Anticholinergic Burden and Dementia: Associations, Mechanisms, and the Over-the-Counter Exposure Nobody Counts

An evidence synthesis · Holistic Quality LLC

Author: Levi Robey · Holistic Quality LLC · **Contact:** levi@holisticquality.io

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> **How this was produced.** We searched PubMed for primary longitudinal cohort and case-control studies reporting an adjusted effect estimate (hazard ratio, odds ratio, rate ratio) for anticholinergic drug exposure against an outcome of incident dementia, incident Alzheimer's disease, or longitudinal cognitive decline. A broad query ("anticholinergic burden AND dementia AND cohort/risk") returned 231 records; these were screened alongside targeted searches for named cohorts and national databases and for the first-generation-antihistamine class specifically. Reviews, meta-analyses, scale-validation papers, acute-delirium studies, cross-sectional-only designs, and studies of anticholinergics used to *treat* dementia were excluded. Twenty-two primary studies met inclusion. Every effect size quoted below was extracted from, and independently re-verified against, the source abstract on PubMed; every study is linked by DOI. Where studies disagree, we say so. This mirrors the methodology-transparency commitments made across the Holistic Quality regulator surface (see the Regulator's Bill of Rights): cite everything, say where the evidence is contested, and make the method legible.

Abstract

Medications with anticholinergic (antimuscarinic) activity are among the most widely used drugs in older adults, and a large body of observational research links cumulative exposure to them with an increased risk of dementia. This synthesis assembles 22 primary longitudinal cohort and case-control studies published between 2006 and 2026 — spanning national health databases in the UK, USA, Korea, Taiwan, Canada, France, the Netherlands, and China,

and totalling several million participants — together with the meta-analyses and mechanistic literature that surround them.

The association is real, directionally consistent, and dose-responsive. In the largest and best-designed studies it survives long exposure-lag windows intended to rule out reverse causation, with adjusted hazard/odds ratios for the highest-exposure groups clustering around 1.1 to 1.5. It is coherent with a well-established mechanism: the cholinergic hypothesis of Alzheimer's disease.

Three honest limits constrain what this means. First, no randomized trial has ever tested a dementia endpoint; all of the dementia-specific evidence is observational, and confounding by indication — the fact that the conditions these drugs treat (depression, insomnia, incontinence, parkinsonism) are themselves linked to dementia — is a live and only partly resolvable alternative explanation. Second, the signal is not uniform across drug classes: it concentrates in anticholinergic antidepressants, bladder antimuscarinics, antiparkinson, and antipsychotic drugs, whereas the two best class-resolved studies do **not** find the first-generation antihistamine class independently significant. Third, this synthesis therefore cannot and does not claim that any single drug "causes" dementia.

Diphenhydramine — the prototypical first-generation antihistamine, and the most common strong anticholinergic available over the counter as a sleep aid and allergy remedy — is used here as the exemplar of an under-counted exposure, not as a drug with its own proven dementia hazard. The public-health point is narrow and defensible: cumulative anticholinergic burden is a plausibly modifiable risk factor, much of it is self-administered and invisible to prescribers, and minimizing unnecessary long-term use is prudent regardless of whether the association is ultimately causal.

1. Background: why anticholinergic drugs and the brain

Acetylcholine is a principal neurotransmitter of learning and memory. The **cholinergic hypothesis of Alzheimer's disease** — the observation that degeneration of cholinergic neurons in the basal forebrain tracks the cognitive decline of Alzheimer's, and the basis on which cholinesterase-inhibitor drugs (donepezil, rivastigmine, galantamine) were developed — makes the cholinergic system a natural place to look for pharmacological harm. Drugs that *block* muscarinic acetylcholine receptors do the pharmacological opposite of the drugs used to treat dementia.

That anticholinergic drugs cause **acute, reversible** cognitive impairment in older adults is not in dispute. Diphenhydramine in particular is a strong central antimuscarinic that readily crosses the blood-brain barrier; at ordinary doses it measurably impairs attention and psychomotor performance, and in overdose it produces a well-characterized anticholinergic delirium reversible with cholinesterase inhibitors (Fratta 2023) [27]. On the strength of this acute toxicity, expert reviews and the Beers Criteria for potentially inappropriate medication in older adults have long recommended that diphenhydramine be avoided in the elderly (Schroeck 2016) [26].

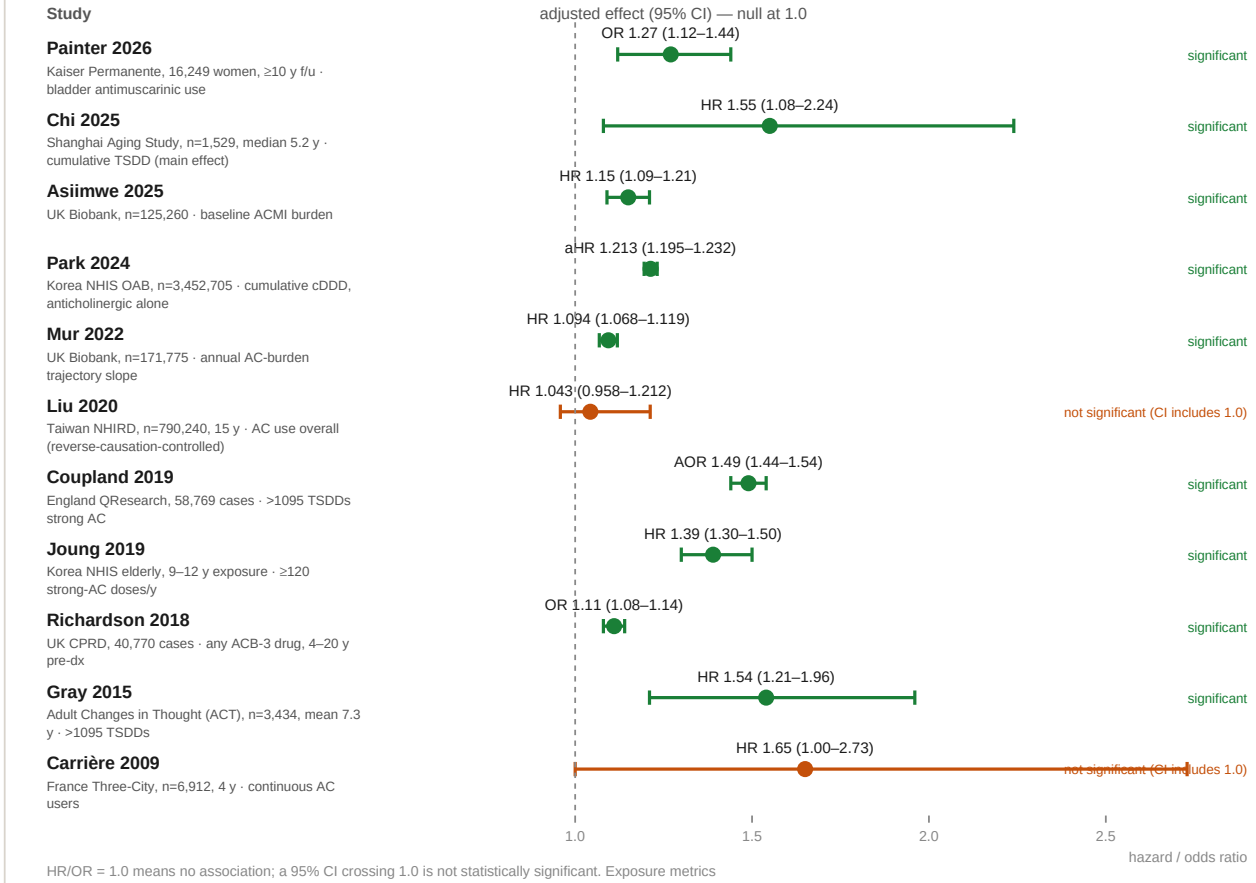
The open scientific question — the subject of this synthesis — is different and harder: does *cumulative, long-term* exposure to anticholinergic drugs raise the risk of **permanent** dementia, over and above the acute effect that resolves on discontinuation?

2. The epidemiology, cohort by cohort

The primary evidence is summarized in Appendix Table 1 and discussed below, grouped by the strength of the design against the central threat of reverse causation (that early, undiagnosed dementia leads to the prescribing, rather than the reverse). The individual adjusted effect estimates across the 22 primary studies were assembled by design tier and direction of finding; no pooled summary estimate is reported, because the effect measures (HR / OR / IRR) and exposure metrics differ across studies and were not meta-analysed — each study's own reported estimate at its highest or stated exposure is used, against a reference of 1.0.

Adjusted effect of cumulative anticholinergic exposure on incident dementia / Alzheimer's disease across primary cohorts

Source: Appendix Table 1; each estimate + 95% CI equals the cited study's reported value (grep-verified vs its archived PubMed snapshot).



HR/OR = 1.0 means no association; a 95% CI crossing 1.0 is not statistically significant. Exposure metrics differ across studies (see Appendix Table 1) — the 1.0 line is the comparable anchor, not the magnitude.

Forest plot of the adjusted effect estimate (HR or OR) with 95% CI at each study's highest or stated exposure contrast, for the primary longitudinal cohort and (nested) case-control studies whose outcome is incident dementia or Alzheimer's disease. Every point estimate and interval equals the value the cited study reports (verified against its PubMed record; see Appendix Table 1). Green = 95% CI excludes 1.0 (statistically significant); orange = CI includes 1.0 (not significant). Softer endpoints — Franklin 2026 (mild behavioral impairment, a prodrome) and Wu 2017 (short-term cognitive decline) — are discussed in the text and Appendix Table 1 but are not plotted here, to keep the axis endpoint-comparable. Because exposure contrasts differ across studies, the 1.0 null line is comparable across studies but the absolute magnitudes are not directly.

2.1 The landmark long-lag cohorts (the load-bearing evidence)

Three studies are load-bearing precisely because they were built to blunt reverse causation, and the association persisted anyway.

Gray 2015 — Adult Changes in Thought (ACT), USA. A prospective cohort of 3,434 adults aged ≥65 with no dementia at entry, using ten years of computerized pharmacy dispensing data to quantify cumulative exposure as total standardized daily doses (TSDDs). A clear dose-response was observed: the adjusted hazard ratio for the highest exposure category (>1095 TSDDs, roughly three-plus years of daily use) versus no use was **1.54 (95%**

CI 1.21–1.96) for dementia, with a similar pattern for Alzheimer's disease; lower exposure categories were not significant. Critically, the most recent 12 months of exposure were excluded to avoid counting drugs prescribed for prodromal symptoms. The most common contributing classes were tricyclic antidepressants, **first-generation antihistamines**, and bladder antimuscarinics (Gray 2015) [1].

Coupland 2019 — QResearch, England. A very large nested case-control study: 58,769 dementia cases and 225,574 matched controls, exposure measured as TSDDs of 56 strong anticholinergic drugs 1–11 years before diagnosis. The adjusted odds ratio rose to **1.49 (95% CI 1.44–1.54)** in the highest exposure band, with a population-attributable fraction of about 10.3%. The association held when exposure was restricted to 3–13 years (OR 1.46) and 5–20 years (OR 1.44) before diagnosis — a strong reverse-causation stress test. By class, the significant signals were for anticholinergic antidepressants, antiparkinson, antipsychotic, bladder antimuscarinic, and antiepileptic drugs (Coupland 2019) [2].

Richardson 2018 — CPRD, UK. A case-control study of 40,770 dementia cases and 283,933 controls, exposure coded on the Anticholinergic Cognitive Burden (ACB) scale 4–20 years before diagnosis. The overall association for any ACB-3 (definite anticholinergic) drug was modest — **OR 1.11 (95% CI 1.08–1.14)** — but rose with cumulative exposure and, importantly, persisted for exposure **15–20 years** before diagnosis. The signal was concentrated in antidepressant, urological, and antiparkinson drugs; gastrointestinal anticholinergics were **not** distinctively linked. The authors explicitly framed the interpretive fork: a class-specific causal effect, *or* drugs prescribed for the very earliest symptoms of dementia (Richardson 2018) [3].

2.2 Recent large cohorts and biobanks (2019–2026)

Newer data broadly reinforce the association while adding modern, genetically-informed cohorts:

- **Asiimwe 2025 — UK Biobank + US All of Us.** Baseline anticholinergic burden was associated with incident dementia in both cohorts: **HR 1.15 (1.09–1.21)** in UK Biobank (n=125,260) and **1.06 (1.04–1.09)** in All of Us (n=92,047), with death modeled as a competing risk and the APOE ε4 effect replicated. The authors state plainly that causal inference is not possible (Asiimwe 2025) [16].
- **Mur 2022 — UK Biobank.** In 171,775 participants with linked prescription records, the slope of anticholinergic-burden trajectory predicted dementia (**HR 1.094, 1.068–1.119**), but the association held only for some classes (antidepressants, antiepileptics, antidiuretics) — and the estimate varied by which of 15 anticholinergic scales was used, underlining that "burden" is not a single well-defined exposure (Mur 2022) [15].
- **Joung 2019 — Korean NHIS.** Dose-dependent increase in incident Alzheimer's with cumulative strong-anticholinergic exposure over 9–12 years: **HR 1.39 (1.30–1.50)** for ≥120 doses/year, rising to **1.83 (1.56–2.14)** in the "young-old" (aged 60–64 at baseline). The long required exposure window is itself a reverse-causation safeguard (Joung 2019)

[14].

- **Chi 2025 — Shanghai Aging Study.** Cumulative burden (TSDD) was associated with incident dementia (**HR 1.55, 1.08–2.24**); the effect was markedly amplified in participants who also had high plasma neurofilament light (combined **HR 6.34, 1.90–21.20**), suggesting anticholinergic exposure interacts with underlying neurodegeneration rather than acting alone (Chi 2025) [20].

2.3 The overactive-bladder cluster — read with caution

A distinct group of studies compares anticholinergic bladder drugs against mirabegron, a non-anticholinergic β3-agonist used for the same condition, as an "active comparator":

- **Park 2024 — Korean NHIS**, the single largest study in this synthesis (N=3,452,705): anticholinergic monotherapy **aHR 1.213 (1.195–1.232)** and combination therapy 1.345 (1.323–1.366) versus mirabegron for new-onset dementia (Park 2024) [17].
- **Matta 2021 — Ontario (ICES)**, nested case-control, 11,392 cases: solifenacin **OR 1.24 (1.08–1.43)** and darifenacin 1.30 (1.08–1.56) versus mirabegron — but **no association for oxybutynin or trospium**, which the authors attribute to protopathic bias (Matta 2021) [18].
- **Painter 2026 — Kaiser Permanente**, 16,249 women with ≥10 years' follow-up: bladder antimuscarinic use **OR 1.27 (1.12–1.44)** for incident dementia/cognitive impairment (Painter 2026) [19].

A caveat that must travel with this cluster: the active-comparator design is not as clean as it appears, because in Park 2024 mirabegron — the supposedly inert reference — *itself* showed a dose-dependent dementia association (aHR ~1.06), leading the authors to conclude that "no drugs could be concluded as safe." The most parsimonious reading is that overactive bladder and lower-urinary-tract dysfunction are partly **prodromal markers of neurodegeneration**, so some of the signal in every bladder-drug study reflects the underlying condition, not the drug's pharmacology. This cluster corroborates the class pattern but should not be read as clean causal evidence.

2.4 The mixed, attenuating, and null studies (given equal weight)

Honesty requires foregrounding the studies that qualify or contradict the association:

- **Liu 2020 — Taiwan (N=790,240)**, one of the largest and most rigorously reverse-causation-controlled studies (dementia diagnoses in the first 2 and 4 years excluded), found **no overall association** (HR 1.043, 0.958–1.212); risk rose only at extreme burden (ACB ≥5) and very long duration (Liu 2020) [9].
- **Hafdi 2019 — preDIVA, Netherlands.** Persistent high burden gave HR 1.95 (1.13–3.38), but this **collapsed to 0.42 (0.06–3.01)** once antidepressant and antipsychotic users were removed — the authors concluded the signal reflected confounding by indication (Hafdi 2019) [7].

- **Andre / MAPT 2018 — France.** No association with cognitive decline on any of four anticholinergic scales (Andre 2018) [8].
- **Ancelin 2006 — France.** A strong cross-sectional association with mild cognitive impairment (OR 5.12) but **no difference in incident dementia at 8 years** (Ancelin 2006) [5].
- **Carrière 2009 — Three-City, France.** Incident dementia was raised in continuous users (**HR 1.65, 1.00–2.73**) but not in those who discontinued (1.28, 0.59–2.76) — the discontinuation contrast is among the more encouraging findings for the "modifiable" framing (Carrière 2009) [4].
- **Grossi 2019 — MRC CFAS, UK.** Positive for high-potency (ACB-3) recurrent use, especially in the cognitively intact, but null for lower-potency (ACB 1–2) drugs (Grossi 2019) [6].

Additional positive primary studies include Hsu 2017 and Hsu 2021 (Taiwan; large but with no described lag window; some subgroup odds ratios are very high and are best read as exploratory) [10] [11], Wu 2017 (short-term decline) [12], Risacher 2016 (ADNI, imaging and decline in cognitively normal adults) [13], and Franklin 2026 (NACC; anticholinergic burden associated with incident mild behavioral impairment, a dementia prodrome — HR 1.07, 1.02–1.14; a softer endpoint than dementia) [21]. Pham Nguyen 2025 found no overall association with Parkinson's-disease dementia [22].

2.5 What the meta-analyses conclude

Pooled analyses point the same way while flagging low certainty. Zheng 2021 (14 studies, ~1.56 million subjects) found anticholinergic use associated with all-cause dementia and Alzheimer's with a dose-dependent relationship [23]. The Taylor-Rowan 2022 Cochrane review (18 studies, 102,684 subjects) — restricted to people with existing cognitive impairment — rated the evidence for accelerated cognitive decline as **low to very-low certainty**, with the clearest pooled signal being for mortality rather than cognition [24]. A 2026 systematic review of bladder antimuscarinics in women found no cognitive effect in short randomized trials but increased dementia risk in multi-year cohorts (pooled OR 1.33 / HR 1.24) — the recurring pattern of null short RCTs alongside positive long observational data (Maguire 2026) [25].

Appendix Table 1 (below) is the full 22-study epidemiology table with verbatim effect sizes.

3. Mechanism and its evidentiary status

The mechanistic case is plausible and coherent, though most of it is indirect:

- **Muscarinic receptor blockade in a system already central to memory** (well-established pharmacology; strong plausibility).

- **The cholinergic deficit of Alzheimer's disease** provides a specific reason chronic antimuscarinic exposure could accelerate or unmask decline (well-established as the basis of cholinesterase-inhibitor therapy; the *causal* link from drug exposure to neurodegeneration is inferred, not demonstrated).
- **Neuroimaging correlates:** Risacher 2016 reported that cognitively normal older adults on anticholinergic medication had reduced brain glucose metabolism, greater atrophy, and worse memory and executive performance [13] — consistent with a biological effect, but cross-sectional imaging cannot establish direction.
- **Biomarker interaction:** Chi 2025's finding that the association is amplified in people with high neurofilament light suggests the drug and underlying neurodegeneration act together [20].

A key distinction the mechanism does **not** yet resolve: whether chronic anticholinergic exposure produces *durable* neurodegeneration, or whether it chronically *masks* cognitive reserve in a way that is diagnosed as dementia but is partly pharmacological. The discontinuation findings (Carrière 2009) hint at at least partial reversibility.

4. Causal appraisal (Bradford Hill)

Within the three studies that reported effect estimates by cumulative-exposure band (Gray, Coupland, Joung), risk rose monotonically with exposure. A dose–response gradient is the strongest single Bradford Hill criterion the observational evidence supplies here.

- **Strength of association:** modest in the best studies — adjusted HR/OR roughly 1.1–1.5 at highest exposure. (Larger subgroup estimates exist but are not the headline.)
- **Consistency:** good at the level of total burden and specific classes across many countries and data systems; imperfect — at least one very large study (Liu 2020) is null overall.
- **Dose-response:** repeatedly demonstrated (Gray, Coupland, Joung, Park, Zheng). One of the stronger Hill criteria here.
- **Temporality:** partially satisfied. The strongest designs push exposure years to decades before diagnosis (Gray, Coupland, Richardson, Joung), which argues against pure reverse causation — but does not eliminate confounding by indication.
- **Plausibility / coherence:** high, via the cholinergic hypothesis.
- **Experiment: not met.** No randomized trial has tested a dementia endpoint; short cognitive RCTs are null.
- **Analogy / specificity:** weak — the effect is not specific to one drug or class, and the class pattern (below) complicates a simple "anticholinergic → dementia" story.

Verdict: a consistent, dose-responsive association that is biologically plausible and partly robust to reverse causation, but for which causality remains **unproven**. Confounding by indication is the most important unresolved alternative explanation.

5. The honest complication: confounding by indication and the class pattern

Two facts sit at the center of an honest reading.

First, the conditions treated are themselves tied to dementia. Depression, insomnia, urinary urgency, and parkinsonian symptoms can be early manifestations of — or independent risk factors for — the neurodegenerative process that later presents as dementia. When Hafdi 2019 removed psychotropic users, the association vanished. When Matta 2021 examined individual bladder drugs, the pattern (oxybutynin and trospium null; solifenacin and darifenacin positive) did not track cleanly with anticholinergic potency, which the authors read as protopathic bias. When Park 2024's non-anticholinergic comparator itself predicted dementia, it suggested the *indication* carries risk. None of this proves the association is entirely confounded — the long-lag survival in Gray, Coupland, and Richardson argues it is not — but it means the true causal effect, if any, is smaller than the crude association.

Second, the class pattern cuts against a naive "diphenhydramine causes dementia" claim. Across the two best class-resolved studies (Coupland 2019, Richardson 2018), the long-term signal concentrates in anticholinergic antidepressants, bladder antimuscarinics, antiparkinson, and antipsychotic drugs — and the first-generation antihistamine and gastrointestinal classes are **not** independently significant. Gray 2015 counted antihistamines among the top contributors to total burden, which is the strongest indirect support for a diphenhydramine signal, but no class-resolved study since has isolated the antihistamine class as an independent driver. Any claim about diphenhydramine specifically must rest on its membership in the total-burden signal and its established acute toxicity — not on drug-specific long-term dementia evidence, which does not exist. Concretely: the class-specific adjusted odds ratios (Coupland 2019, highest exposure) concentrate in the psychotropic and urological classes, while the antihistamine class that includes diphenhydramine — and the gastrointestinal class — were reported as not independently significant (concordant with Richardson 2018). This is the empirical basis for framing diphenhydramine as an exemplar of total anticholinergic burden rather than a proven independent cause of dementia.

6. The over-the-counter angle: the exposure nobody counts

Almost the entire dementia-risk literature is built on **prescription** data — pharmacy dispensing records, insurance claims, primary-care prescribing databases. Diphenhydramine's distinctive feature is that its largest use is **not** captured there: it is sold over the counter as the active ingredient in ubiquitous sleep aids (ZzzQuil, Unisom SleepGels,

Tylenol PM, Advil PM) and allergy products (Benadryl). A person taking a nightly OTC sleep aid for years accrues exactly the kind of cumulative anticholinergic burden the prescription studies associate with risk — while remaining invisible to every data system used to study it.

This is the report's genuinely under-covered contribution, and it is defensible **without** overclaiming causation:

1. Diphenhydramine is a strong anticholinergic (undisputed).
2. Cumulative anticholinergic burden is associated with dementia risk in dose-responsive fashion (this synthesis).
3. Chronic OTC sleep-aid and allergy use is a large, unmonitored source of exactly that burden (exposure fact).
4. Guidance already recommends minimizing anticholinergic exposure in older adults on the basis of acute harm and the Beers Criteria (established).

The prudent public-health conclusion follows from (1)–(4) even if the long-term dementia association is ultimately non-causal: unnecessary chronic anticholinergic exposure is worth minimizing, and consumers self-medicating for sleep or allergies generally do not know that the "PM" in their nightly tablet is a strong anticholinergic at all.

7. Limitations

- **All dementia-endpoint evidence is observational.** No RCT has tested it, and none easily could.
- **Confounding by indication is pervasive and only partly addressable** (§5).
- **"Anticholinergic burden" is not one exposure.** 15+ competing scales with poor inter-agreement; effect sizes shift with scale choice (Mur 2022).
- **Outcomes are heterogeneous** — all-cause dementia, Alzheimer's, MCI, mild behavioral impairment, and cognitive-decline slopes are not interchangeable; softer endpoints (Franklin, Ancelin, Risacher) should carry less weight.
- **Diphenhydramine is not studied in isolation**; its role is inferred from class membership.
- **The largest OTC exposure is unmeasured** in nearly all source studies — a gap that runs in the direction of *under*-counting exposure, which would bias observed associations toward the null but also means real-world burden is higher than the prescription data capture.
- **Publication and surveillance effects** are possible; positive findings in this area attract attention.

8. Conclusion

The weight of evidence — 22 primary studies across five continents of data, dose-responsive, coherent with a specific mechanism, and robust to long reverse-causation lag windows in the strongest designs — supports a real association between cumulative anticholinergic burden and dementia risk. It does not establish causation, and the association is neither uniform across drug classes nor free of the confounding-by-indication problem that shadows all pharmaco-epidemiology of this kind.

For diphenhydramine specifically, the honest statement is narrow and firm: it is the exemplar of a strong anticholinergic whose largest use is unmonitored and over-the-counter; it contributes to exactly the burden the literature associates with risk; its acute cognitive harm and "avoid in older adults" status are already established; and minimizing unnecessary chronic use is prudent on those grounds alone, independent of whether the long-term dementia association proves causal. What the evidence does **not** support — and what this document does not claim — is that diphenhydramine has been shown to cause dementia.

Key gaps

- **No experimental test on the dementia endpoint.** No randomized or quasi-experimental study has tested whether *reducing* anticholinergic burden lowers incident dementia; deprescribing trials to date measure short-term cognition, not adjudicated incident dementia.
- **Diphenhydramine is not studied in isolation.** The single largest over-the-counter anticholinergic exposure has no standalone long-term incident-dementia study; its contribution is inferred from class membership, not measured directly.
- **"Anticholinergic burden" is not one exposure.** Fifteen-plus competing scales with poor inter-agreement mean effect sizes shift with scale choice (Mur 2022); there is no harmonized, pharmacologically anchored metric.
- **Over-the-counter exposure is unmeasured.** Nearly all source cohorts use prescription-only data, so the largest real-world source of burden is systematically under-counted — a gap that biases observed associations toward the null while meaning true exposure is higher than the data capture.
- **Confounding by indication is only partly addressable.** The active-comparator (mirabegron) cluster shows the *indication itself* — overactive bladder — may be a prodromal marker of neurodegeneration, so no purely observational design can fully separate drug from indication (§5).

Priority research directions

- **A deprescribing trial powered for incident dementia**, or a target-trial emulation using linked pharmacy plus over-the-counter purchase data, to test the causal question the observational literature cannot.

- **Cohorts that capture OTC antihistamine and sleep-aid purchases** (pharmacy-sales or loyalty-card linkage) so the unmonitored exposure is measured directly rather than inferred.
- **Harmonization of anticholinergic-burden scales** against a common receptor-affinity-weighted pharmacological reference, with pre-registered analysis, so effect sizes stop depending on scale choice.
- **Biomarker-stratified designs** (e.g. plasma neurofilament light, as in Chi 2025) to distinguish a drug effect from underlying neurodegeneration.
- **Active-comparator designs beyond the bladder class** to further reduce confounding by indication.

These directions would sharpen, not overturn, the central reading of the current evidence: a consistent, dose-responsive **association** between cumulative anticholinergic burden and dementia risk that is not established as causal and is shadowed throughout by confounding by indication.

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All citations were independently verified against their published sources on PubMed; associations are not assertions of causation.

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Competing interests. The author is the founder and principal of Holistic Quality LLC, the commercial publisher of this report, which develops regulator-facing safety-data and

compliance products in areas that include pharmacological and environmental exposure; a sibling property, the Institute for Cognitive Sovereignty, may cite this work in public advocacy. These constitute a competing interest. Mitigation: every effect size and citation was independently source-verified against its published PubMed record, the limits of the evidence — and the explicit boundary between association and causation — are stated throughout, and the author retained sole editorial control.

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Sensitive-topic note. Dementia is a distressing subject. This document is about population-level medication risk, not individual prognosis, and is not a basis for self-diagnosis. Consult a clinician before starting or stopping any medication.

Appendix Table 1

Primary studies of anticholinergic drug exposure and incident dementia or long-term cognitive decline (n = 22)

Scope and inclusion. Primary longitudinal cohort and (nested) case-control studies reporting an adjusted effect estimate (HR / OR / aHR / IRR) for anticholinergic drug exposure against incident dementia, incident Alzheimer's disease, or longitudinal cognitive decline / MCI-to-dementia progression. Reviews, meta-analyses, anticholinergic-burden scale-validation papers, acute-delirium studies, cross-sectional-only designs, and studies of anticholinergics used to *treat* dementia were excluded. Evidence identified via PubMed (broad "anticholinergic burden AND dementia AND cohort/risk" query, 231 records, plus targeted named-cohort and antihistamine-class searches). Every effect estimate below was extracted from and independently re-verified against the source abstract on PubMed. Studies are ordered newest → oldest; the **§** column cross-references the section of the main report in which each study is discussed.

Section-code key (§): L = landmark long-lag design (report §2.1) · **C** = large cohort / biobank (§2.2) · **B** = overactive-bladder active-comparator cluster (§2.3) · **O** = other, mixed, attenuating, or null (§2.4). **Signal key: +** positive · **±** mixed / conditional · **0** null.

#	Study (year)	§	Country · data source	Design	N	Exposure metric	Outcome	Adjusted effect at highest / stated exposure (95% CI)	Signal
1	Asiimwe (2025)	C	UK · US — UK Biobank + All of Us	Prospective cohort ×2, competing-risk	125,260 · 92,047	Baseline ACMI burden	Incident dementia	HR **1.15 (1.09–1.21)** UKB; **1.06 (1.04–1.09)** AoU	+
2	Painter (2026) [a]	B	USA — Kaiser Permanente N. California	Retrospective cohort, ≥10 y f/u	16,249 women	Bladder antimuscarinic use / burden	Incident dementia/cognitive impairment	OR **1.27 (1.12–1.44)**	+
3	Franklin (2026) [b]	O	USA — NACC	Cohort, cognitively unimpaired, time-varying	4,865	Time-varying ACB	Incident mild behavioral impairment (prodrome)	HR **1.07 (1.02–1.14)**	+
4	Chi (2025) [c]	C	China — Shanghai Aging Study	Prospective cohort, median 5.2 y	1,529	Cumulative ACB + TSDD (1 y pre-baseline)	Incident dementia	HR **1.55 (1.08–2.24)** TSDD; **6.34 (1.90–21.20)** high TSDD + high NfL	+
5	Pham Nguyen (2025)	O	USA — UPenn Parkinson's cohort	Prospective, time-varying ACB	PD patients	Time-varying ACB	Incident Parkinson's-disease dementia	Not associated overall (no significant HR)	0
6	Park (2024) [d]	B	Korea — NHIS (overactive bladder)	Retrospective cohort, active comparator	3,452,705	Cumulative cDDD vs mirabegron	New-onset dementia	aHR **1.213 (1.195–1.232)** AC alone; **1.345 (1.323–1.366)** combination	+
7	Mur (2022) [e]	C	UK — UK Biobank (linked GP Rx)	Prospective cohort	171,775	Annual AC-burden trajectory (15 scales)	Incident dementia	HR **1.094 (1.068–1.119)** (trajectory slope)	+

#	Study (year)	§	Country · data source	Design	N	Exposure metric	Outcome	Adjusted effect at highest / stated exposure (95% CI)	Signal
8	Taylor-Rowan — see report §2.5 meta-analysis	—	—	*(Cochrane meta-analysis — not a primary study; listed in main report)*	—	—	—	—	—
9	Matta (2021) [d]	B	Canada — Ontario (ICES)	Nested case-control, active comparator	11,392 cases · 29,881 controls	Specific OAB antimuscarinic vs mirabegron (6–12 mo)	Incident dementia / AD	Solifenacin OR **1.24 (1.08–1.43)**; darifenacin **1.30 (1.08–1.56)**; oxybutynin & trospium **null**	±
10	Liu (2020) [f]	O	Taiwan — NHIRD	Retrospective matched cohort, time-dependent	790,240	AC use; ACB bands; duration	Incident dementia (15 y)	HR **1.043 (0.958–1.212)** overall (NS); ↑ only at ACB ≥5 & ≥1460 days	0
11	Coupland (2019)	L	England — QResearch	Nested case-control	58,769 cases · 225,574 controls	TSDDs of 56 strong AC drugs (1–11 y pre-index)	Incident dementia	AOR **1.49 (1.44–1.54)** >1095 TSDDs; held 5–20 y lag; PAF ≈10.3%	+
12	Grossi (2019)	O	UK — MRC CFAS	Prospective cohort (~8 y)	8,216	ACB-3 vs ACB 1–2; ever / recurrent	Incident dementia	Recurrent ACB-3 IRR **1.68 (1.00–2.82)**; ACB-3 in MMSE>25 **2.28 (1.32–3.92)**; ACB 1–2 **0.89 (0.68–1.17)**	±
13	Hafdi (2019) [g]	O	Netherlands — preDIVA	Prospective cohort (median 6.7 y)	3,526	Persistent ACB (baseline + 2 y)	Incident dementia	Persistent HR **1.95 (1.13–3.38)** → **0.42 (0.06–3.01)** excl. psychotropics	±
14	Hsu (2021) [h]	O	Taiwan — NHIRD / LHID	Longitudinal cohort (GEE)	116,043	ACB + ARS (monthly cumulative)	Incident dementia	Age 65–74, ACB "3": aOR **9.15 (8.38–9.99)** *(subgroup; exploratory)*	+

#	Study (year)	§	Country · data source	Design	N	Exposure metric	Outcome	Adjusted effect at highest / stated exposure (95% CI)	Signal
15	Joung (2019)	L	Korea — NHIS elderly cohort	Population cohort (9–12 y exposure)	NHIS elderly cohort	Cumulative strong-AC doses/year	Incident Alzheimer's disease	HR **1.39 (1.30–1.50)** ≥120 doses/y; **1.83 (1.56–2.14)** young-old	+
16	Richardson (2018)	L	UK — CPRD	Case-control	40,770 cases · 283,933 controls	ACB-scale DDDs (4–20 y pre-dx)	Incident dementia	Any ACB-3 drug OR **1.11 (1.08–1.14)**; held 15–20 y; GI class not linked	+
17	Andre / MAPT (2018)	O	France — MAPT	Longitudinal, time-varying, 4 scales	1,396	ADS / ACB / ARS / Durán	Cognitive decline (3 y)	HR **1.14 (0.95–1.38)** score 1; **0.92 (0.65–1.30)** score 3 (NS)	0
18	Wu (2017)[i]	O	Taiwan — veterans' homes	Retrospective cohort (2 serial MMSE)	274 men	ACB, AC(+) vs AC(−)	Short-term cognitive decline (~6 mo)	OR **2.69 (1.36–5.31)**; excl. antipsychotics **2.24 (1.26–3.99)**	+
19	Hsu (2017)[h]	O	Taiwan — LHID	Population cohort (GEE)	116,043	ARS / ACB / DBI-Ach (monthly)	Incident dementia	Age 65–74, ACB 1→≥4: aOR **3.13 → 10.01** *(subgroup; exploratory)*	+
20	Risacher (2016)[b]	O	USA — ADNI + IMAS	Longitudinal, cognitively normal at baseline	451	≥1 medium/high-AC medication; total burden	Cognitive/clinical decline; brain atrophy & metabolism	Worse memory/executive & greater atrophy (P = .04); longitudinal HR in full text	+
21	Gray (2015)	L	USA — Adult Changes in Thought (ACT)	Prospective cohort (mean 7.3 y)	3,434	Cumulative TSDDs over 10 y (pharmacy)	Incident dementia + Alzheimer's	HR **1.54 (1.21–1.96)** >1095 TSDDs; dose-response P < .001; last 12 mo excluded	+

#	Study (year)	§	Country · data source	Design	N	Exposure metric	Outcome	Adjusted effect at highest / stated exposure (95% CI)	Signal
22	Carrière (2009)	O	France — Three-City (3C)	Population cohort (4 y)	6,912	Reported AC use; continuous vs discontinued	Incident dementia + cognitive decline	Continuous users HR **1.65 (1.00–2.73)**; discontinued **1.28 (0.59–2.76)** (NS)	±
23	Ancelin (2006)	O	France — 63 GP practices	Longitudinal cohort (8 y)	372	Continuous AC use (prior year)	Prevalent MCI + incident dementia	MCI OR **5.12 (P = .001)**; incident dementia at 8 y: **no difference**	±

Rows are numbered for reference within this appendix; row 8 is a placeholder noting the Cochrane meta-analysis (Taylor-Rowan 2022), which is discussed in report §2.5 but is not a primary study and is therefore not counted among the 22. Twenty-two primary studies are tabled (rows 1–7, 9–23).

Footnotes.

- [a] Painter (2026): women only; excluded pre-existing dementia/cognitive impairment; ≥10-year follow-up.
- [b] Softer / non-dementia endpoint — Franklin measures incident *mild behavioral impairment* (a dementia prodrome); Risacher's primary endpoints are neuroimaging and cognitive-test performance. Both carry less weight than adjudicated incident dementia.
- [c] Chi (2025): the **HR 6.34** estimate is a joint high-burden × high-neurofilament-light subgroup effect, not the main-effect estimate (HR 1.55); it should be read as an interaction/exploratory finding, not a headline effect size.
- [d] Active-comparator (mirabegron) design. **Caveat:** in Park (2024) the non-anticholinergic comparator mirabegron *itself* showed a dose-dependent dementia association (aHR ≈ 1.06), consistent with overactive bladder being partly a prodromal marker of neurodegeneration. This cluster corroborates the class pattern but is not clean causal evidence (see report §2.3, §5).
- [e] Mur (2022): effect estimate varied by which of 15 anticholinergic scales was applied — illustrates that "anticholinergic burden" is not a single, well-defined exposure.
- [f] Liu (2020): among the largest and most rigorously reverse-causation-controlled studies (dementia diagnoses in the first 2 and 4 years after exposure excluded); null overall — the principal counterweight to the positive body of evidence.

- [g] Hafdi (2019): the positive persistent-use estimate collapses to null once antidepressant/antipsychotic users are excluded — the authors attribute the signal to confounding by indication.
- [h] Hsu (2017, 2021): very large odds ratios derive from age-stratified subgroup analyses with no described exposure-lag window; treated as exploratory, not headline, estimates.
- [i] Wu (2017): small, short-term (~6-month) cognitive-decline endpoint rather than adjudicated incident dementia.

Abbreviation key. ACB = Anticholinergic Cognitive Burden scale · ACMI = Anticholinergic Medication Index · ADS = Anticholinergic Drug Scale · aHR = adjusted hazard ratio · AoU = All of Us Research Program · ARS = Anticholinergic Risk Scale · CI = confidence interval · cDDD = cumulative defined daily dose · DBI-Ach = Drug Burden Index (anticholinergic component) · DDD = defined daily dose · GEE = generalized estimating equations · HR = hazard ratio · ICES = Institute for Clinical Evaluative Sciences (Ontario) · IRR = incidence rate ratio · LHID = Longitudinal Health Insurance Database (Taiwan) · MBI = mild behavioral impairment · MCI = mild cognitive impairment · MMSE = Mini-Mental State Examination · NACC = National Alzheimer's Coordinating Center · NfL = neurofilament light chain · NHIRD/NHIS = National Health Insurance Research Database / Service · NS = not statistically significant · OR = odds ratio · PAF = population-attributable fraction · TSDD = total standardized daily dose.

Direction summary.

- **Positive (14):** Gray 2015, Coupland 2019, Richardson 2018, Hsu 2017, Hsu 2021, Wu 2017, Risacher 2016, Asiimwe 2025, Park 2024, Painter 2026, Chi 2025, Mur 2022, Joung 2019, Franklin 2026 (prodrome endpoint).
- **Mixed / conditional (5):** Carrière 2009 (continuous users only), Grossi 2019 (high-potency only), Hafdi 2019 (attenuates to null on excluding psychotropics), Ancelin 2006 (MCI yes, incident dementia no), Matta 2021 (positive for some OAB drugs, null for oxybutynin/trospium).
- **Null (3):** Liu 2020 (overall), Andre / MAPT 2018, Pham Nguyen 2025.

Completeness statement. Targeted searches confirmed that Cache County, the Rotterdam Study, Framingham, Whitehall, and the Nurses' Health Study have no standalone anticholinergic-exposure → incident-dementia effect-size paper indexed in PubMed under standard search terms; their absence reflects the literature, not an omission. The major national health-insurance databases (UK, Korea, Taiwan, Canada) and prospective biobanks (UK Biobank, All of Us) are represented. On this basis the primary-study evidence base is considered saturated for the purpose of this synthesis.

Provenance. All bibliographic data and effect estimates were retrieved from and verified against PubMed. Associations tabulated here are not assertions of causation (see main report §4–§5).