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Postmenopausal hormone therapy and Alzheimer's disease, dementia, and Parkinson's disease: a systematic review and time-response meta-analysis

Minghua Wu [a,b*], Min Li [a,b], Jun Yuan [a,b], Sen Liang [a,b], Zhaoyao Chen [a,b], Min Ye[c*], Paul M Ryan[d], Cain Clark[e], Shing Cheng Tan[f], Jamal Rahmani[g], Hamed kord Varkaneh[g], Akshaya Srikanth Bhagavathula[h]

[a] Department of neurology, Jiangsu Province Hospital of Chinese Medicine, 55 Hanzhong, Nanjing, Jiangsu Province, 210029, China

[b] The Affiliated Hospital of Nanjing University of Chinese Medicine, 55 Hanzh ng, Nanjing, Jiangsu Province, 210029, China

[c] Department of Neurology, Affifiliated BenQ Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, 210019, China

[d] School of Medicine, University College Cork, Cork, Ir land

[e] School of Life Sciences, Coventry University, Covent y, CV1 5FB, United Kingdom

[f] UKM Medical Molecular Biology Institute, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

[g] Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, National Nutrition and Food Technology Rese rch Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[h]Department of internal medici e, College of Medicine and Health Sciences, UAE University, Al Ain, UAE

*Address c rresp ndence to: First Corresponding author, Minghua Wu (sebastian80.n.ut@gmail.com), The Affiliated Hospital of Nanjing University of Chinese Medicine, 55 Hanzhong, Nanjing, Jiangsu Province, 210029, China. Second Corresponding author, Min Ye (yemin197001@sina.com), Department of Neurology, Affifiliated BenQ Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, 210019, China

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Abstract

Hormone therapy continues to be a favourable option in the management of menopausal symptomatology, but the associated risk-benefit ratios with respect to neurodegenerative diseases remain controversial. The study aim was to determine the relation between menopausal hormone

therapy and Alzheimer's disease, dementia, and Parkinson's disease in human subjects. A literature search was performed in PubMed/Medline, Cochrane collaboration, and Scopus databases from onset of the database to September 2019. Random-effects model was used to estimate pooled odd ratio (OR) and 95% confidence intervals (CI). Subgroup analysis was performed based on the type and formulation of hormone. In addition, the time-response effect of this relationship was also assessed based on duration of hormone therapy. Associations between hormone therapy and Alzheimer's disease, dementia, and Parkinson's disease in menopausal women were reported in 28 studies. Pooled results with random effect model showed a significant association between hormone therapy and Alzheimer's disease (OR 1.08, 95% CI 1.03 -1.14, I_2: 69%). This relationship was more pronounced in patients receiving the combined estrogen-progestogen formulation. Moreover, a significant non-linear time-response association between hormone therapy and Alzheimer's disease was also identified ($Coef_1$ = 0.0477, p_1<0.001; $Coef_2$ = -0.0932, p_2<0.001). Similarly, pooled analysis revealed a significant association between hormone therapy and all-cause dementia (OR 1.16, 95% CI 1.02 -1.31, I_2: 19%). Interestingly, no comparable relationship was uncovered between hormone therapy as a whole and Parkinson's disease (OR 1.14, 95% CI 0.95-1.38, I2: 65%); however, sub-group analysis revealed a significant relationship between the disease and progestog n (OR 3.41, 95% CI 1.23 - 9.46) or combined estrogen-progestogen formulation use (OR 1.49, 95% CI 1.34 - 1.65). Indeed, this association was also found to be driven by duration of exposure ($Coef_1$ =0.0626, p_1=0.04). This study reveals a significant direct relationship between the use of certain hormonal therapies and Alzheimer's disease, all-cause dementia, and Parkinson's disease in menopausal women. However, the association appears to shift in direct after five years in the context of A zheimer’s disease, adding further weight to the critical window or timing hypothesis of neurodegeneration and neuroprotection.

Keyword: Hormone the apy; Me opause; Alzheimer's disease; Parkinson's disease.

1. Introducti n

Alzheimer’s disease and Parkinson’s disease remain the most prevalent neurodegenerative disorders worldwide (1). While the two diseases are entirely distinct in their pathogenesis, they occasionally converge upon the coexistence of dementia. Dementia is a clinical syndrome of major cognitive impairment with a variety of underlying etiologies, the most common being Alzheimer’s disease, with several other vascular causes following in prevalence and Parkinsonian-related dementia representing a relatively uncommon but further debilitating presentation of the syndrome. While

there exist several competing or complementary hypotheses on the development of Alzheimer's and Parkinson's disease, the exact underlying etiologies remain uncertain and no single lifestyle or genetic factor can be implicated at present. Interestingly, however, Alzheimer's and dementia are notably imbalanced between sexes, with significantly higher prevalence and indeed incidence rates in females (2). Although female longevity goes some of the way in explaining this prevalence disparity, researchers have now begun to query the involvement of sex-dependent hormones in the pathogenesis of these diseases.

The vasomotor symptomatology which so often accompanies the menopause can be debilitating and life-limiting for certain women. In line with this, the use of hormone therapy (HT) to negate such symptoms has become commonplace due to the ease of administration and efficacy f such treatments (3, 4). These therapies involve the application of estrogen, or its bioequivalent f rm, either alone or in combination with progesterone or its synthetic forms (3, 4). The esults f the Women's Health Initiative indicate that while HT is an effective treatment for meno ausal symptom reduction, there are various risks associated with their use which are not entirely negligible (5). For example, while it was suggested that HT may decrease risk of hip fracture and colorectal cancer, there also appears to be an increased risk of breast cancer and stroke (5). How v r, the impact of hormone replacement therapy on risk of cognitive impairment and neurodegene ative disorders remains highly contentious (6).

Although a number of studies have been conducted to examine the relationship between HT and the aforementioned neurodegener tive disorders, the results remain inconsistent and fail to bring consensus to the field. In order to ddress these inconsistencies in the literature and to further explore factors which potentially may drive these discrepancies, we performed a time-response meta-analysis evaluating the influence of me opausal HT on Alzheimer's disease, Parkinson's disease and all-cause dementia development.

2. Materials and methods

2.1. Search Strategy

The MOOSE were followed to conduct this meta-analysis (7). A comprehensive systematic literature searches of related studies was conducted in PubMed/MEDLINE, Scopus, and Cochrane databases from inception to September 2019. Supplementary Table 1 outlines the specific search strategies applied for each database. The references from relevant papers were examined to identify any

additional studies and an email alert service was activated in order to avoid missing any new articles published after the completion of our systematic search.

2.2. Inclusion criteria

Studies which met the following inclusion criteria were considered for this review: 1) authors investigated the association between menopausal HT and Alzheimer's disease, dementia, or Parkinson's disease; 2) used a case-control, controlled trial, or cohort design; 3) reported appropriate estimates for outcomes or provided the data required for derivation of these estimates. All review papers, editorials, letter to editor, non-human studies, *in vitro* research, case reports, ecological studies, or letters without sufficient data were excluded from this study.

2.3. Data extraction and quality assessment

Screening of studies was conducted using a predesigned screening form and two independent authors screened studies according to the inclusion criteria in a two step rocess: title and/or abstract screening, followed by full text screening. Any discrepancies which arose during screening were resolved by senior author. Subsequently, two authors ind p nd ntly extracted the following relevant data from the included studies: first author, year of publication, study location, type of used hormone, design of study, number of participants, age, identified confounding factors, and summary estimates with 95% CIs of Alzheimer's disease, dementia, and arkinson's disease. The fully adjusted models were used for all analysis in this study. The Newcastle-Ottawa Quality Assessment Scale (NOS) used to quality assessment of the included studies (8) .

2.4. Statistical analysis

All statistical analyses in this meta-analysis were performed using STATA 14.0 statistical software (Stata Corporation, College Station, Texas, USA). The random-effects model (DerSimonian and Laird) was applied in rder to combine outcomes results (9). The mean (or median) in each category of HT was considered as the reference category, when authors did not provide this data. Heterogeneity among results of included studies was estimated with Cochran's Q test and I_2 statistic. Meta-regressions based on baseline age of participants and subgroup analysis of HT based on design of primary study, as well as the type of hormone used, were conducted to identify potential sources of heterogeneity. In addition, sensitivity analysis was run to examin the effect of each study on the pooled result. The trim and fill approach was used to adjust for publication bias among included

studies. Potential curvilinear associations between duration of HT and incidence of Alzheimer's disease, dementia, and Parkinson's disease were evaluated with three knots in 10%, 50%, and 90% of the distribution by restricted cubic splines method(10). Finally, publication bias was evaluated using the funnel plot, Begg's and Egger's test.

3. Results

3.1. Literature search

Figure 1 presents a flow chat of the systematic search and inclusion of studies in this meta-analysis. through this comprehensive systematic search of PubMed/Medline, Sc pus, and Cochrane collaboration databases, 731 papers were initially identified, of which 216 were f und to be duplicates. From remaining studies, 480 papers failed to meet the inclusion crite ia and were excluded during title and/or abstracts screening, while an additional seven records we e excluded following full text evaluation. Ultimately, 28 papers were included in this meta-analysis (11-38).

3.2. Study characteristics and quality assessment

Tables 1 displays the relevant information of all includ d studi s. The studies, which were published between 1994-2019, included 14 case-control studies (11, 13, 15, 22, 26-28, 30-34, 37, 38), two RCTs (14, 19), and 12 cohort studies (12, 16-18, 20, 21, 23- 25, 29, 35, 36). The primary locations included USA, UK, Finland, Denmark, French, Ita y, and Canada. No participants with a prior diagnosis of Alzheimer's disease, dementia, or P rkinson's disease at baseline were included in the cohort studies or RCTs included. The studies ex mined applied hormone therapies which were composed of estrogen, progesterone (or its derivatives), or a combined formulation of the two hormones. The majority of included studies we e found to be of high quality according to Supplemental Table 2, with 11 returning a score of nine (12, 16, 17, 20-22, 24, 27, 33, 35, 38).

3.3. Associati n f HT use with neurodegenerative disease

Fourteen studies containing 19 arms reported on the relationship between HT and Alzheimer's disease as outcome measure (11, 12, 20, 24, 26, 29-32, 34-38). The pooled OR (95% CI) in the hormone-treated versus hormone-naïve was OR 1.08 for Alzheimer's disease (95% CI 1.03 -1.14, I^2: 69%) (Fig. 2). Furthermore, five studies with nine arms reported dementia OR as their outcome measure (14, 19, 21, 24, 25) and the combined analysis identified a significant direct relationship between HT use and

dementia (OR 1.16, 95% CI 1.02 -1.31, I_2: 19%). Finally, in ten studies with 22 arms (15-19, 22, 23, 27, 28, 33) the association between Parkinson's disease in HT was not found to be significant (OR 1.14, 95% CI 0.95-1.38, I_2: 65%).

3.4. Association of HT formulation with neurodegenerative disease

We subsequently stratified studies for Alzheimer's disease and Parkinson's disease based on the formulation of used hormone (Figure 3) and the design of the primary studies (Supplementary Fig. 1). These analyses showed that different hormone have varying effects on disease occurrence (heterogeneity between group was p=0.005 for Alzheimer's disease results and p=0.002 for Parkinson's disease). Indeed, the relationship between HT and Alzheimer's disease was f und to be stronger in patients using the combined estrogen-progestogen formulati n (OR 1.16, 95% CI 1.12 - 1.21), while progestogen only (OR 1.13, 95% CI 1.10 - 1.17) and est ogen nly therapies remained associated with the disease, but displayed a slighty less concerning effect level (OR 1.09, 95% CI 1.06 - 1.11). The relationship between HT and Parkinson's disease was found to be strongest in patients using the progestogen only therapy (OR 3.41, 95% CI 1.23 9.46), while the combined estrogen-progestogen formulation also displayed disease association, but again with a more modest effect size (OR 1.49, 95% CI 1.34 -1.65). Interestingly, our meta-analysis sugg sts that estrogen-only formulations have no significant associations with Parkinson's disease development (OR 1.08, 95% CI 0.90 - 1.22).

3.5. Effect of study design on HT-neurodegenerative disease interaction

Interestingly, while a significant rel tionship was identified between HT and Alzheimer's disease in the included case-control studies (OR 1.12, 95% CI 1.10 - 1.13), no such effect was detected in the included cohort studies (OR 0.89, 95% CI 0.76 - 1.04). Conversely, the relationship between HT and Parkinson's disease was significant in cohort studies (OR 1.39, 95% CI 1.28 - 1.52) and not the included case-control st dies (OR 0.96, 95% CI 0.74 - 1.26). Moreover, the relationship between HT and dementia was significant in the included RCTs (OR 1.16, 95% CI 1.02 - 1.32), but the same effect was not achieved in the included cohort studies (OR 1.13, 95% CI 0.97 - 1.33). Finally, meta-regression based on baseline age of participants did not reveal this variable as a source of heterogeneity for Alzheimer’s disease, Parkinson's disease, or dementia diagnosis (Supplemental Fig 2).

3.6. Time-response analysis

A significant association between duration of HT and Alzheimer's disease, which is direct in initial five years and inverse in subsequent years ($Coef_1$ =0.0477, p_1<0.001; $Coef_2$ = -0.0932, p_2<0.001), was noted in the present meta-analysis (Fig 4). The combined OR was significant and direct between duration of HT and Parkinson's disease in first 5 years of HT ($Coef_1$ =0.0626, p_1=0.04), but non-significant in years afterwards ($Coef_2$ = -0.0427, p_2=0.21).

3.7. Publication bias

Supplementary Figure 3 includes funnel plots which indicate that there was publication bias among the studies reporting on Alzheimer's disease (Begg's p=0.17 and Egger regression test p=0.02), but not for dementia (Begg's p=0.67 and Egger regression test p=0.77) or Parkinson's disease (Begg's p=0.59 and Egger regression test p=0.05). The 'trim and fill' method was applied in rder to adjust for publication bias identified in Alzheimer's disease reporting studies (Supplemental Table 3). Finally, the sensitivity analysis does not show significant differences beyond the limits of 95% CI of calculated combined results for each of included studies (Supplemental Fig 4).

4. Discussion

HT represents a stalwart of symptomatic management in menopausal women and while such therapies have demonstrated unparalleled efficacy in this application, their association with neurodegenerative disease remains equivocal. As a result, we sought to determine the relationship between menopausal HT and Alzheimer's disease, all-cause dementia, and Parkinson's disease in human subjects. The present meta- n lysis, which included data from case-control, controlled trial and cohort design studies, fou d th t ny HT-use was significantly associated with development of Alzheimer's disease and deme tia of undefined etiology, whilst no such effect was uncovered for Parkinson's disease. In addition, sub-group analysis revealed that combined estrogen-progestogen formulations prod ced higher odds of Alzheimer's disease when compared to therapies containing progestogen, estr gen or estradiol alone. With respect to Parkinson's disease, progestogen only and combined estr gen-progestogen formulations were significantly associated the disease while other therapies were not. Finally, we reveal a significant direct association between duration of HT with Alzheimer's and Parkinson's disease in the first five years of treatment.

A number of observational investigations have previously reported a significant Alzheimer's disease and dementia risk reduction in those prescribed HT (20, 39-42). However, questions remain around the veracity and generalizability of these findings, as the original studies generally lack sufficient

control and selection bias towards healthy females may have existed in HT groups. Indeed, this suspicion was supported by the results of the placebo-controlled WHIMS trial, in which the authors observed an increased risk of impaired cognition and dementia in women using certain forms of HT (43, 44). However, the design of the WHIMS trial itself has not been free of criticism, since HT was commenced more than a decade on from the typical age of menopausal onset, a practice which is not the standard. In addition, the WHIMS cohort were not differentiated according to etiology of cognitive decline and it is conceivably that each process may respond differently to HT exposure (43, 44). Importantly, a recently updated Cochrane review by Marjoribanks et al. concluded that HT is not suitable for the prevention of dementia or cognitive decline in postmenopausal women (45). This lack of protection is an important message to disseminate considering the results f the present meta-analysis, which indicates that HT may in fact be a contributory factor in the devel pment of such neurodegenerative diseases.

Although a number of histological characteristics have been identified as osthumous hallmarks of the pathology, the precise underlying cause of Alzheimer's disease is not entirely understood (46, 47). As a result, it remains a challenge to pinpoint the mechanisms through which HT may interact with the disease, be it in a beneficial or harmful manner. How v r, it has been reported that the risk of Alzheimer's disease may increase in a graded fashion with each full-term pregnancies, an effect which is postulated to be the result of repeated exposure to estrogen-progesterone surges (48). Conversely, several mechanisms exist through which HT may be considered to protect against the disease, including improvements in cerebral b ood f ow (49, 50), increases in dendritic spine density (51-53), and nerve growth factor inter ctions (54). A narrative which arose from cardiovascular outcome observations around HT suggest th t there may be an important temporal nature to the interaction. Specifically, it is suggested that estrogen may only be neuroprotective if initiated soon after menopausal onset, a theo y which largely arose following the WHIMS trials revelations. This speculative hypothesis, otherwise termed the 'critical window' theory, has support in animal-based models (55). The evidence from animal models suggests that HT during the 'critical window' is linked to neuropr tecti n through reduced deposition of β-amyloid, synaptic formation improvements, increased choline acetyltransferase activity, and improvements in cerebral perfusion (56-58). This 'critical window' hypothesis may explain why HT beyond the initial five years was inversely associated with incidence in the context of Alzheimer's disease.

Investigations into the use of HT and risk for Parkinson's disease have yielded inconsistent findings, which suggests that the interaction between HT and Parkinson's disease is complex and multi-faceted

(27, 59-63). Indeed, in the present study, we found no significant association between HT and Parkinson's disease. Despite this, sub-group analysis of specific HT types revealed a significantly higher risk of Parkinson's disease development in those treated with progestogen and combined estrogen-progestogen formulations. Although this putative relationship indeed warrants further elucidation, it is important to note that just a single study examined the effect of progesterone-only HT on Parkinson's disease. Therefore, this result should be replicated, preferably in an RCT setting, before this phenomenon is to be treated as reliable.

In the present mixed-source meta-analysis, we further examined the effect of data origin on the association of HT with neurodegenerative disease through stratification by study design. According to the hierarchy of evidence, RCT-derived data represents the most reliable form f inf rmati n, while case-control and cohort design studies are inferior but relatively equal in their veracity. In the context of Alzheimer's disease, we found that the association with HT was maintained f llowing meta-analysis of case control studies in isolation; however, no such effect was obse ved when cohort studies were examined independently. Contrastingly, when Parkinson's studies were stratified, we found that cohort-derived data showed a significant effect, while case control studies did not. Finally, in the case of dementia, meta-analysis of RCT data maintain d the same effect size and direction, while cohort study-specific meta-analysis revealed no significant association. These results indicate that, while there was a degree of discord amongst study designs, there was no consistent and substantial impact of design on the overall study outcome. In addition, we can be reassured by the fact that no sub-group meta-analysis revealed a significant opposing effect and the RCT-specific meta-analysis of all-cause dementia is in keeping with the overall result.

Strengths and limitations

There are a number of significant strengths of the present work which are important to note. Firstly, the present study has provided better clarity into the effect of HT on Alzheimer's disease, all-cause dementia and Parkinson's disease, by integrating results from 14 case-control (11, 13, 15, 22, 26-28, 30-34, 37, 38), two were RCTs (14, 19), and 12 cohort studies (12, 16-18, 20, 21, 23-25, 29, 35, 36). Furthermore, the sensitivity analysis showed no significant differences beyond the limits of 95% CI of calculated combined results for each of included studies, suggesting that their inclusion was justified and the findings are reliable. Despite the aforementioned strengths, this meta-analysis also possesses several limitations. Although the total included population of pooled participants in the present meta-analysis is considerable, the sample size of several individual studies was relatively small. It is

conceivable that a small sample size may influence the detection of rare outcomes, particularly in relation to less common neurodegenerative diseases (64). Furthermore, the dose and timing may represent impactful factors in determining the neuroprotective or neurodegenerative effects of such treatments and, although we explored the temporal effects, we have not explored any potential dose-response associations. We must also recognise the substantial weight which was attributed to a small number of studies in the Alzheimer's disease meta-analysis. Although weight to each study was related to sample size and precision of that study, as is the gold standard practice of meta-analysis, this has resulted in a disproportionate representation of a select number of studies. Furthermore, we did not have any RCT-derived data to draw from for the Alzheimer's disease and Parkinson's disease meta-analysis. It is recommended that double-blind RCTs be conducted in rder to c nfirm the veracity of our findings, although ethical concerns must be carefully managed in this instance.

5. Conclusion

This study revealed a significant and direct relationship between HT and Alzheimer's disease or all-cause dementia in postmenopausal women. However, this effect is limited to the first five years of therapy in Alzheimer's disease and in fact the direction of association appears to reverse in the years to follow. In addition, certain formulations of HT we e found to be associated with an elevated risk of Parkinson's disease. Although this study integrated data from both observational and controlled trial study designs, the results remain consistent and indicate that large-scale RCT investigations into the long-term safety of different HTs in the context of neurodegenerative disease and cognitive demise are urgently required.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Fig 1**.** Flow chart of included studies.

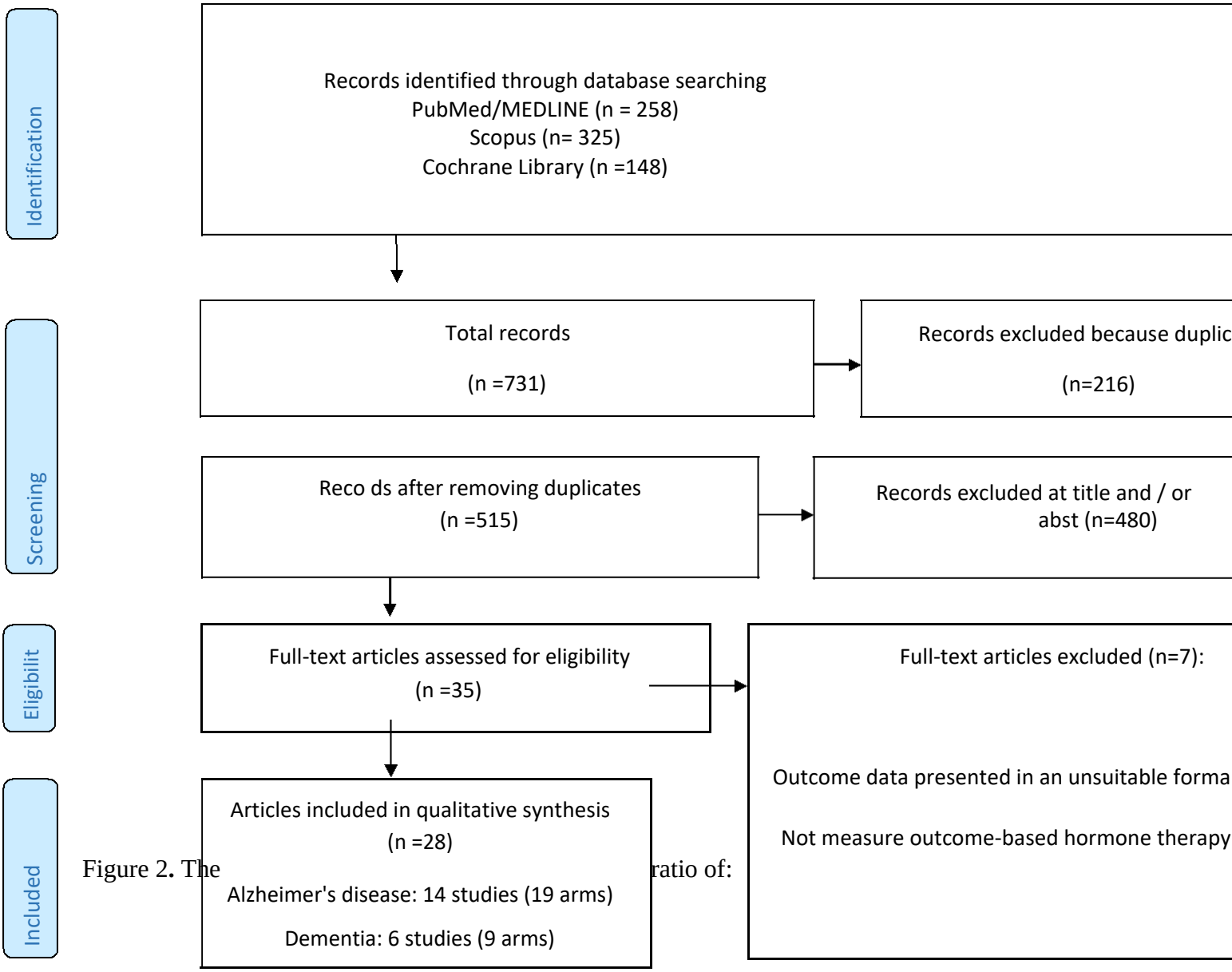
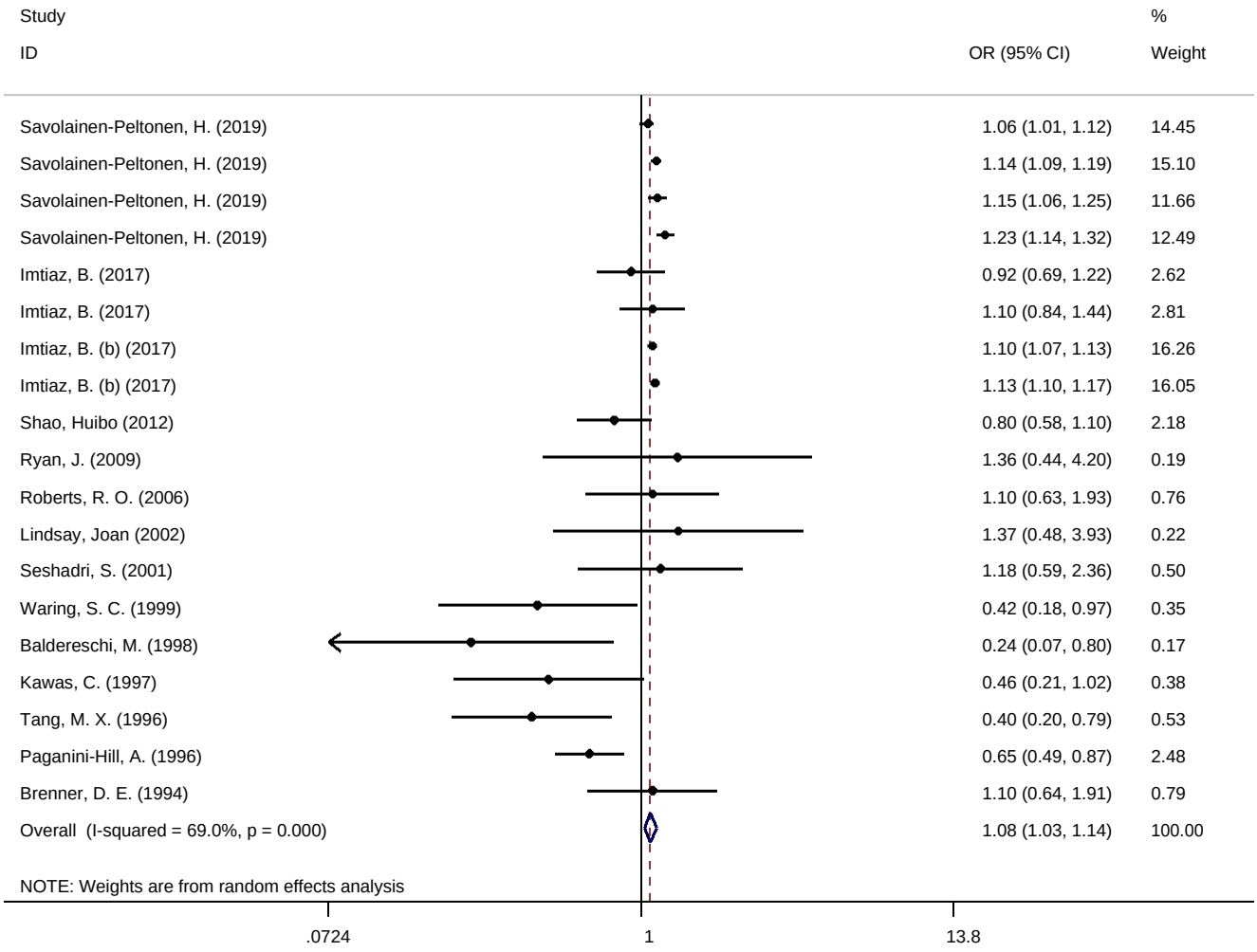
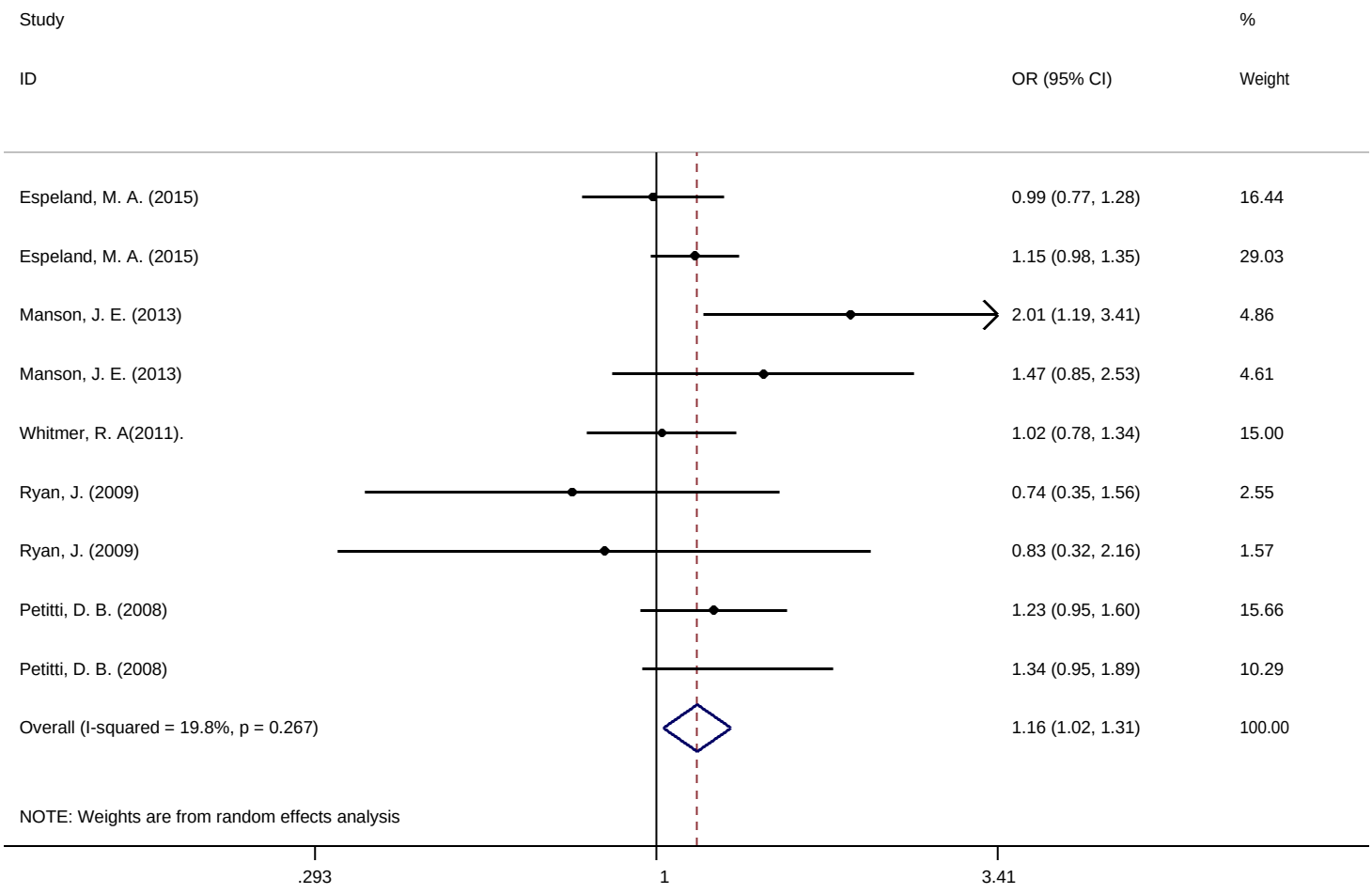


Figure 2**.** The ratio of:

a) Alzheimer's disease



b) Dementia



c) Parkinson's disease

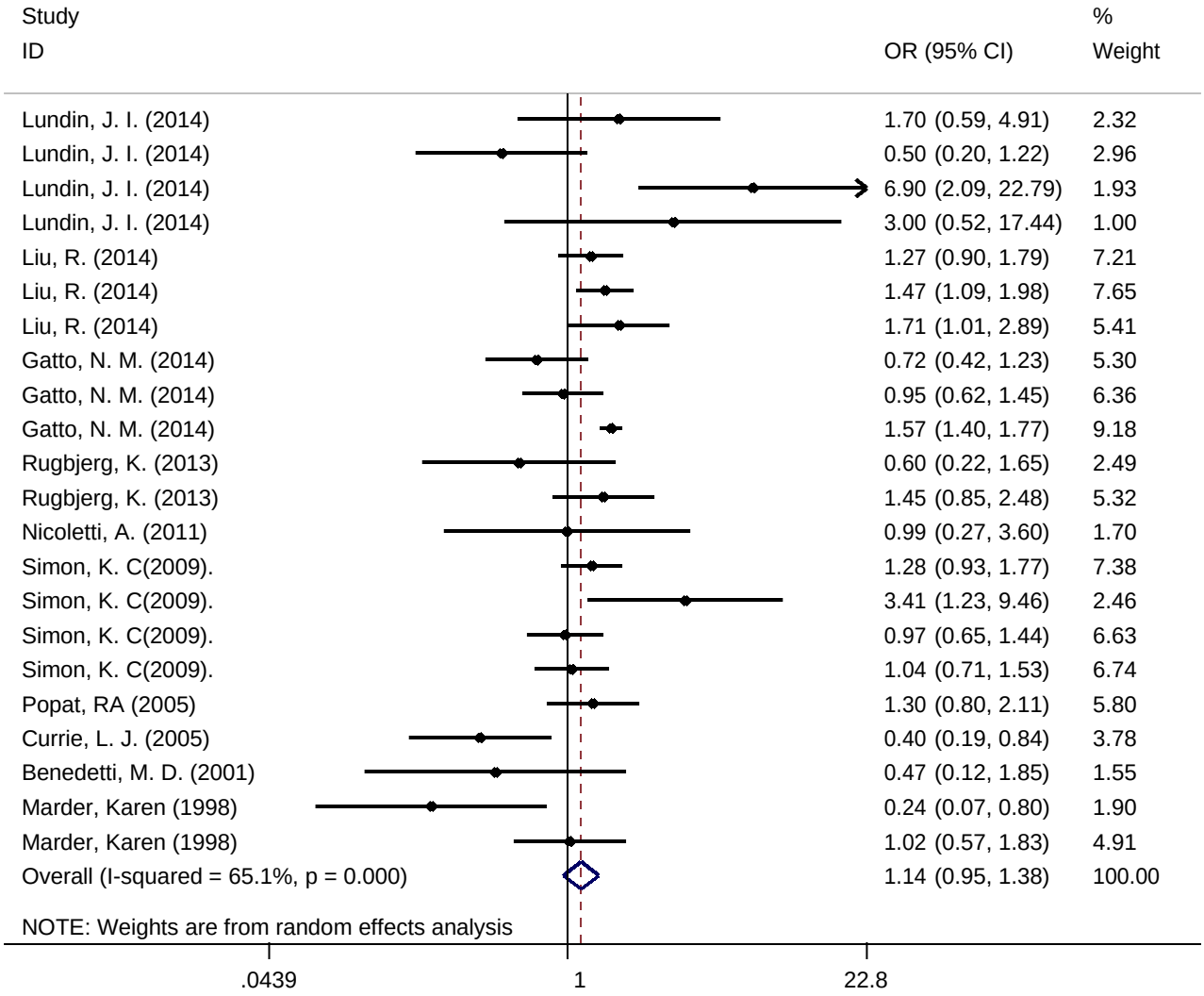
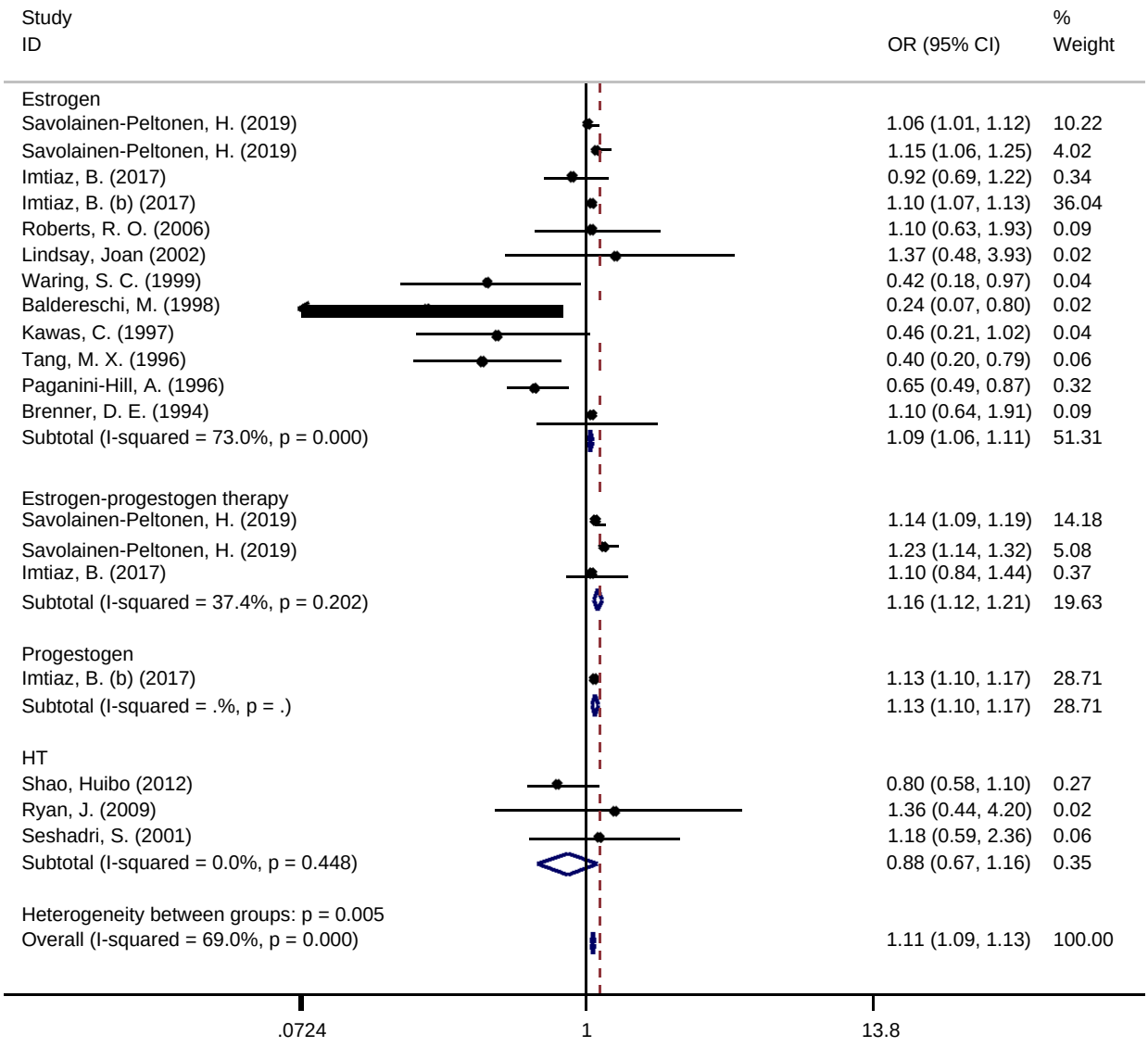


Figure 3**.** The forest plot of s bgro p analysis of Hormone therapy based on type of used hormone and odd ratio of:

a) Alzheimer's disease


Study
ID
OR (95% CI)
%
Weight
Estrogen
Savolainen-Peltonen, H. (2019) 1.06 (1.01, 1.12) 10.22
Savolainen-Peltonen, H. (2019) 1.15 (1.06, 1.25) 4.02
Imtiaz, B. (2017) 0.92 (0.69, 1.22) 0.34
Imtiaz, B. (b) (2017) 1.10 (1.07, 1.13) 36.04
Roberts, R. O. (2006) 1.10 (0.63, 1.93) 0.09
Lindsay, Joan (2002) 1.37 (0.48, 3.93) 0.02
Waring, S. C. (1999) 0.42 (0.18, 0.97) 0.04
Baldereschi, M. (1998) 0.24 (0.07, 0.80) 0.02
Kawas, C. (1997) 0.46 (0.21, 1.02) 0.04
Tang, M. X. (1996) 0.40 (0.20, 0.79) 0.06
Paganini-Hill, A. (1996) 0.65 (0.49, 0.87) 0.32
Brenner, D. E. (1994) 1.10 (0.64, 1.91) 0.09
Subtotal (I-squared = 73.0%, p = 0.000) 1.09 (1.06, 1.11) 51.31
Estrogen-progestogen therapy
Savolainen-Peltonen, H. (2019) 1.14 (1.09, 1.19) 14.18
Savolainen-Peltonen, H. (2019) 1.23 (1.14, 1.32) 5.08
Imtiaz, B. (2017) 1.10 (0.84, 1.44) 0.37
Subtotal (I-squared = 37.4%, p = 0.202) 1.16 (1.12, 1.21) 19.63
Progestogen
Imtiaz, B. (b) (2017) 1.13 (1.10, 1.17) 28.71
Subtotal (I-squared = .%, p = .) 1.13 (1.10, 1.17) 28.71
HT
Shao, Huibo (2012) 0.80 (0.58, 1.10) 0.27
Ryan, J. (2009) 1.36 (0.44, 4.20) 0.02
Seshadri, S. (2001) 1.18 (0.59, 2.36) 0.06
Subtotal (I-squared = 0.0%, p = 0.448) 0.88 (0.67, 1.16) 0.35
Heterogeneity between groups: p = 0.005
Overall (I-squared = 69.0%, p = 0.000) 1.11 (1.09, 1.13) 100.00
.0724
1
13.8

b) Parkinson's disease

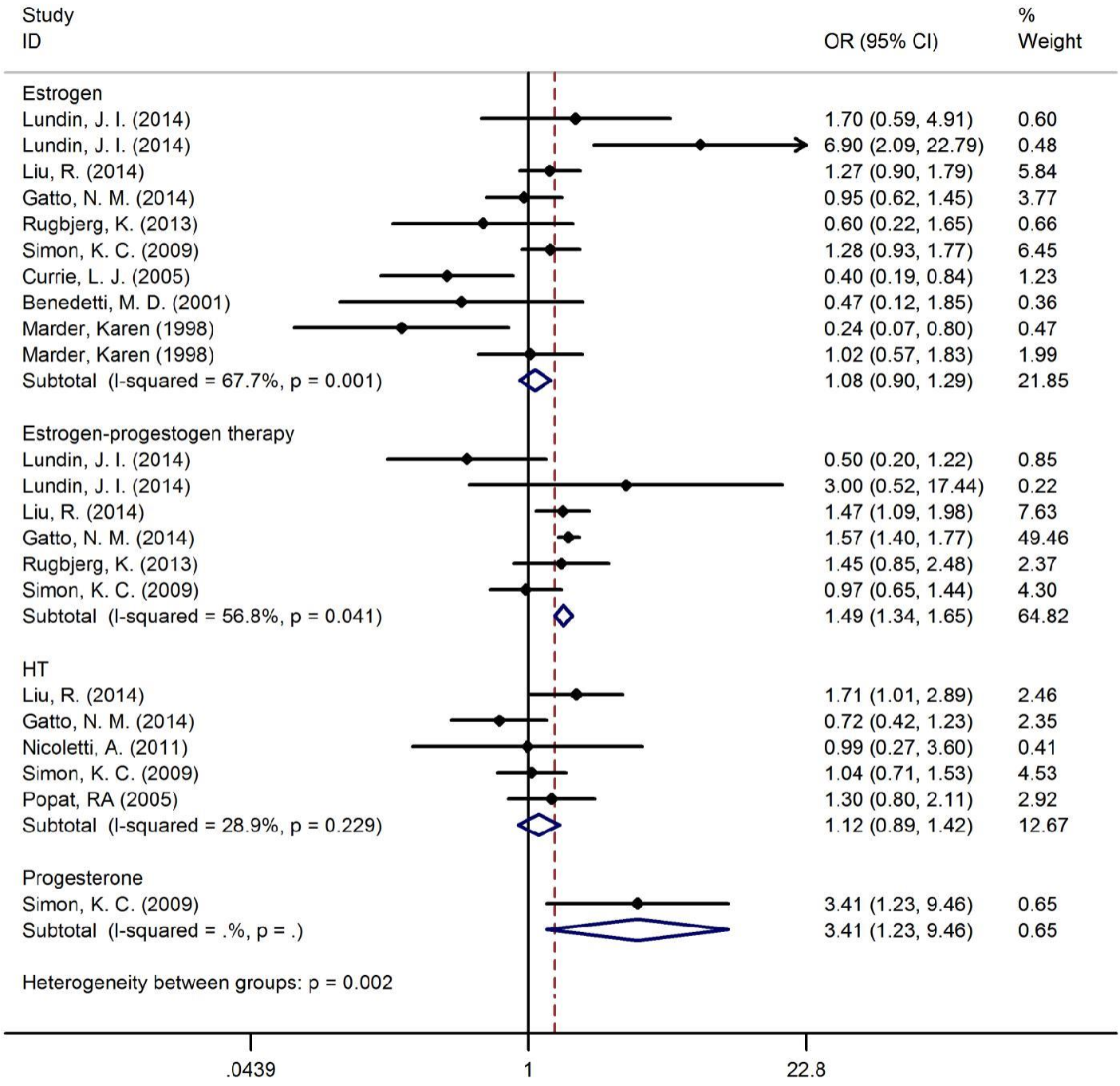
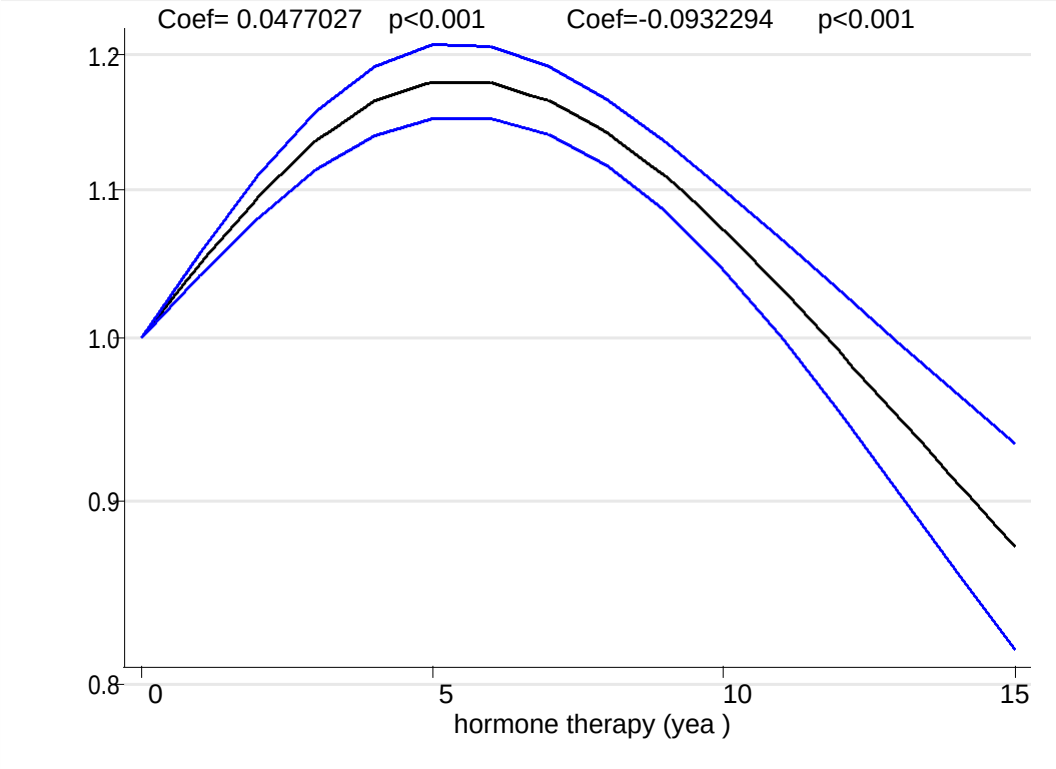


Figure 4**.** The Duration-response analysis of hormone therapy and odd ratio of:

a) Alzheimer's disease



b) Parkinson's disease

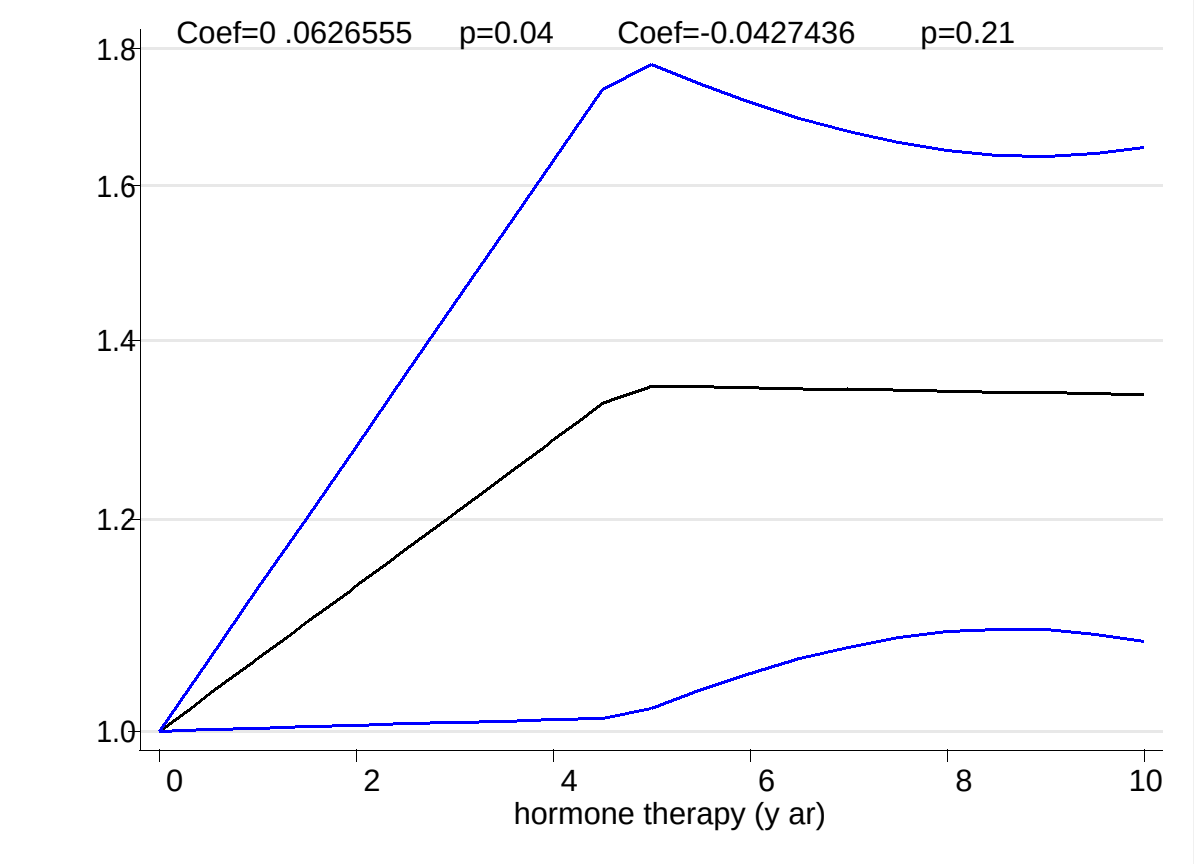


Table 1. Characteristics of included studies

Author	Year	Location	Type of used hormone	Design of study	Age	Participants (n)	Outcome
Savolainen-Peltonen, H.	2019	Fi land	Estradiol and Combination	case-control	-	169478	Alzheimer's disease
Imtiaz, B.	2017	Finland	Estrogen and Combination	cohort	72.3	8195	Alzheimer's disease
Imtiaz, B. (b)	2017	Finland	Estrogen and Progestogen	case-control	81	230580	Alzheimer's disease
Espeland, M. A.	2015	USA	Estrogen and Progestogen	RCT	71	7233	Dementia

Lundin, J. I.	2014	USA	Estrogen and Combination	case-control	68	305	Parkinson's disease
Lindsay, Joan	2002	Canada	Estrogen	Cohort	65<	2208	Alzheimer's disease
Liu, R.	2014	USA	Estrogen and Combination	Cohort	61	119166	Parkinson's disease
Gatto, N. M.	2017	USA	Estrogen and Combination	Cohort	61	2772	Parkinson's disease
Rugbjerg, K.	2013	Denmark	Estrogen and Combination	Cohort	66.6	27466	Parkinson's disease
Manson, J. E.	2013	USA	Estrogen and Combination	RCT	65<		Dementia
Shao, Huibo	2012	USA	Hormone therapy	cohort	74	1768	Alzheimer's disease
Whitmer, R.	2011	USA	Hormone therapy	cohort	48	5504	Dementia
Nicoletti, A.	2011	It ly	Hormone therapy	case-control	64	499	Parkinson's disease
Simon, K.	2009	USA	Estrogen, Progesterone and Combination	Cohort	65.7	121701	Parkinson's disease
Ryan, J.	2009	French	Hormone therapy	cohort	65<	3130	Alzheimer's disease, Dementia
Petitti, D. B.	2008	USA	Estrogen and Combination	cohort	78.7	2906	Dementia
Roberts, R. O.	2006	USA	Estrogen	case-control	-	528	Alzheimer's disease

Popat, RA	2005	USA	Hormone therapy	case-control	-	367	Parkinson's disease
Currie, L. J.	2005	USA	Estrogen	case-control	50	140	Parkinson's disease
Seshadri, S.	2001	UK	Hormone therapy	case-control	65	280	Alzheimer's disease
Benedetti, M. D.	2001	USA	Estrogen	case-control	-	144	Alzheimer's disease
Waring, S. C.	1999	USA	Estrogen	case-control	50	222	Alzheimer's disease
Marder, Karen	1998	USA	Estrogen	case-control	-	1156	Parkinson's disease
Kawas, C.	1997	USA	Estrogen	cohort		472	Alzheimer's disease
Baldereschi, M.	1998	Italy	Estrogen	case control	-	1568	Alzheimer's disease
Tang, M. X.	1996	USA	Estrogen	cohort	74.2	1282	Alzheimer's disease
Paganini-Hill, A.	1996	USA	Estrogen	case-control	87	1439	Alzheimer's disease
Brenner, D. E.	1994	USA	Estrogen	case-control	77	227	Alzheimer's disease