

Is COPD associated with alterations in hearing? A systematic review and meta-analysis

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Background and aims: COPD is an irreversible or persistent airflow obstruction, which affects up to 600 million people globally. The primary purpose of this systematic review was to explore the COPD-based alteration in the auditory system function by conducting a quantitative analysis of presently published data.

Materials and methods: We systematically searched seven diverse electronic databases and manual searching of references to identify relevant studies. Data from the selected studies were rated by two investigators independently in a blinded fashion. Meta-analysis was done on pooled data using Cochrane's Review Manager 5.3.

Results: Sixteen articles received suitable scores and were thus included for further processes. Hearing loss (HL) was defined as a change in pure tone audiometry (PTA) thresholds, auditory brainstem response (ABR), and auditory P300 parameters. ABR wave was significantly elongated in patients with COPD than in controls (standardized mean difference [SMD]=0.27, 95% CI: 0.05–0.48, $P=0.02$). PTA was significantly higher in patients with COPD when compared with controls (SMD=1.76, 95% CI: 0.43–3.08, $P=0.0004$). We found that patients with COPD had a significantly higher latency than controls (SMD=1.30, 95% CI: 0.79–1.80, $P=0.0001$).

Conclusion: COPD patients had considerably greater incidence of HL when compared with controls. Interestingly, although the mean PTA thresholds at every frequency for COPD patients were higher than those for controls, these values were still in the slight to mild HL ranges. Prolonged ABR wave latencies in the COPD patients suggest retro-cochlear involvement. Thus, COPD most frequently clusters with HL, but it is worth noting that alteration in hearing is not always recognized by medical experts as a frequent comorbidity associated with COPD.

Keywords: COPD, hearing loss, systematic review, meta-analysis

Introduction

COPD is an irreversible or persistent airflow obstruction, which affects up to 600 million people globally. COPD is presently one of the major causes of morbidity and mortality in people suffering from chronic illnesses. COPD prevalence is an increasing problem in old age, and globally, the number of COPD patients aged 65 or over is growing.¹ Moreover, the main healthcare resources are expended on COPD as well as beyond its comorbidities, of which half of the costs are attributable to hospital stay.² In recent years, the use of home care services, as well as the involvement of the patients in observing and managing their illness in cooperation with the health professionals have increased.³ The central nervous function may be adversely affected by COPD.⁴ Several studies have also been performed on the effect of COPD on different structures of the auditory system in COPD patients.

The mechanotransduction mechanism of the inner ear is extremely reliant on the oxygen supply to the cochlea, so that any significant reduction in oxygen locally may

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have a marked effect on hearing sensitivity.⁵ Atis et al⁶ and Gupta et al⁷ recorded auditory brainstem responses (ABRs) in individuals with airflow obstruction and found that auditory nerve and brainstem functions have been influenced in these patients. Conversely, Abdel Dayem et al⁸ and Cunningham et al⁹ reported absence of significant changes in auditory function between chronic respiratory insufficiency and control participants.

Pure tone audiometry (PTA) is a behavioral test used to measure hearing sensitivity and to determine the degree and type of hearing impairment.¹¹ ABRs are acoustically stimulated signals that represent synchronous neural activation along the auditory pathways from the auditory nerve to the brainstem nuclei. ABRs can be used for hearing threshold estimations and for neurodiagnostic purposes.¹² The recording results are represented as a series of positive peaks (I–V) that are recorded from the human scalp within 10 ms of a single appropriate acoustic stimulus. The first two peaks (waves I and II) are generated by the auditory nerve, and the subsequent peaks (waves III–V) actually have multiple generators, meaning that they are produced by the pooled electrical activity of several nuclei in the auditory brainstem. The auditory P300 is an event-related potential commonly elicited in signal detection tasks. The P300 provides an objective measure of cognitive function in the auditory system.¹⁰

The primary purpose of this systematic review was to explore the COPD-based alteration in the auditory system function by conducting a quantitative analysis of presently published data. We compared PTA thresholds, ABR, and auditory P300 parameters in COPD patients and controls. Besides, the results of this review may provide an insight into the potential association between COPD and hearing loss (HL).

Materials and methods

Search strategy

We systematically performed a literature search according to PRISMA guidelines. Potential articles were identified through the following electronic databases: MEDLINE, PubMed, EMBASE, Biosis Preview, ISI Web of Science, National Institute for Health and Clinical Excellence, and Scopus. The search terms included (hearing loss OR hearing impairment OR hearing damage OR hearing difficulty OR hearing disorder OR auditory impairment OR auditory damage OR auditory dysfunction OR deaf) AND (COPD). The search was conducted up to April 2018 with no language limits.

Inclusion and exclusion criteria

All observational studies using a prospective cohort or cross-sectional design (studies with controls) on hearing assessment in adult COPD patients using conventional PTA, ABR, or auditory P300 were included. Studies in which the control population was not subjected to the same hearing tests as the COPD patients, the diagnosis of COPD was based on self-report, or the hearing assessment was not standardized were excluded. Furthermore, letters, editorials, commentaries, conference abstracts, animal or biochemical studies, and case reports were not eligible for evaluation.

Study selection

A spreadsheet was used for this purpose accounting for authors, study titles, study design, outcomes, type of hearing screening measure, and statistical analysis. Data from the selected studies were rated by two investigators (AB and FR) independently in a blinded fashion. Scores were then compared using the Pearson correlation coefficient to determine the interrater reliability. Correlation coefficient >0.80 was considered acceptable for a significance level of $\alpha < 0.05$. All divergence among reviewers was resolved by consensus.

The articles considered eligible were further subjected to “quality assessment” using the modified Newcastle–Ottawa Quality Assessment scale for nonrandomized studies.

Statistical analysis

We used the standardized weighted mean difference with 95% CI to estimate a pooled effect size for each outcome of interest. Data were pooled with both fixed effects and random effects models. Statistical heterogeneity was explored using the chi-squared test at 5% significance level ($P < 0.05$). I^2 statistic was used to quantify variation across studies results. Between-studies variance was also estimated using tau-squared (τ^2) statistic, and funnel plot was used to investigate publication bias visually. All analyses were conducted with Review Manager Software version 5.3 (The Nordic Cochrane Center).

Results

A total of 116 articles were found through the initial search; 18 other studies were recognized through a reference search of the selected studies. After screening of titles and abstracts, 32 articles entered the full-text articles review process, and 11 of these were excluded (Figure 1). Finally, 16 of the potentially selected studies received suitable scores and were

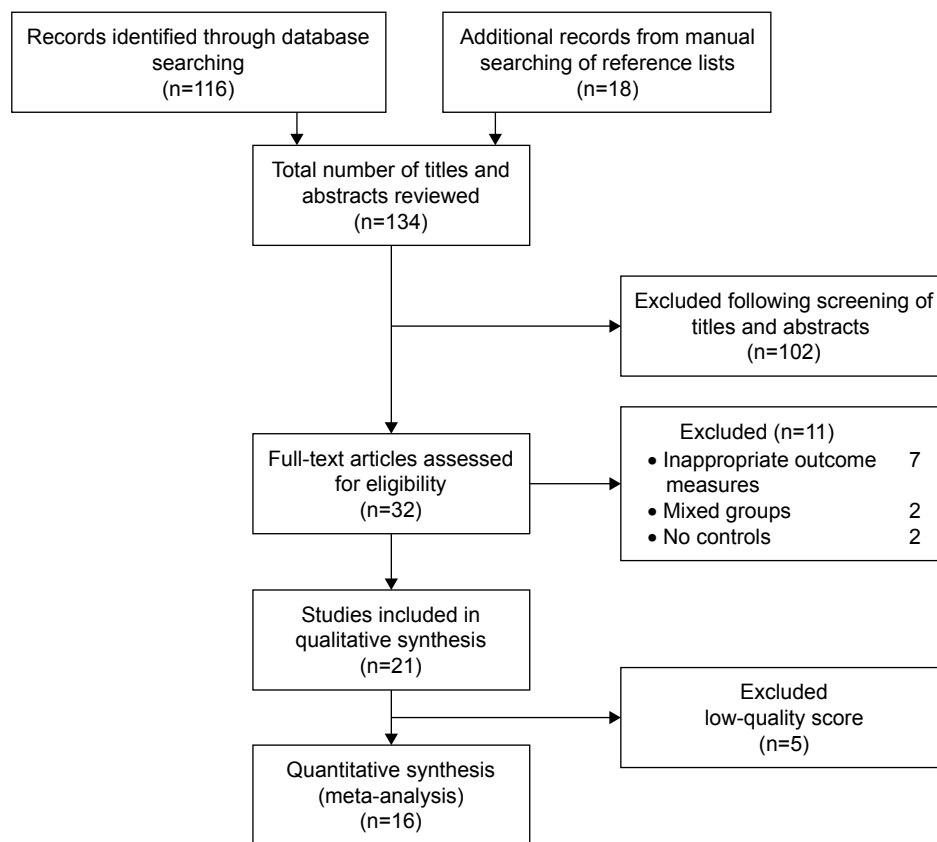


Figure 1 Flow diagram for study selection of studies looking at the effects of COPD on hearing function.

thus included for further processes. The basic information and characteristics of the recruited studies are listed in Table 1.

We used the Newcastle–Ottawa scale to assess the quality of selected studies. All included studies received overall scores of >6 (Table 2).

ABR wave latencies

Left ear

ABR waves' latencies of the left ear were found only in seven studies.^{7,11–16} Though the heterogeneity was relatively high, all absolute peak latencies (waves I–V) were significantly

Table 1 Characteristics of the included studies

Author(s)	Country	Publication year	Participants (controls/COPDs)	Method of hearing assessment
Atiş et al ⁶	Turkey	2001	21/21	ABR
Kamenski et al ¹⁸	Austria	2015	97/97	PTA
El-Kady et al ⁵	Egypt	2006	30/60	PTA, ABR
Abdel Dayem et al ⁸	Egypt	2017	25/100	PTA
Cunningham et al ⁹	USA	1985	12/15	PTA
Kabali and Kabali ¹⁶	India	2013	30/30	ABR
Shalabi et al ¹⁵	Egypt	2012	15/40	ABR
Gupta et al ⁷	India	2008	40/40	ABR
Gupta et al ¹⁹	India	2013	40/40	Auditory P300
Mourad et al ²⁰	Egypt	2017	20/40	Auditory P300
Al-Tahan et al ²¹	Saudi Arabia	2002	25/32	Auditory P300, ABR
Kayacan et al ¹⁴	Turkey	2001	20/32	ABR
Parlewar and Shaikh ¹¹	India	2016	50/50	ABR
Waseem ¹²	India	2018	30/25	ABR
Hafez et al ¹³	Egypt	2009	30/30	ABR
Parlewar and Shaikh ¹⁷	India	2016	50/50	ABR

Abbreviations: ABR, auditory brainstem response; PTA, pure tone audiometry.

Table 2 Assessment of study quality (Newcastle–Ottawa scale quality indicator)

Author(s)	Selection	Comparability	Outcome
Atiş et al ⁶	4/5	1/2	2/3
Kamenski et al ¹⁸	4/5	1/2	2/3
El-Kady et al ⁵	4/5	2/2	3/3
Abdel Dayem et al ⁸	5/5	1/2	3/3
Cunningham et al ⁹	3/5	1/2	2/3
Kabali and Kabali ¹⁶	4/5	2/2	2/3
Shalabi et al ¹⁵	4/5	2/2	2/3
Gupta et al ⁷	3/5	1/2	2/3
Gupta et al ¹⁹	3/5	1/2	2/3
Mourad et al ²⁰	4/5	2/2	2/3
Al-Tahan et al ²¹	3/5	1/2	2/3
Kayacan et al ¹⁴	3/5	2/2	2/3
Parlewar and Shaikh ¹¹	4/5	2/2	2/3
Waseem ¹²	3/5	2/2	2/3
Hafez et al ¹³	3/5	1/2	2/3
Parlewar and Shaikh ¹⁷	4/5	2/2	2/3

prolonged for patients with COPD than those of controls (Figure 2). Furthermore, the interpeak latency intervals I–III of ABR waves was significantly elongated in patients with COPD than in controls (standardized mean difference [SMD]=0.27, 95% CI: 0.05–0.48, $P=0.02$; Figure 3), whereas IPLs were not significantly prolonged for both I–V and III–V peak intervals (Figure 3).

Right ear

ABR waves' latencies of the right ear were found only in seven studies.^{7,11–16} In spite of the relatively high heterogeneity, most peaks' absolute latencies (I, III, VI, and V) were significantly longer for patients with COPD than those of controls, and only for wave II, this increment was not statistically significant ($P=0.12$; Figure 4). Interpeak intervals of ABR waves (I–III, I–V, and III–V) showed a significant prolongation in COPD subjects compared to controls (Figure 5).

Both ears

ABR waves' latencies of both ears were found only in two studies.^{6,17} ABR wave I latencies were significantly different between the two study groups ($Z=1.86$, $P=0.06$, $I^2=27\%$). However, waves III and V latencies were nonsignificantly longer for patients with COPD than the healthy controls (Figure 6).

The difference between the IPLs of ABR waves was not significantly prolonged for both waves I–III and I–V, whereas the IPLs were significantly prolonged in the patient with COPD for waves III–V (SMD=0.51, 95% CI: 0.23–0.79, $P=0.0004$; Figure 7).

PTA thresholds

Four studies reported the mean pure tone threshold averages for both COPD and control individuals.^{5,8,9,18} Our findings indicated that the overall pooled mean audiometry thresholds were significantly higher in patients with COPD when compared with control cases (SMD=1.76, 95% CI: 0.43–3.08, $P=0.0004$; Figure 8). The pooled mean PTA thresholds at 500, 1,000, 2,000, 4,000, and 8,000 Hz for 115 subjects with COPD and 40 controls are shown in Figure 9. The highest values are obtained for 500 and 1,000 Hz. Interestingly, although the mean PTA thresholds at every frequency for COPD patients were higher than those for controls, considering the classification of the degree of HL of the American Speech–Language–Hearing Association, these values were still in the slight to mild HL ranges. The PTA thresholds decreased with increasing frequencies for both COPD and control groups, with SMDs being very significant at lower frequencies.

Auditory P300

Three studies provided data on mean auditory P300 latencies for both COPD and control subjects.^{19–21} The pooled P300 latencies were performed for 112 cases and 85 controls. We found that patients with COPD had a significantly higher latency than controls (SMD=1.30, 95% CI: 0.79–1.80, $P=0.0001$; Figure 10).

Discussion

The current meta-analysis indicated that PTA of hearing thresholds is significantly increased in the COPD subjects than in controls. In addition, hearing thresholds were higher in COPDs at every frequency when compared with controls with increasing magnitude as the frequencies got higher. However, although the degree of HL in COPD patients was not remarkable (PTAs <40 dB HL), COPD can be regarded as a risk for developing mild or subclinical hearing impairment. Abdel Dayem et al⁸ reported that the COPD patients have significantly higher hearing thresholds across low to high frequencies and the thresholds have markedly increased trend at high frequencies (4,000 and 8,000 Hz).

It has been suggested that patients with COPD have evidence of systemic inflammation, especially when the disease is in severe phase or during exacerbations. Several inflammatory cytokines (tumor necrosis factor- α , IL-6, CXCL8 [IL-8], and IL-18) have been implicated in the circulation of COPD patients. These cytokines are increased in sputum and bronchioalveolar lavage fluid, suggesting the role of overspill of inflammatory mediators from the lung.

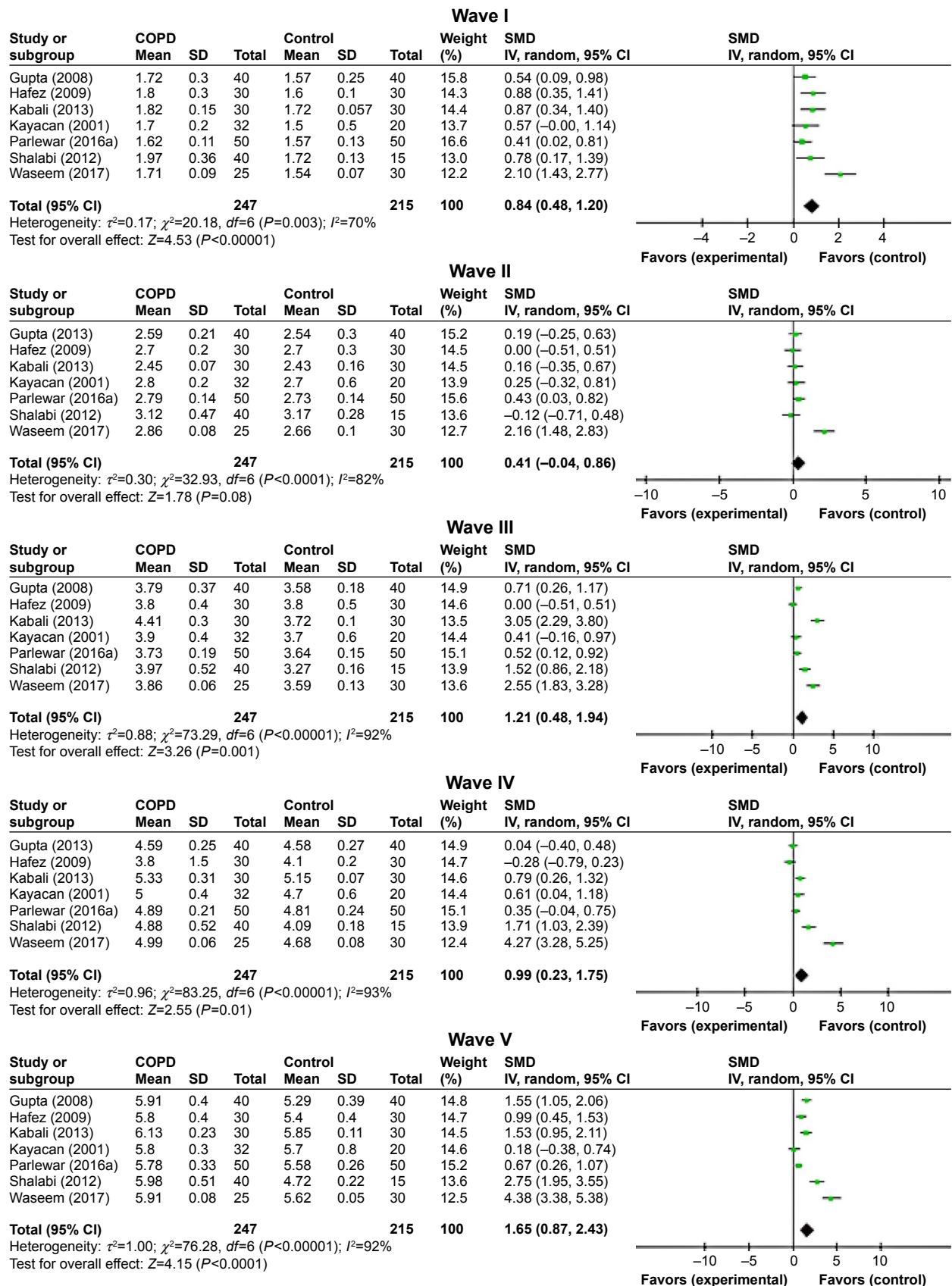


Figure 2 Forest plots of SMD for ABR waves' latencies for both COPD patients and controls.
Notes: Bars and diamonds indicate 95% CI. The weights of each study in the meta-analysis are indicated. Analysis model was random effect considering high heterogeneity; effect measure was SMD.
Abbreviations: ABR, auditory brainstem-evoked responses; *df*, degrees of freedom; IV, inverse variance; SMD, standardized mean difference.

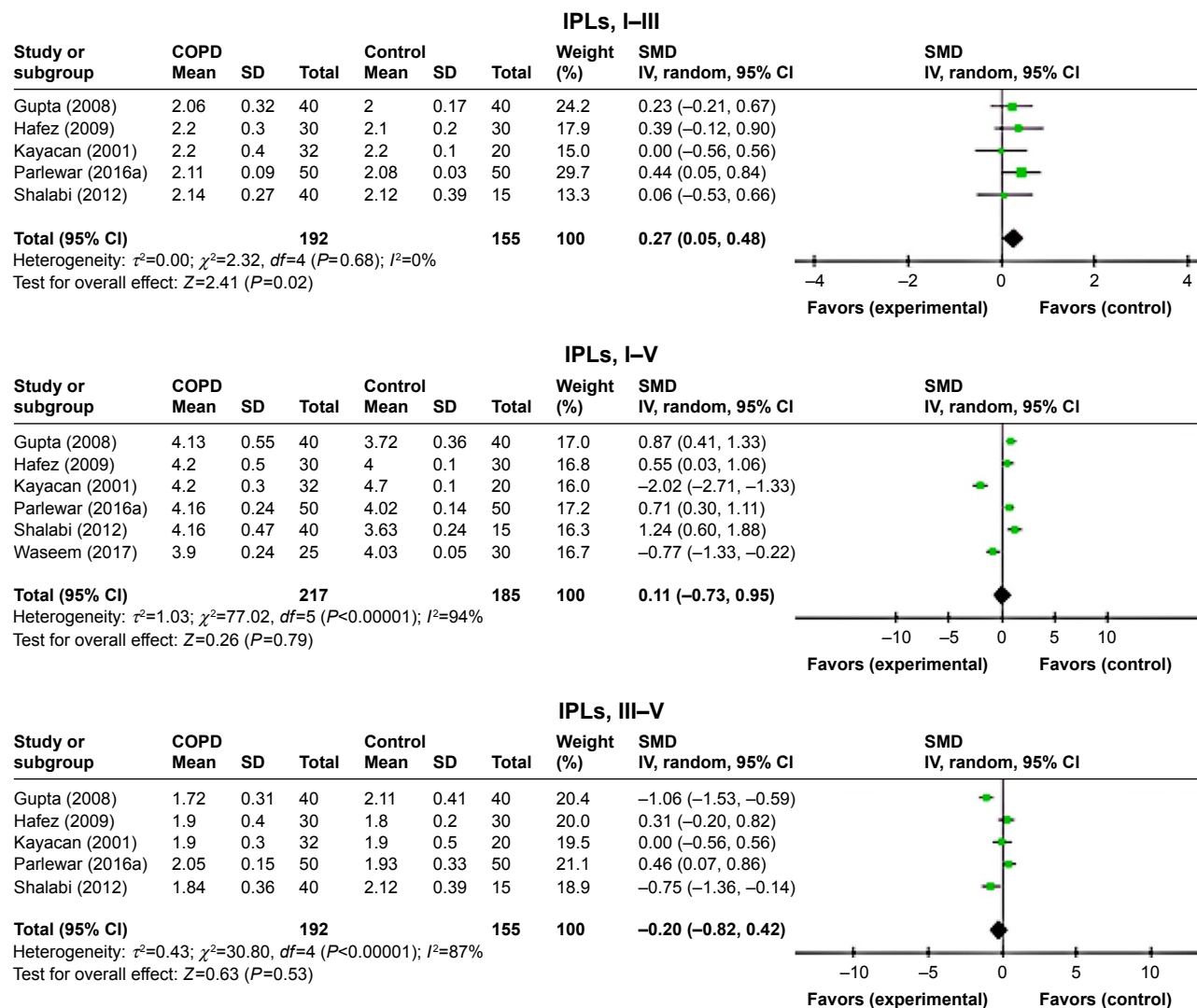


Figure 3 Forest plots of SMD for ABR waves' interpeak latencies for both COPD patients and controls. **Notes:** Bars and diamonds indicate 95% CI. The weights of each study in the meta-analysis are indicated. Analysis model was random effect considering high heterogeneity; effect measure was SMD. **Abbreviations:** ABR, auditory brainstem-evoked responses; *df*, degrees of freedom; IV, inverse variance; SMD, standardized mean difference.

The elements of this systemic inflammation may be responsible for the systemic manifestations of COPD and may worsen comorbid diseases such as HL.²²⁻²⁴

The transduction mechanism of the inner ear and the transmission of nerve impulses along the auditory pathway are highly dependent upon cochlear oxygen supply.¹⁹ Then, any considerable reduction in oxygen supply can affect the processes of generation and transmission of auditory nerve impulses at the level of the auditory system and leads to hearing impairment.⁷ A decrement in the availability of oxygen to the cochlea also has a marked effect on the cochlear potentials, including endolymphatic potential. Johnstone and Sellick²⁵ explained the reduction in auditory sensitivity via a decrease of endolymphatic potential; this potential contributes to the extraordinary high sensitivity of the mammalian

cochlea. However, Kamenski et al's¹⁸ findings do not support the hypothesis that there is a clinically relevant difference in the hearing performance of patients with COPD which is assessed by PTA.

Our study showed that COPD is associated with a specific damage to the auditory brainstem function. Analyses of ABR wave latencies and interpeak latencies with pooled data analyses revealed significantly longer wave latencies in patients with COPD than in controls. The ABR wave latencies provide information on how fast electrical sound signals are transmitted through various parts of the auditory brainstem. Hence, the elongation of these latencies would suggest that there is a delay in the conduction of auditory signals. These outcomes supported that COPD might be a cause of certain dysfunctions of the central and peripheral

auditory pathways. Neuronal involvement is common among chronic respiratory complications. It is, therefore, not surprising that neurons at the brainstem level would show remarkable alternations with the COPD disorder.

Atis et al⁶ reported a high rate of ABR abnormalities (76.1%) in patients with severe COPD. In their study, the most prominent ABR abnormalities were prolonged wave I peak latencies and low wave I peak amplitude, which represent

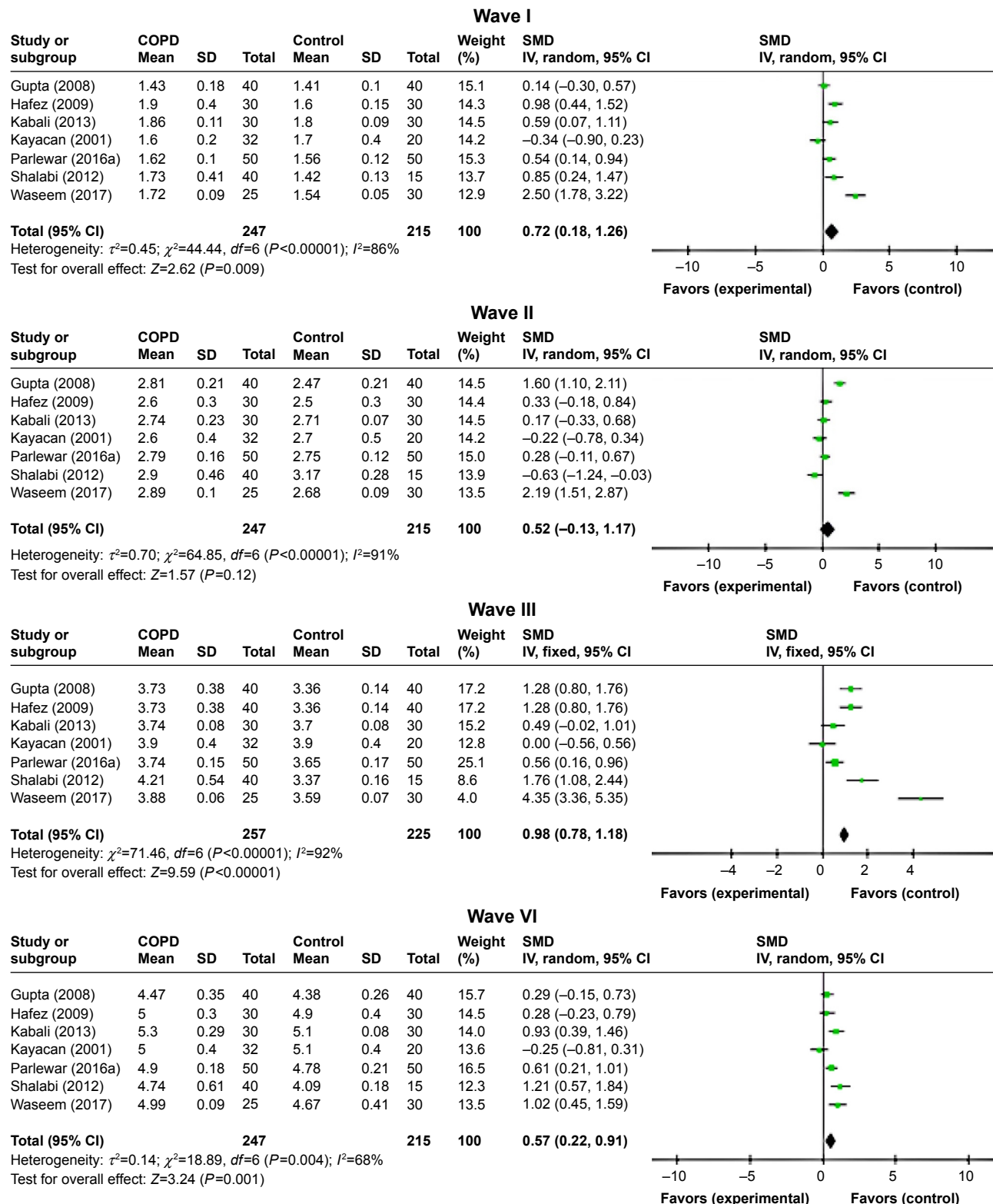


Figure 4 (Continued)

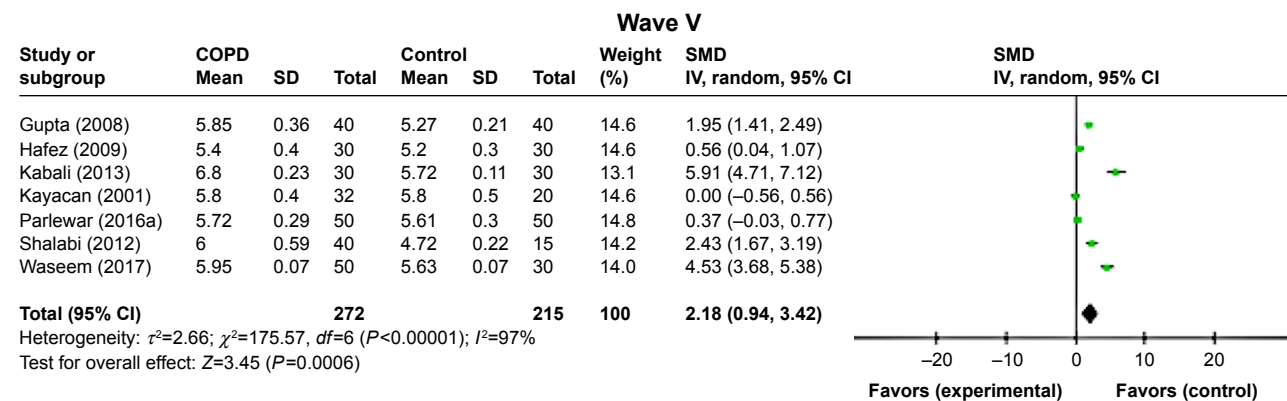


Figure 4 Forest plots of SMD for ABR waves' latencies for both COPD patients and controls.
Notes: Bars and diamonds indicate 95% CI. The weights of each study in the meta-analysis are indicated. Analysis model was random effect considering high heterogeneity; effect measure was SMD.
Abbreviations: ABR, auditory brainstem-evoked responses; *df*, degrees of freedom; IV, inverse variance; SMD, standardized mean difference.

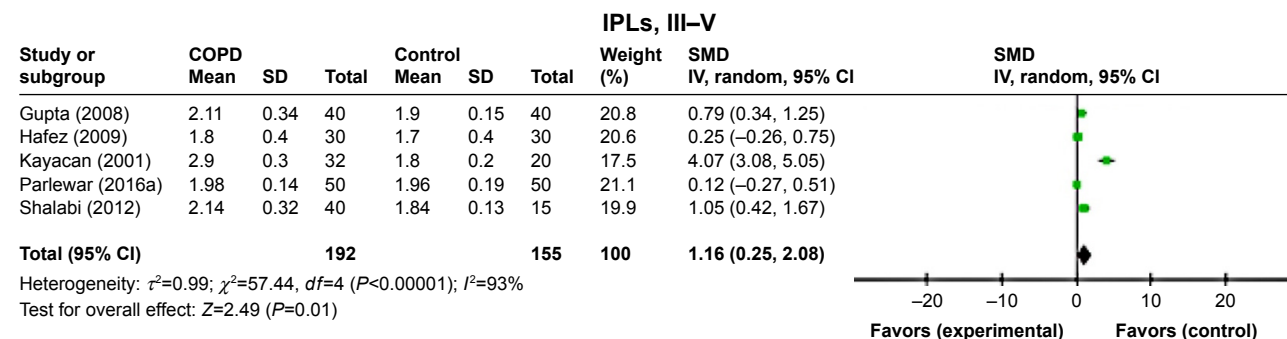
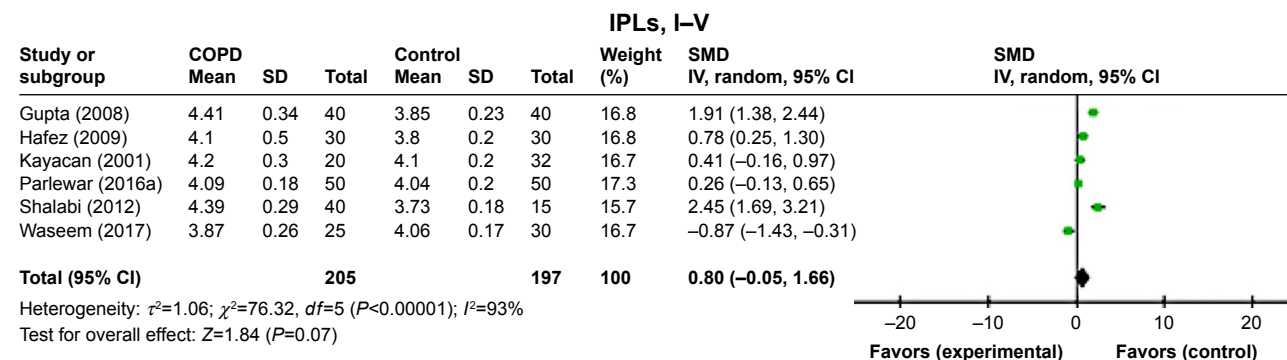
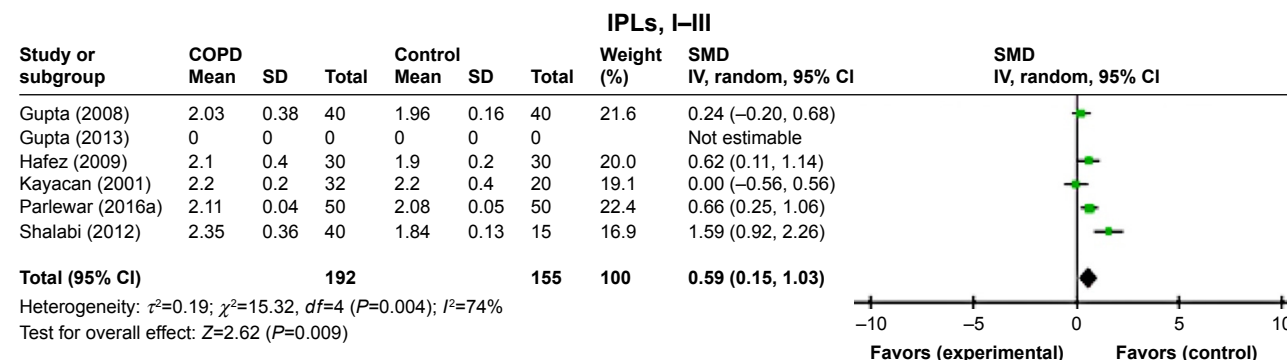


Figure 5 Forest plots of SMD for ABR waves' interpeak latencies for both COPD patients and controls.
Notes: Bars and diamonds indicate 95% CI. The weights of each study in the meta-analysis are indicated. Analysis model was random effect considering high heterogeneity; effect measure was SMD.
Abbreviations: ABR, auditory brainstem-evoked responses; *df*, degrees of freedom; IV, inverse variance; SMD, standardized mean difference.

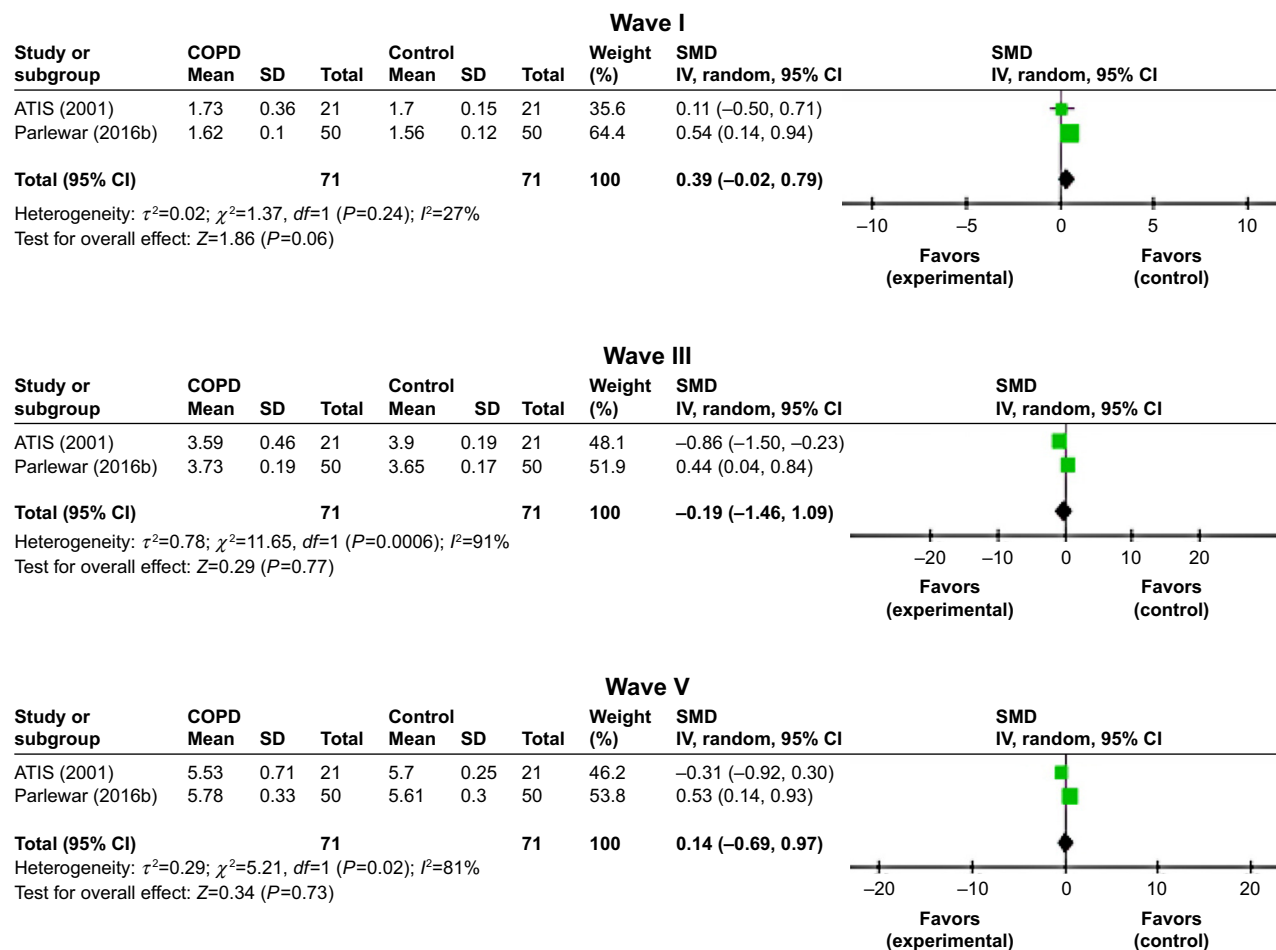


Figure 6 Forest plots of SMD for ABR waves' latencies for both COPD patients and controls.

Notes: Bars and diamonds indicate 95% CI. The weights of each study in the meta-analysis are indicated. Analysis model was random effect considering high heterogeneity; effect measure was SMD.

Abbreviations: ABR, auditory brainstem-evoked responses; *df*, degrees of freedom; IV, inverse variance; SMD, standardized mean difference.

the function of eight cranial nerves (peripheral component of the auditory system). No significant correlation was found between ABR abnormalities and results of spirometric and arterial blood gas parameters (eg, hematocrit, PaCO₂, FEV₁%, pH, PaO₂, FEV₁/FVC) in COPD patients. Gupta et al's⁷ findings demonstrated that 65% (26/40) of COPD subjects had abnormal ABRs, which were more common in the form of prolonged absolute peak latencies (waves I, III, and V) and interpeak intervals (I–III and III–V) in both sides. They also found no correlation or poor correlation between ABR abnormalities and pulmonary function test parameters. In contrast to Gupta et al⁷ and Atis et al's⁶ investigations, Nakano et al²⁶ and Barbieri et al's²⁷ studies revealed no significant differences in ABR parameters between patients with chronic respiratory insufficiency and controls.

COPD has been found to cause a general cognitive decline such as attention, psychomotor speed, memory and learning, visuospatial skill, and auditory perception.^{28–30} Analyses of auditory P300 latency with pooled data analyses

revealed significantly prolonged latencies for COPD patients than controls. The auditory P300 potential is reflective of sensory and cognitive functions. P300 is related to the activity of associative cortical areas and represents conscious recognition, auditory information recognition and memory context updating.^{30–32} P300 latency can be used as a marker of cognitive performance (central processing time), and its delay has already been suggested in different metabolic encephalopathies.³³ Al-Tahan et al²¹ observed that auditory evoked potential latencies, particularly those of P300, were significantly prolonged in patients with chronic respiratory difficulty, in spite of a majority of cases having normal mental state examination (78%). These findings indicate that subclinical cognitive dysfunction (encephalopathy) is common in this group of patients.

The underlying mechanisms of cognitive impairments in COPD remain a controversial issue. Hypoxemia, hypercapnia, or vascular comorbidities have been proposed as possible causes of brain alterations in patients

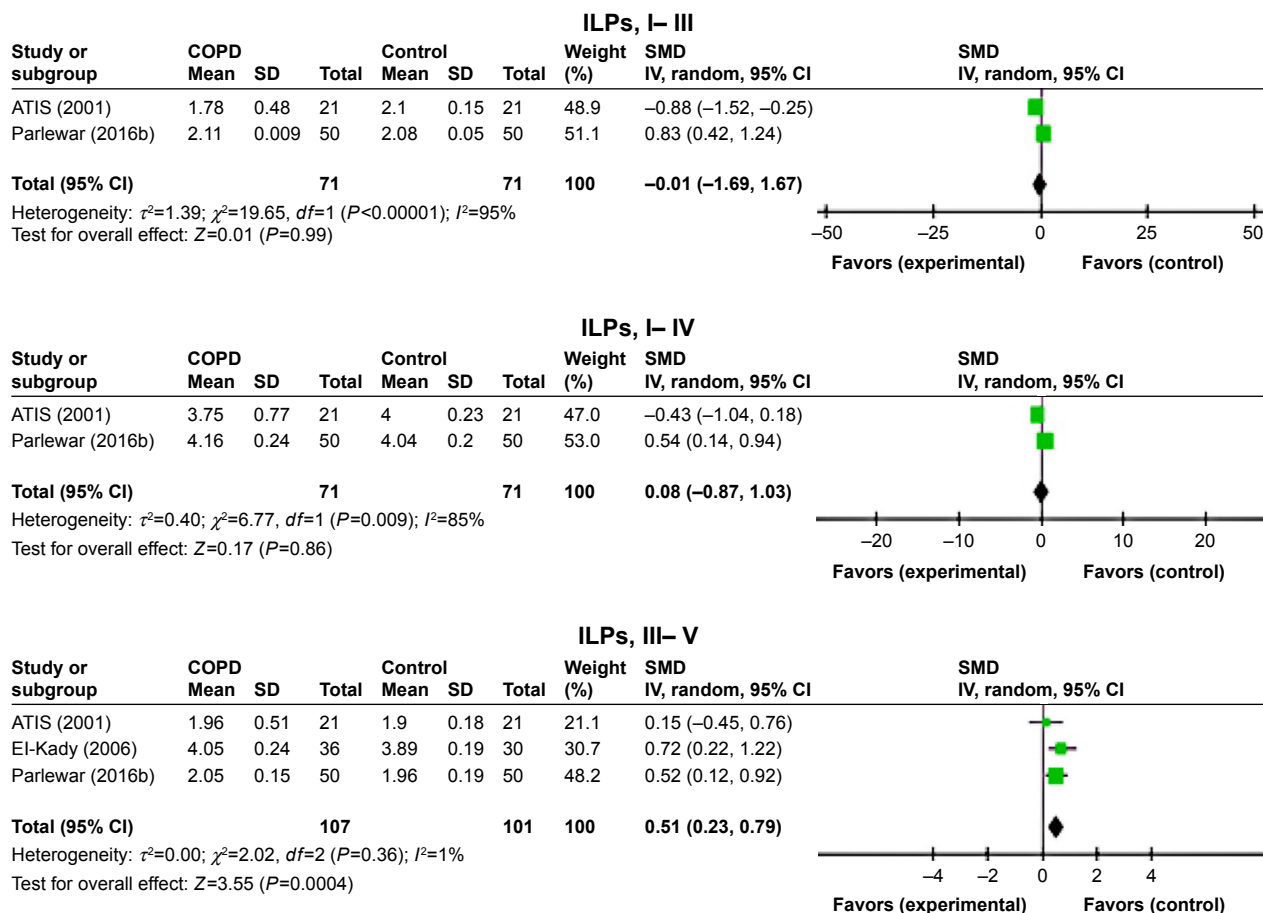


Figure 7 Forest plots of SMD for ABR waves' interpeak latencies for both COPD patients and controls. **Notes:** Bars and diamonds indicate 95% CI. The weights of each study in the meta-analysis are indicated. Analysis model was random effect considering high heterogeneity; effect measure was SMD. **Abbreviations:** ABR, auditory brainstem-evoked responses; *df*, degrees of freedom; IV, inverse variance; SMD, standardized mean difference.

with COPD.^{34,35} Ortapamuk and Naldoken⁴ reported that individuals with severe COPD may develop changes in brain perfusion due to hypoxemia, leading to cognitive impairment. In an experimental design, Guo et al³⁶ suggested that chronic asthma affects synaptic structure and long-term potentiation, and neurogenesis induced by intermittent hypoxia during

the disease course might contribute to higher cognitive (language, learning, and memory) dysfunctions.

Our results indicated that there is some heterogeneity (a high I^2 value of >80%) in the findings of the involved articles, which may be attributed to many differences in the studies included. This can be due to disparities in the

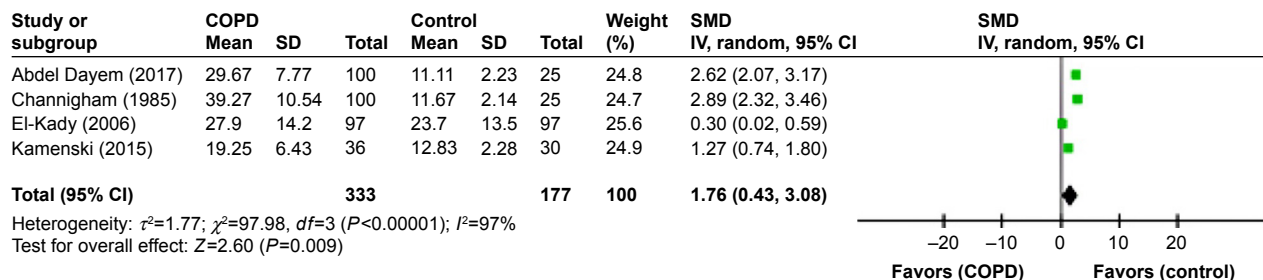


Figure 8 Forest plots of studies showing overall SMD for PTA thresholds in patients with COPD and controls at various frequencies. **Notes:** Bars and diamonds indicate 95% CIs. The weights of each study in the meta-analysis are indicated. Analysis model, random effect; effect measure is mean difference. **Abbreviations:** *df*, degrees of freedom; IV, inverse variance; PTA, pure tone audiometry; SMD, standardized mean difference.

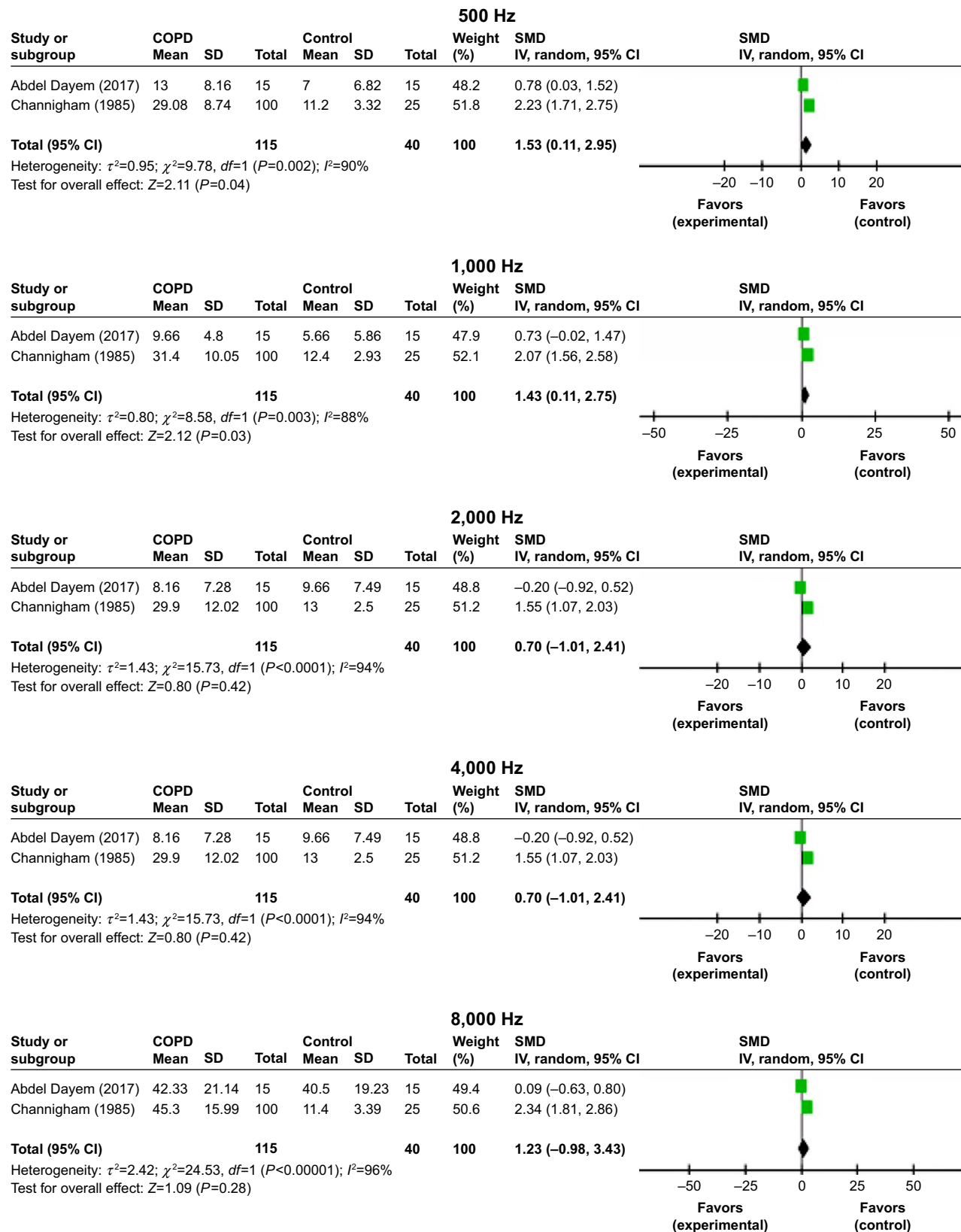


Figure 9 Forest plots of studies showing overall SMD for PTA thresholds in patients with COPD and controls at 500, 1,000, 4,000, 6,000, and 8,000 Hz. Bars and diamonds indicate 95% CIs.

Notes: The weights of each study in the meta-analysis are indicated. Analysis model, random effect; effect measure is mean difference.

Abbreviations: *df*, degrees of freedom; IV, inverse variance; PTA, pure tone audiometry; SMD, standardized mean difference.

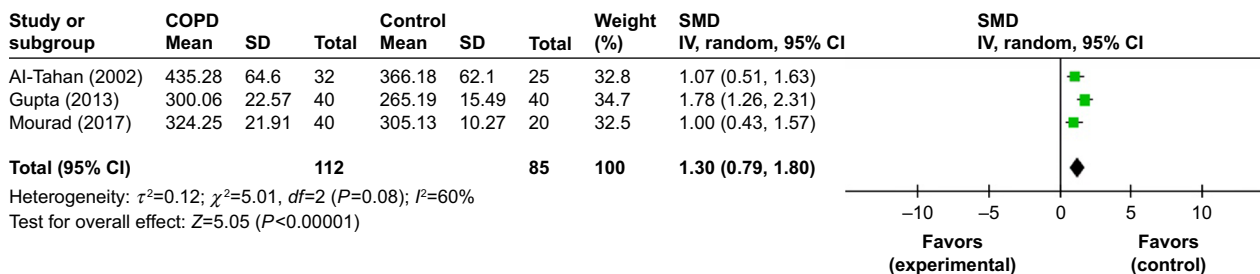


Figure 10 Comparison of P300 latency between COPD and control groups. **Abbreviation:** *df*, degrees of freedom.

sample sizes, dissimilarities in population, difference in the proportions of COPD to control contributors, and variations in HL incidence.

Limitations

There are a few limitations that could be potential sources of bias in this meta-analysis (Supplementary material). First, our analysis is based on the findings of observational studies; therefore, it is impossible to control residual confounders linking COPDs and hearing impairment. Second, it seems that the duration and severity of COPD can influence the strength of the association between disease and HL and produce between-study heterogeneity in the association, but there is not enough information regarding duration and severity of COPD in the included studies. Third, publication bias is inevitable because researchers are not as likely to report negative results. Its possibility could not be ruled out even if it were not statistically derived.

Conclusion

COPD patients had considerably greater incidence of HL when compared with controls. Interestingly, although the mean PTA thresholds at every frequency for COPD patients were higher than those for controls, these values were still in the slight to mild HL ranges. Prolonged ABR wave latencies in the COPD patients suggest retro-cochlear involvement. Thus, COPD most frequently clusters with HL, but it is worth noting that alteration in hearing is not always recognized by medical experts as a frequent comorbidity associated with COPD.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

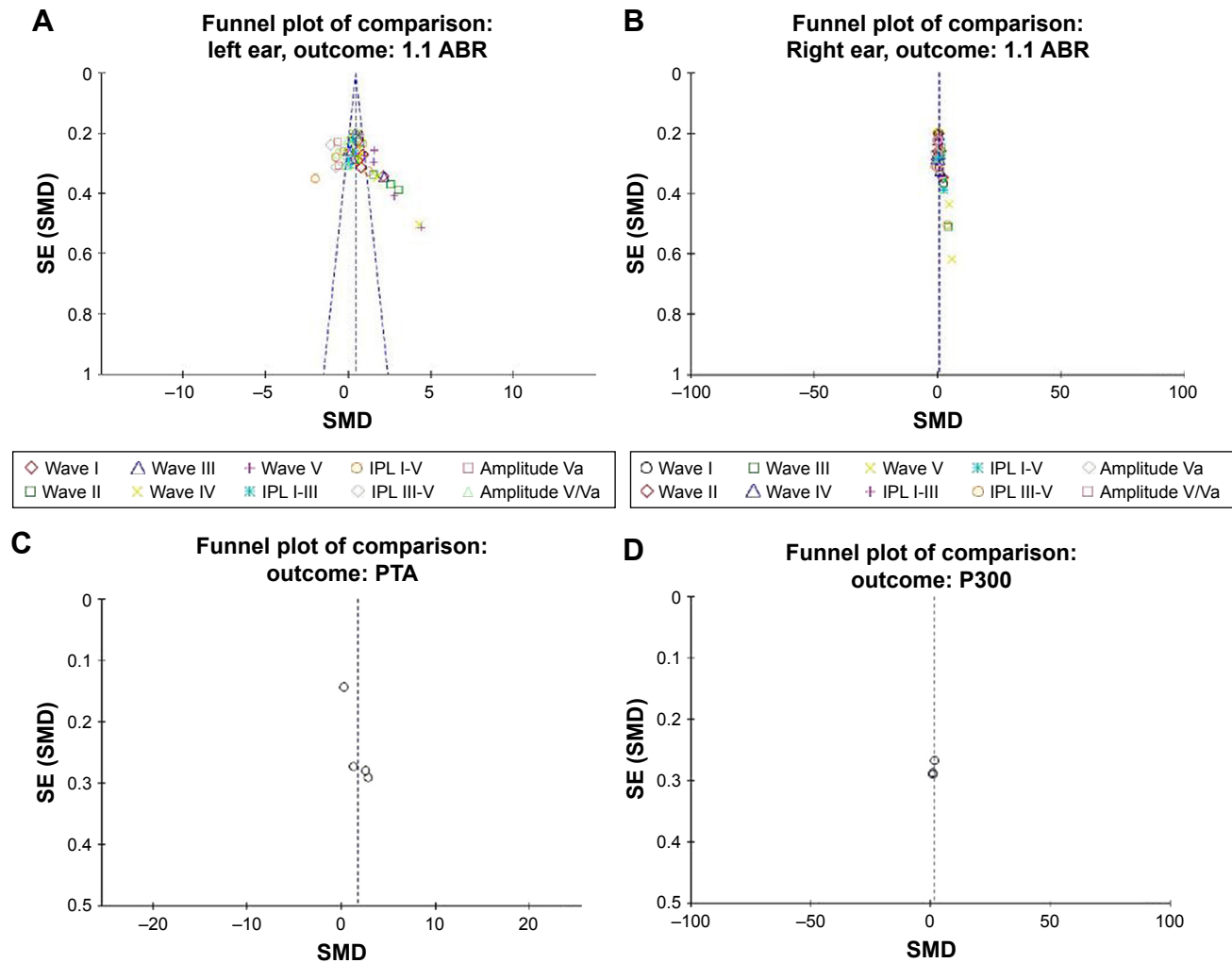


Figure S1 Potential sources of bias in this meta-analysis, funnel plots of comparison in both group and sub-group analysis (A–D).
Abbreviations: ABR, auditory brainstem response; PTA, pure tone audiometry; SE, standard error; SMD, standardized mean difference.

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