and use of antipsychotic drugs.

At baseline, 146 subjects were invited to participate in the study; 136 were included (response rate 93.2%). Ten subjects were excluded, due to only partial participation in the audiometric tests. For subject group characteristics see Table 1. The baseline investigation was carried out from May 2006 to January 2008. Of the 136 persons who were examined, 43 had a diagnosis of AD, 59 had MCI, and 34 belonged to the reference group of subjects with SMC [8].

The participants were followed over time with the same audiological test battery applied after 1.5 years [13] and 5 years (mean 5.1, SD 0.9, range 4–7 years) during the period 2012–2014. Forty-seven subjects (28 females and 19 males) were eligible for re-examination at this follow-up. Thirty-one subjects were deceased at the time of follow-up, 16 subjects were not able to come due to medical reasons, 12 subjects declined further testing, 3 subjects had moved from the area, and 27 subjects did not respond to repeated invitations or could not be localized. Diagnoses at the time of follow-up were reviewed by the same specialist in gerontology. The distribution between the three study groups at baseline and the diagnostic outcome 5 years later are presented in Figure 1. All tests were performed by one experienced clinical audiologist.

**Fig. 1.** Diagram showing the longitudinal diagnostic outcome regarding the three study groups from baseline to follow-up. AD, Alzheimer's disease; MCI, mild cognitive impairment; SMC, subjective memory complaints.



### Pure-Tone Audiometry

Pure-tone audiometry included air conduction thresholds at 0.125–8 kHz and was performed according to ISO 8253-1 [14]. The equipment was a GN Resound Orbiter 922 version 2 audiometer equipped with TDH-39 earphones, and the testing was performed in a sound-attenuating booth.

### Speech Tests

Speech audiometry was carried out in two settings: speech perception in quiet (SPQ) and speech perception in background noise (SPN). The SPQ test was performed as a prelude to SPN according to ISO 8253-3 [14]. The test material consisted of PB monosyllabic words in Swedish. In the SPN test, 50-sentence lists were presented through a CD player at a comfortable level chosen by the subject in a fixed speech-weighted background noise at a 4-dB signal-to-noise ratio as described by Magnusson [15].

### Dichotic Digits Test

The DDT was presented in lists containing series of two digits according to a previously described Swedish test protocol [16]. The two-digits test was performed under two different conditions: (1) directed recall, where the subject was asked to repeat what was heard only in the right or in the left ear, respectively, and (2) free recall, where the subject was asked to repeat what was heard in both ears, without specifying in which ear it was heard [8]. The test lists were delivered through a CD player, an audiometer (Madsen OB922), and earphones (Telephonics TDH-39).

### Statistical Methods

The Kruskal-Wallis test was used to assess differences in DDT results between the three groups; a nonparametric test was used because of skewed data. The analyses were conducted in Statistica version 13 (StatSoft Scandinavia AB). All group-wise assessments were based on group affiliations at follow-up.

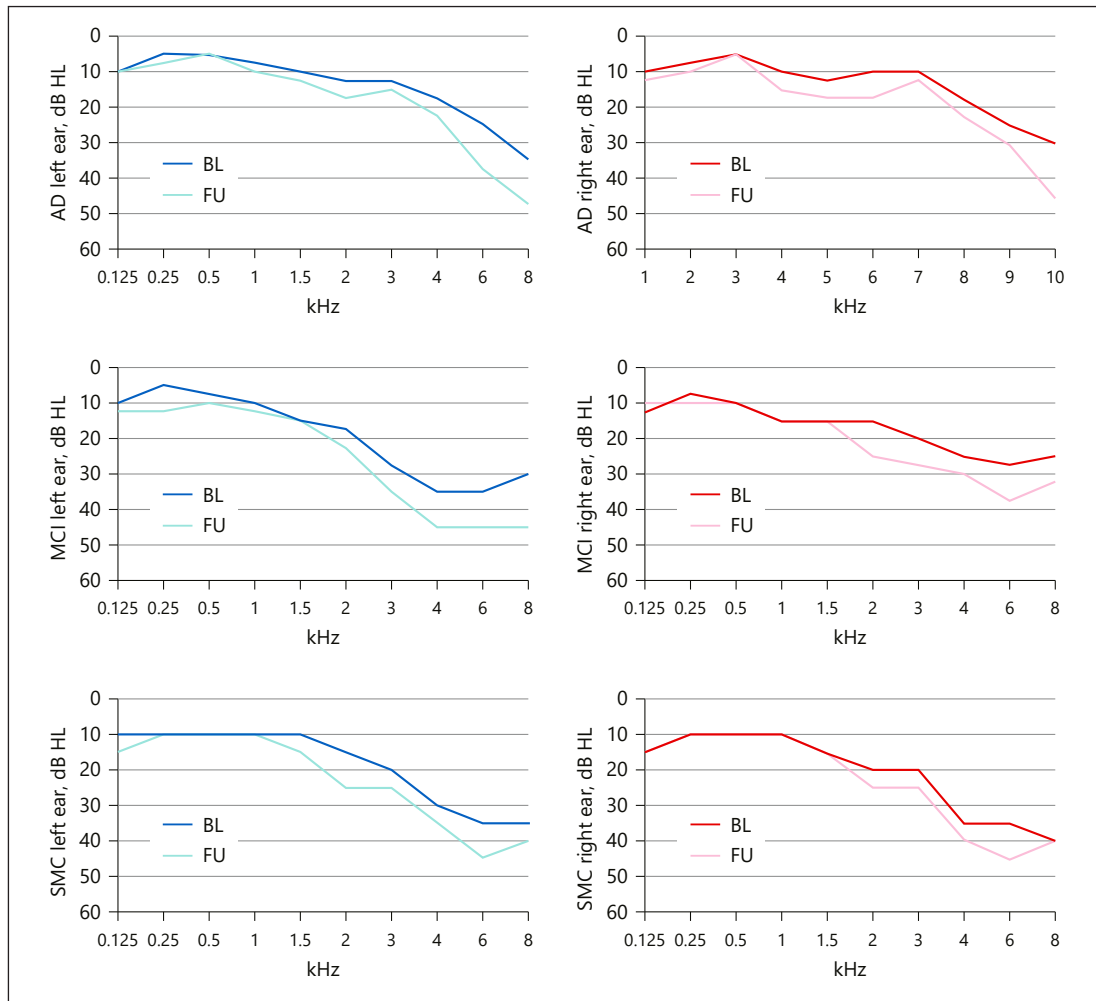
## Results

### Pure-Tone and Speech Audiometry

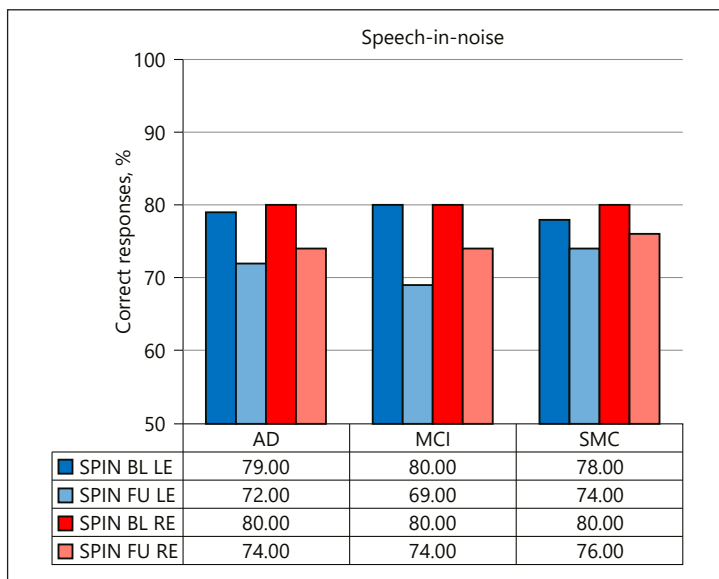
There were no significant differences between the three groups regarding decline of the pure-tone thresholds (Fig. 2) or results in the speech-in-noise test (Fig. 3) over the 5-year study period.

### Dichotic Digits Test

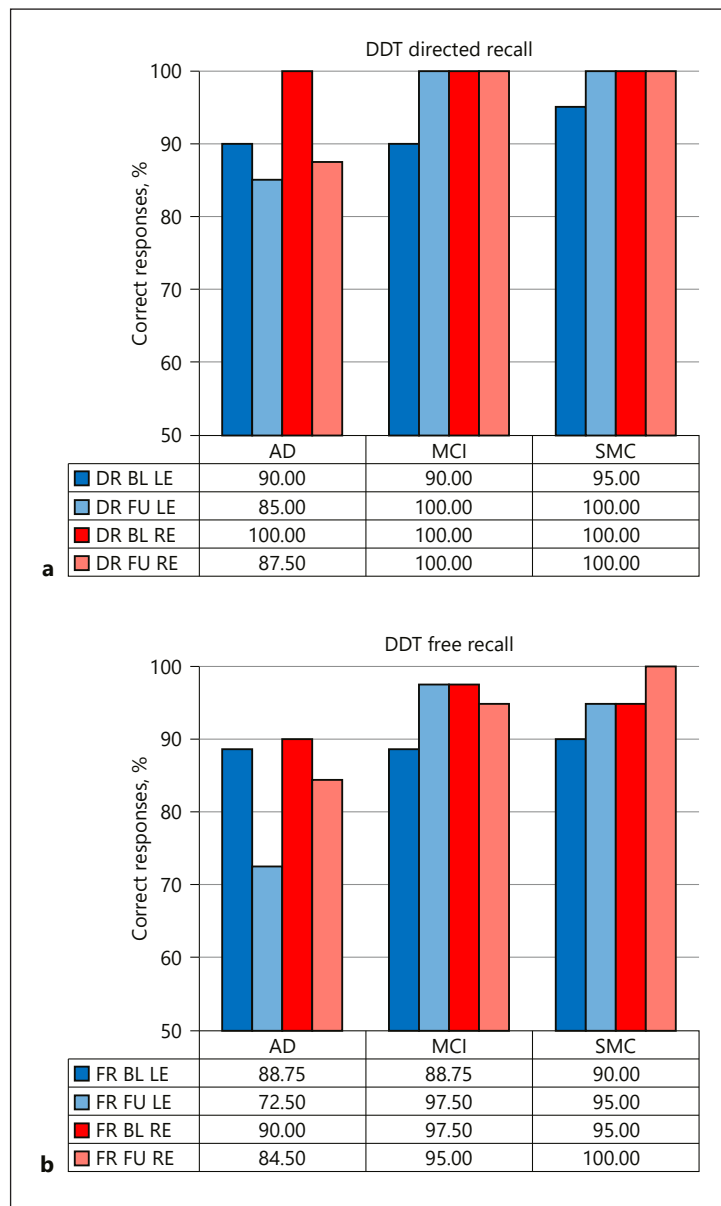
At baseline, the test scores for central auditory function were high in all three groups (median DDT scores 89–100%). At the 5-year follow-up, 8 subjects had AD, including 3 from



**Fig. 2.** Median pure-tone thresholds of the three study groups at baseline and follow-up. AD, Alzheimer's disease; BL, baseline; FU, follow-up; HL, hearing loss; MCI, mild cognitive impairment; SMC, subjective memory complaints.



**Fig. 3.** Speech-in-noise test results at baseline and follow-up, left and right ear. AD, Alzheimer's disease; BL, baseline; FU, follow-up; LE, left ear; MCI, mild cognitive impairment; RE, right ear; SMC, subjective memory complaints.



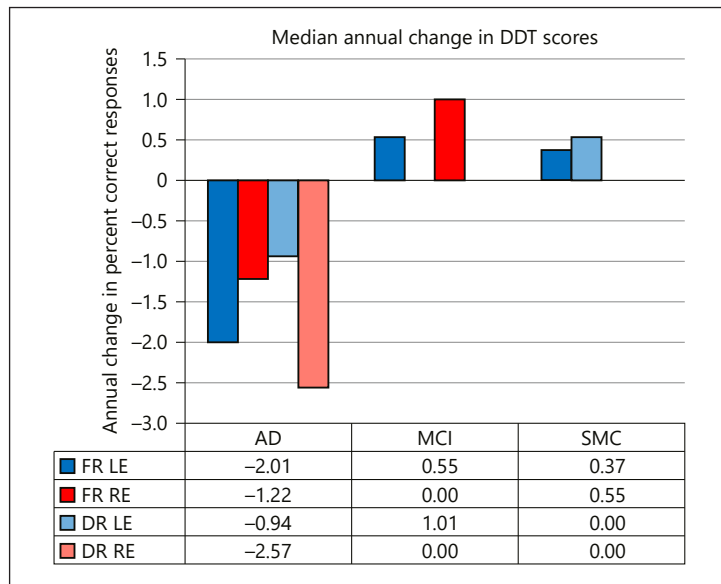
**Fig. 4.** **a** DDT directed recall, left and right ear. **b** DDT free recall, left and right ear. AD, Alzheimer's disease; BL, baseline; DDT, dichotic digits test; DR, directed recall; FR, free recall; FU, follow-up; LE, left ear; MCI, mild cognitive impairment; RE, right ear; SMC, subjective memory complaints.

**Table 2.** *p* values of between-group differences in annual change in DDT scores as shown in Figure 5

	KW	AD-MCI	AD-SMC	MCI-SMC
FR LE	0.19	0.22	0.40	1.00
FR RE	0.02	0.76	0.02	0.32
DR LE	0.06	0.06	0.50	0.41
DR RE	0.01	0.01	0.02	1.00

AD, Alzheimer's disease; DDT, dichotic digits test; DR, directed recall; FR, free recall; KW, Kruskal-Wallis nonparametric ANOVA; LE, left ear; MCI, mild cognitive impairment; RE, right ear; SMC, subjective memory complaints.

**Fig. 5.** Mean annual change in percent of DDT scores, free and directed recall, left and right ear in the three study groups. AD, Alzheimer's disease; DDT, dichotic digits test; DR, directed recall; FR, free recall; LE, left ear; MCI, mild cognitive impairment; RE, right ear; SMC, subjective memory complaints.



the AD group at baseline and 5 who had converted from MCI. At follow-up, the central auditory function tested with DDT was within normal limits in the SMC group, with DDT scores between 95 and 100%. The DDT scores were reduced in the AD group with scores between 73 and 88%. The MCI subjects had DDT scores between 95 and 100%. This is illustrated in Figure 4. A comparison of the rate of mean annual change between the groups from baseline to follow-up showed that the right ear in the AD group had a significantly higher rate of decline compared to the other two groups (Fig. 5; Table 2). The decline in the left ear did not differ significantly between the groups.

## Discussion

### Discussion of Results

In this 5-year follow-up of peripheral and central auditory function, we found that DDT performance deteriorated significantly in the group that had AD at baseline or developed AD during the study period. A comparison of intergroup decline showed that the right ear in the AD group deteriorated significantly compared to the other groups. The left ear also declined in the AD group, but not significantly in the intergroup comparison. Since the left ear generally performs poorer than the right ear, this might be regarded as an unexpected finding. One explanation may be that the group was very small, another that the left ear scored significantly below the right ear already at baseline [8], with a possible catch-up effect for the right ear at follow-up. No significant changes in DDT scores over time were seen in subjects belonging to and remaining in the other two groups. On the contrary, the MCI and SMC groups scored somewhat better at follow-up compared to baseline. This was probably due to a learning effect explained by the repeated testing.

No differences were shown in peripheral auditory function, other than what was expected for age, between the study groups.

Two cohort studies by Gates et al. [9, 17] investigated whether CAPD might precede the onset of AD. One study was part of the Framingham Heart Study [17], where a population-based cohort ( $n = 740$ ) was examined with a test of CAPD (synthetic sentence identification,



ipsilateral competition). Two percent of the participants in this study had CAPD at baseline. Of the 15 subjects with CAPD at baseline, 7 (47%) developed probable AD at follow-up up to 12 years after the baseline testing, compared to 33 (5%) of the 725 participants without CAPD. Thus, CAPD had a positive predictive value of 47% for subsequent AD, but sensitivity was only 17.5%. In the other investigation, a cohort ( $n = 274$ ) belonging to a study of aging and dementia was studied at baseline with a test battery consisting of three tests sensitive to deficits of the processing of speech or digits [9]. Twenty percent of the participants had memory impairment without dementia. At follow-up 10–48 months later, 23 had developed dementia diagnoses (AD in 21 cases). Of these patients, 18 came from the memory-impaired group and 5 from the cognitively normal group. Moderate impairment of one of the tests (dichotic sentence identification test) was associated with an increased risk of AD. DDT results were also associated with an increased risk of AD, but the test was not a significant predictor when moderate impairment was present. In both studies the authors reported that tests sensitive to CAPD might be indicators of incipient AD. They recommended that elderly patients with very poor scores on central auditory tests be considered candidates for evaluation of cognitive function.

In the present study, only few patients ( $n = 5$ ) developed AD, and this number was too small to permit far-reaching conclusions. The different outcomes between the studies of Gates et al. [9, 17] and the present study can partly be explained by different study designs and by different methods of analysis. In the present study, the baseline groups were selected and partly compromised regarding cognition, while in the two studies by Gates et al., the baseline groups were population based. It is possible that the central auditory function contrast between SMC and dementia patients is less than that between the general population and AD patients.

#### *Discussion of Methods*

The same test battery as the one performed at baseline was carried out at the 5-year follow-up test session. However, the dropout frequency was considerable, especially for those with AD at the baseline investigation. This resulted in small numbers of participants, which limits statistical analyses and conclusions.

### **Conclusions**

Those patients who had AD at baseline or progressed from MCI to AD during the longitudinal study had a significantly higher rate of decline of DDT scores of the right ear compared to those without dementia. Our study indicates that DDT performance reflects an ongoing process which might result in dementia.

### **Acknowledgments**

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### **Statement of Ethics**

The study was approved by the regional ethics review board in Stockholm, 2005/914-31 and 2014/2087-31-2.



## Disclosure Statement

The authors have no conflicts of interest to declare. None of the sponsors played any role in the design, execution, analysis, interpretation, or writing of this study.

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