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RESEARCH ARTICLE

Preventing Alzheimer's disease within reach by 2025: Targeted-risk-AD-prevention (TRAP) strategy

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Abstract

Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disease that currently affects 6.2 million people in the United States and is projected to impact 12.7 million worldwide in 2050 with no effective disease-modifying therapeutic or cure. In 2011 as part of the National Alzheimer's Project Act, the National Plan to Address Alzheimer's Disease was signed into law which proposed to effectively prevent AD by 2025, which is rapidly approaching. The preclinical phase of AD can begin 20 years prior to diagnosis, which provides an extended window for preventive measures that would exert a transformative impact on incidence and prevalence of AD.

Methods: A novel combination of text-mining and natural language processing strategies to identify (1) AD risk factors, (2) therapeutics that can target risk factor pathways, and (3) studies supporting therapeutics in the PubMed database was conducted. To classify the literature relevant to AD preventive strategies, a relevance score (RS) based on STRING (search tool for the retrieval of interacting genes/proteins) score for protein–protein interactions and a confidence score (CS) on Bayesian inference were developed. To address mechanism of action, network analysis of protein targets for effective drugs was conducted. Collectively, the analytic approach, referred to as a targeted-risk-AD-prevention (TRAP) strategy, led to a ranked list of candidate therapeutics to reduce AD risk.

Results: Based on TRAP mining of 9625 publications, 364 AD risk factors were identified. Based on risk factor indications, 629 Food and Drug Administration-approved drugs were identified. Computation of ranking scores enabled identification of 46 relevant high confidence (RS & CS > 0.7) drugs associated with reduced AD risk. Within these candidate therapeutics, 16 had more than one clinical study supporting AD risk reduction. Top-ranked therapeutics with high confidence emerged within lipid-lowering, anti-inflammatory, hormone, and metabolic-related drug classes.

Discussion: Outcomes of our novel bioinformatic strategy support therapeutic targeting of biological mechanisms and pathways underlying relevant AD risk factors with

high confidence. Early interventions that target pathways associated with increased risk of AD have the potential to support the goal of effectively preventing AD by 2025.

KEYWORDS

Alzheimer's, bioinformatics, prevention, risk factors

1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease leading to cognitive and neurological disabilities that ultimately result in loss of autonomy and independent living.[1–3] AD has a preclinical phase that can begin 20 years prior to diagnosis.[1,2] The underlying pathophysiology of AD is complex, with multiple schools of thought ranging from the amyloid cascade hypothesis,[4,5] tau-based mechanisms,[5,6] metabolism/ bioenergetic–based theories including lipid dysregulation,[7,8] among others.[9–13] It is estimated that 11% of people over the age of 65 will develop AD.[2] Currently an estimated 6.2 million persons are living with AD in the United States, a number projected to increase to 13.8 million by 2050[2] and 152 million worldwide.[14] Of note, women are at two-fold greater life-time risk for AD relative to men and comprise more than 60% of persons living with the disease.[11,12,15,16] In 2021, the annual cost for AD patient health care will be $355 billion.[2]

In 2011, the National Plan to Address Alzheimer's Disease, as part of the National Alzheimer's Project Act (NAPA), was signed into law with the goal to prevent and effectively treat AD by 2025.[17] Because underlying mechanisms leading to AD can occur up to 20 years before diagnosis, the window of opportunity to prevent and delay the disease is substantial. While double-blind placebo-controlled prevention trials for AD are not executable by 2025, it is possible to determine, based on clinical standard-of-care, the effect of therapies that target AD risk factors for their impact on AD risk. Projections estimated that a 1-year delay in AD onset by 2020 would result in roughly 9 million fewer cases in 2050.[18]

Based on this rationale, we developed a computational approach to evaluate therapeutics that target known AD risk factors for their impact on risk of developing AD. Specifically, we conducted a combination of text-mining and natural language processing strategies to mine all currently available literature and combined this search with two ranking systems: (1) a relevance score based on STRING (search tool for the retrieval of interacting genes/proteins) scores formula used in scoring protein–protein interaction and (2) a confidence score using a Bayesian inference approach to classify the body of literature relevant to preventive strategies for AD. Using our targeted-risk-AD-prevention (TRAP) strategy, a ranked list was generated for therapeutics associated with reduced risk of AD. Finally, a system biology analysis was conducted to evaluate drug-target interaction networks underlying identified therapeutics to identify mechanisms of actions along with potential for synergistic and combinatorial effects.

Outcomes of our novel bioinformatic TRAP strategy supports therapeutic targeting of biological mechanisms and pathways underlying AD risk factors. Based on our analyses, we propose that early interventions that target pathways associated with increased risk of AD have the potential to support the goal of effectively preventing AD by 2025.

2 | METHODS

The computationally driven TRAP strategy, described in detail below, aims at identifying: (1) risk factors associated with AD (Figure 1A), (2) therapeutics prescribed to treat AD risk factors (Figure 1B), and (3) the most promising preventative strategies for AD based on the clinical and pre-clinical studies available that demonstrate their potential benefit on AD (Figures 2, 3). The TRAP strategy utilized PubMed[19] and the Medical Subject Headings (MeSH) thesaurus.[20] MeSH is a controlled and hierarchically organized medical vocabulary produced by the National Library of Medicine and is used for indexing articles for PubMed. Different MeSH terms are assigned to PubMed articles allowing for the classification of medical publication content. MeSH terms are also classified by subject categories (e.g., diagnosis, complications) with more specific terms arranged beneath broader terms.[20]

2.1 | AD risk factor identification and therapeutic selection

Risk factors associated with AD were identified by first querying abstracts, titles, and MeSH terms of publications in PubMed containing both *"Alzheimer"* and *"risk factor"* words (Query 1, Figure 1A). Next, MeSH terms related to the selected publications were extracted and mined to identify the final list of risk factors for AD (Query 2, Figure 1A). MeSH terms belonging to the MeSH categories *Diagnosis, Complications, Prevention & control*, and *Drug Therapy* were retained, whereas all MeSH terms that did not correspond to diseases, complications, or potential risk factors were eliminated. From this, a set of risk factors was obtained for AD (e.g., *hypertension, type 2 diabetes, hypercholesterolemia*, etc.). A further step of filtering was manually performed to exclude the MeSH terms corresponding to a diagnosis of AD as a risk factor (e.g., *Alzheimer's disease, dementia, memory disorders*, etc.).

Step 2 of the initial analysis (Figure 1B) involved identification of Food and Drug Administration (FDA) therapeutics currently approved

for AD-associated risk factors to identify the pool of potential preventive therapeutics.

To identify MeSH terms of FDA-approved drugs, DrugBank[21] and Therapeutic Target Database (TTD)[3] repositories (Query 3, Figure 1B) were queried for drug-disease associations. FDA-approved drugs for AD treatment were not included (e.g., donepezil, galantamine, rivastigmine, memantine, and idebenone[22]).

2.2 | Drug study relevance score

For each drug approved for an AD risk factor identified in the previous steps, PubMed was used to retrieve publications relative to AD and the drug of interest (Figure 2) as *"(Alzheimer*[MeSH Terms] AND "Drug"[MeSH Terms]) OR (Alzheimer*[Title/Abstract] AND "Drug"[Title/Abstract])"* (Figure 2, Query 4). To avoid overrepresentation of therapeutic candidates, review articles were not included.

Subsequently, a point scoring system with a maximum of 100 points for each publication was developed based on abstract content to weight the relevance of a drug with associated AD risk (Table 1). To assess potential of a drug to prevent AD, the highest score (100 points) was assigned when both the "*drug of interest*" (50 points) and "*Alzheimer*" (25 points) words appeared in the title and the word "*risk*" or "*diagnosis*" of AD (25 points) appeared within five words to the word "*Alzheimer*" in the abstract or in the title. The range of words considered do not include stop words, that is, a set of commonly used words in English, such as "the," "of," and "a." We developed a tiered point system based on the location of the scored words contained within the title or first and last sentence of the abstract (Table 1). The schema for score generation appears in Table 1.

Because each drug could be associated with multiple publications, an overall relevance score (RS) for each drug *d* was developed:

$$RS(d) = 1 - \prod_{i}^{npub} \left(1 - \frac{S_i}{100}\right)$$

where *npub* was the total number of publications related to the drug *d* and S_i was the score in points apportioned to the publication *i*. This RS function was derived from a STRING protein–protein interaction (PPI) scoring system used to assign a PPI strength of the supporting evidence as per Vitali et al.[23–25] Based on the STRING score, a RS threshold of 0.7 was selected to consider a drug relevant to study objective to identify therapeutics with potential to prevent AD. Impact of a publication was reflected in a greater RS relative to summation of individual subscores (points associated to a single publication). Multiple publications supporting a single drug was reflected in a higher RS.

To specifically identify clinical study publications, titles and abstracts of clinical- and population-level studies (retrospective/prospective studies, clinical trials) were mined for common key words used to report clinical findings (i.e., "*Odds ratio,*" "*Relative risk,*" "*Hazard ratio*") (Figure 2, Query 5).

HIGHLIGHTS

- Alzheimer's disease (AD) prevention therapeutics target initiating mechanisms of AD not the full range of systems present in AD.
- Thus, therapeutics strategies for preventing AD are not the same as treating AD.
- Therapeutics targeting AD-specific initiating risk factors can prevent or delay the cascade of mechanisms leading to AD.
- We used a novel bioinformatic strategy of targeted-risk-AD-prevention (TRAP) to analyze publications and rank therapeutics.
- We identified promising candidates to prevent AD by 2025 in the current clinical and preclinical pipeline.

RESEARCH IN CONTEXT

1. **Systematic review**: To evaluate potential therapeutics that address the goal of preventing Alzheimer's disease (AD) by 2025, we developed a targeted-risk-AD-prevention (TRAP) strategy. TRAP is based on a computational pipeline to mine PubMed and rank preventive therapeutics that target AD risk factors.
2. **Interpretation**: TRAP analysis identified and ranked specific drugs associated with AD reduced risk. The 16 drugs that reduced AD risk were supported by clinical studies and included metabolic, statin, anti-inflammatory, hormone, cardiac, and psychiatric drug classes.
3. **Future direction**: To achieve maximal success in preventing AD, two criteria will have to met. First, to prevent AD, a precision therapeutic approach for controlling risk factors while also sustaining brain health. Second, to delay AD, a combination of therapies that target multiple risk factors to sustain brain function.

2.3 | Drug risk confidence score

A final screening of therapeutic candidates was performed to classify the publications based on their consensus of impact on AD risk. Abstracts were again mined for "reduced risk" or "elevated risk" words (Figure 3). Reduced risk search words included "*lower,*" "*decrease,*" "*protective,*" "*reduce,*" "*improve,*" "*prevent,*" whereas elevated risk search words included "*elevate,*" "*increase,*" "*deficit,*" "*worsen.*" Because these words are commonly found in medical papers, only publications for a drug and its effect on AD risk were included if the words "reduced risk" or "elevated risk" were found in the range of five words before or after the word "*Alzheimer.*" The range of words considered do not include

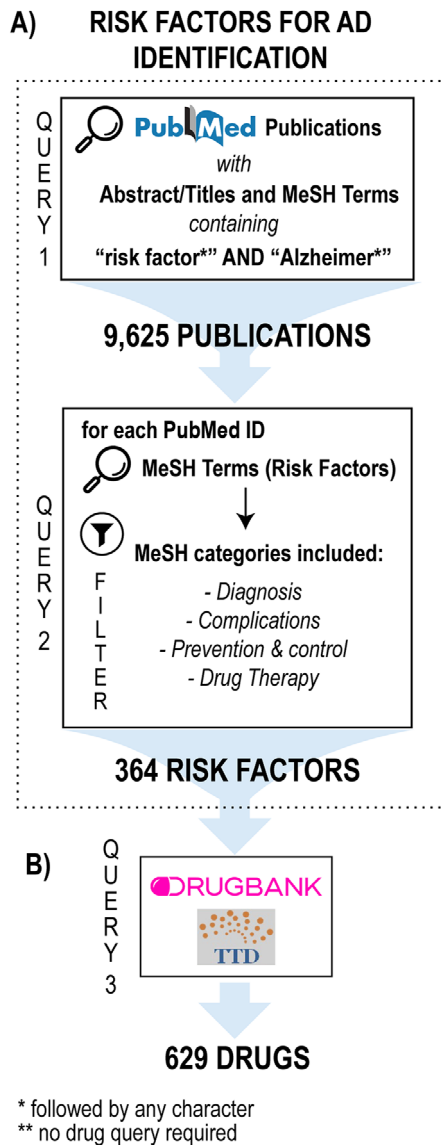**A) RISK FACTORS FOR AD IDENTIFICATION**

FIGURE 1 Targeted-risk-Alzheimer's disease-prevention (TRAP) pipeline part 1. A, Alzheimer's disease risk factor identification. B, Selection of drugs approved to treat risk factors. MeSH, Medical Subject Headings

FIGURE 2 Targeted-risk-Alzheimer's disease-prevention (TRAP) pipeline part 2. Analysis of drug therapies impact on Alzheimer's disease, computation of relevance score (RS), and identification of clinical studies. MeSH, Medical Subject Headings

stop words, e.g. commonly used word in English, such as "the," "of," and "a." Finally, to include only publications in which the impact of AD risk was associated with the drug effect as described in the results or conclusions, risk-associated words were required to occur in the last three sentences of the abstract. For example, studies reporting a list of risk factors for AD in the background of a paper (e.g., diabetes can increase the risk of AD[26]) unrelated to the drug effect were not included in the analysis. This procedure resulted in the definition of a vector for each drug containing "reduced risk" or "elevated risk" for each publication based on the risk words found in the abstract. An overall risk direction for a drug d was defined using a Bayesian inference approach. Confidence of the risk direction (confidence score [CS]) was assigned to each drug based on the number of publications with consensus with the risk. Specifically, the risk direction and confidence score were assigned
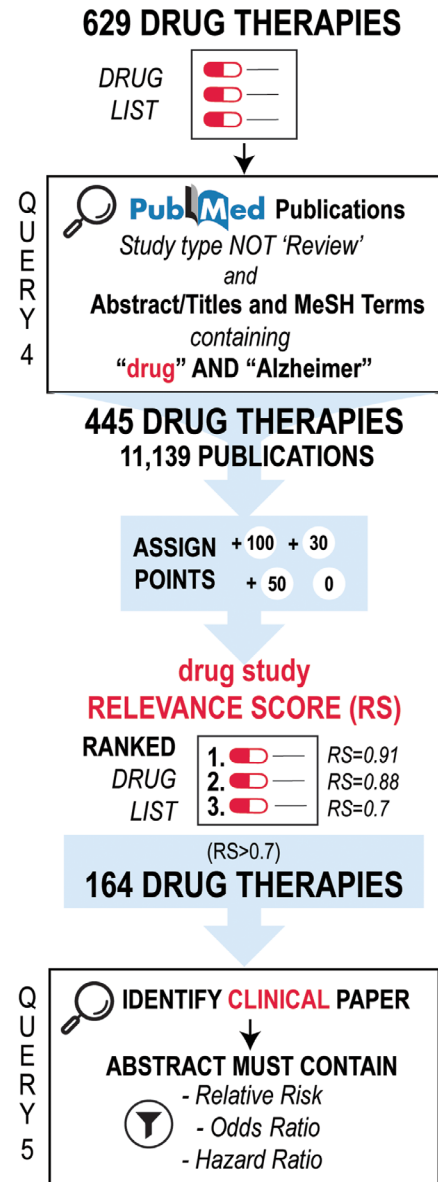
by assuming the risk direction value x associated to each publication related to a drug were distributed as Binomial distribution with n and π parameters as:

$$f(x|\pi) = Binom(x|\pi; n)$$

where the prior distribution π is distributed as a Beta with a and b parameters

$$g(\pi) = Beta(\pi|a; b)$$

with $= b = 2$. Therefore, π is posterior distributed as a Beta as well:
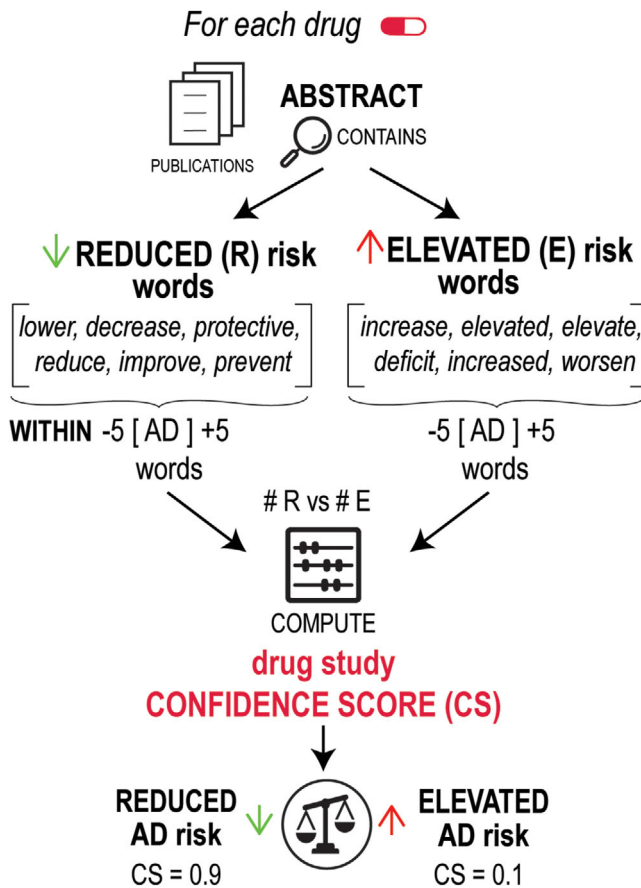
$$g(\pi|x) = Beta(\pi|a'; b')$$

FIGURE 3 Targeted-risk-Alzheimer's disease-prevention (TRAP) pipeline part 3. Computation of confidence score (CS) to evaluate and rank therapeutic effect on Alzheimer's disease (AD) risk

where $a' = a + x$ and $b' = b + n - x$, where n is the total number of publications associated to a drug and x is the number of publications reporting reduced or elevated AD risk. The confidence score $CS(d)$ for a drug d to reduce AD risk was defined as the mode of this distribution:

$$CS(d) = Mode(g(\pi|x)) = \frac{a' - 1}{a' + b' - 2}$$

The resulting CS values ranged from 0 to 1, with a score of 1 indicating that 100% of the publications confirmed that drug d impacted AD risk in a single direction. In contrast, a CS of 0.5 corresponded to inconclusive risk direction for d because the number of publications reducing or elevating AD risk were equivalent. For example, if a drug has $n = 100$ publications of which 70 reported reduced risk ($x = 70$), the $CS^+(d) = 0.702$ because $a' = 2 + 70$ and $b' = 2 + 100 - 70$ indicat-

ing high confidence for the drug to reduce AD risk. In contrast, if a drug is associated with a single publication, then $n = 1$ and the study reporting reduced AD risk $x = 1$, $CS(d)$ results in a CS of 0.666 where $a' = 2 + 1$ and $b' = 2 + 1 - 1$ indicating the drug may reduce AD risk but is associated with lower confidence for efficacy to prevent AD. The same process was used to determine whether a drug elevates risk of AD. Drugs surpassing a CS threshold of 0.7 were included.

2.4 | Drug-target networks

Drug-target interactions (DTIs) were extracted from DrugBank[21] to construct DTI networks as previously described in Torrandell-Harlow et al.[27] Networks were visualized by using Cytoscape software 3.8.2.[28]

3 | RESULTS

Based on the TRAP strategy to detect AD risk factors, 9625 publications were identified that linked a medical condition to AD (Figure 1A). Based on this analysis, 364 individual risk factors were identified from the relative MeSH terms (Figure 1A, Figure S1 in supporting information). Within the risk factors, there were well-documented medical conditions previously associated with risk of AD including diabetes,[29] hypertension,[30] cardiovascular diseases,[31] and stroke/vascular diseases[32] (Table S1 in supporting information). Replication of well-documented AD risk factors validates the first aspects of the TRAP strategy.

Based on the AD risk factor list, 629 FDA-approved drugs were identified based on medical use indications annotated in the DrugBank and TTD databases (Figure 1B, Table S2 in supporting information). These results were used to generate a pipeline to identify publications reporting a risk factor therapeutic with risk of AD, which resulted in 11,139 publications (Figure 2) for 445 drugs (Table S2).

Computation of a RS enabled filtering of publications that did not meet the threshold (RS < 0.7) resulting in a total of 164 ranked drugs (Table S3 in supporting information). Within this drug set, 53 therapeutics had at least one clinical study associated with AD risk (Table S3).

Computation of a CS enabled categorization and further ranking of therapeutics based on direction of AD risk modification (Table S4 in supporting information). CS ranking and thresholding (CS >= 0.7) identified a total of 46 drugs associated with reduced risk of AD (Table 2, Table S4). Of the 46 identified drugs, 16 were reported in at least one clinical study of AD risk reduction (Table 2), while the remaining 30 were in the pre-clinical pipeline and were not supported by clinical

TABLE 1 Point values for study relevance ranking

	IF "*Alzheimer*" in:	Score		IF "*Drug*" in:	Score
	Title	25 points		Title	50 points
OR	First abstract sentence	15 points	OR	First abstract sentence	30 points
OR	Last abstract sentence	15 points	OR	Last abstract sentence	30 points
+	IF '**Risk/Diagnosis**' within -5[AD]+5 words	25 points			

TABLE 2 Drugs supported by clinical studies resulting from TRAP pipeline

Drug name	# Total reports*	# Reports included in stats†	# Positive reports	# Negative reports	CS	RS	Drug category
Pioglitazone	115	11	11	0	0.923	1	Metabolic
Ibuprofen	180	18	17	1	0.900	1	Anti-inflammatory
Indomethacin	118	8	8	0	0.900	1	Anti-inflammatory
Atorvastatin	101	15	14	1	0.882	1	Statin
Pravastatin	41	6	6	0	0.875	1	Statin
Simvastatin	140	19	17	2	0.857	1	Statin
Estradiol	509	80	65	15	0.805	1	Hormone
Celecoxib	82	8	7	1	0.800	1	Anti-inflammatory
Rosuvastatin	18	3	3	0	0.800	0.995	Statin
Lisinopril	9	3	3	0	0.800	0.987	Cardiac
Vitamin A	73	17	14	3	0.789	1	Other
Valproic acid	83	12	10	2	0.786	1	Psychiatric
Naproxen	77	12	10	2	0.786	1	Anti-inflammatory
Diclofenac	27	6	5	1	0.750	1	Anti-inflammatory
Metformin	146	13	10	3	0.733	1	Metabolic
Testosterone	260	39	29	10	0.732	1	Hormone

*Total number of publications including the drug of interest and the word "Alzheimer."
†Total number of publications including words associated with reduced risk of AD.
CS, confidence score; RS, relevance score.

studies (Table S5 in supporting information). PubMed IDs for all publications related to the ranked drugs appear in supplemental Tables S4.

Top therapeutics supported by clinical studies (Table 2) with reduced AD risk included five anti-inflammatories (e.g., ibuprofen, indomethacin), four lipid-lowering (e.g., pravastatin, simvastatin), two metabolic-related (pioglitazone and metformin), two hormone (estradiol and testosterone), one psychiatric (valproic acid), one cardiac (lisinopril) therapeutic, and vitamin A.

Additionally, TRAP analysis identified therapeutics in the pre-clinical pipeline for which no clinical study was found to support their potential to reduce AD risk (Table S5). These drugs included 11 cardiac (e.g., telmisartan, nitroprusside, and verapamil), five metabolic-related (e.g., liraglutide, rosiglitazone), four anxiety/psychiatric (e.g., fluoxetine, citalopram), and three anti-inflammatory (e.g., flurbiprofen, capsaicin) drugs.

Drug therapies in the reduced risk category that were supported by clinical studies are plotted based the number of publications on reduced AD risk and CS (Figure 4A) to visualize the impact and magnitude of evidence for each therapy type. Therapeutics targeting the metabolic, inflammatory, and cholesterol biosynthesis pathways generated the strongest confidence preventing AD. Results of TRAP analyses indicated that three out of five statin drugs were in the top confidence scored drugs (CS > .850) with atorvastatin and pravastatin gaining the highest confidence scores (CS = 0.882 and CS = 0.875) to reduce AD risk, respectively. Ibuprofen and indomethacin resulted in the highest confidence scored anti-inflammatory therapeutics (CS = 0.900). The highest ranked metabolic therapeutic was pioglita-

zone with a CS of 0.923. Although the hormone therapies, estrogen and testosterone had the greatest number of supporting publications (509 and 260, respectively) with 65 and 29 associated with reduced AD risk, the variability of results across publications impacted CS ranking and resulted in a CSs of 0.805 for estradiol and 0.732 for testosterone.

Analysis of drug-target networks for preventive therapeutics resulted in 96 nodes (16 drugs and 80 proteins) and 102 edges (Figure 4B), where on average a drug was associated with six proteins (i.e., average degree of drug nodes = 6).

As expected, therapeutics within the same category shared common targets and pathways of action. For example, all the anti-inflammatory drugs act on inhibition of the genes *PTGS1* and *PTGS2*, components of the COX/inflammatory pathway. Similarly each statin shares a common target, HMGCR, whereas specific statins target pathways unrelated to cholesterol such as HDAC2 and ITGAL.[33] Further, the estrogen receptor ESR1 is targeted by both the estradiol and testosterone hormone therapies. Of note, lisinopril, metformin, and vitamin A are multi-target drugs that do not overlap with other nodes in the network.

4 | DISCUSSION

AD is a major focus of biomedical and clinical research with pharmaceutical and academic groups conducting clinical trials of candidate treatments[34,35] and preventive interventions.[36,37] With the recent failures of large, phase 3 clinical trials[38–41] and the extended timeline for effective treatment development, preventive strategies are of even
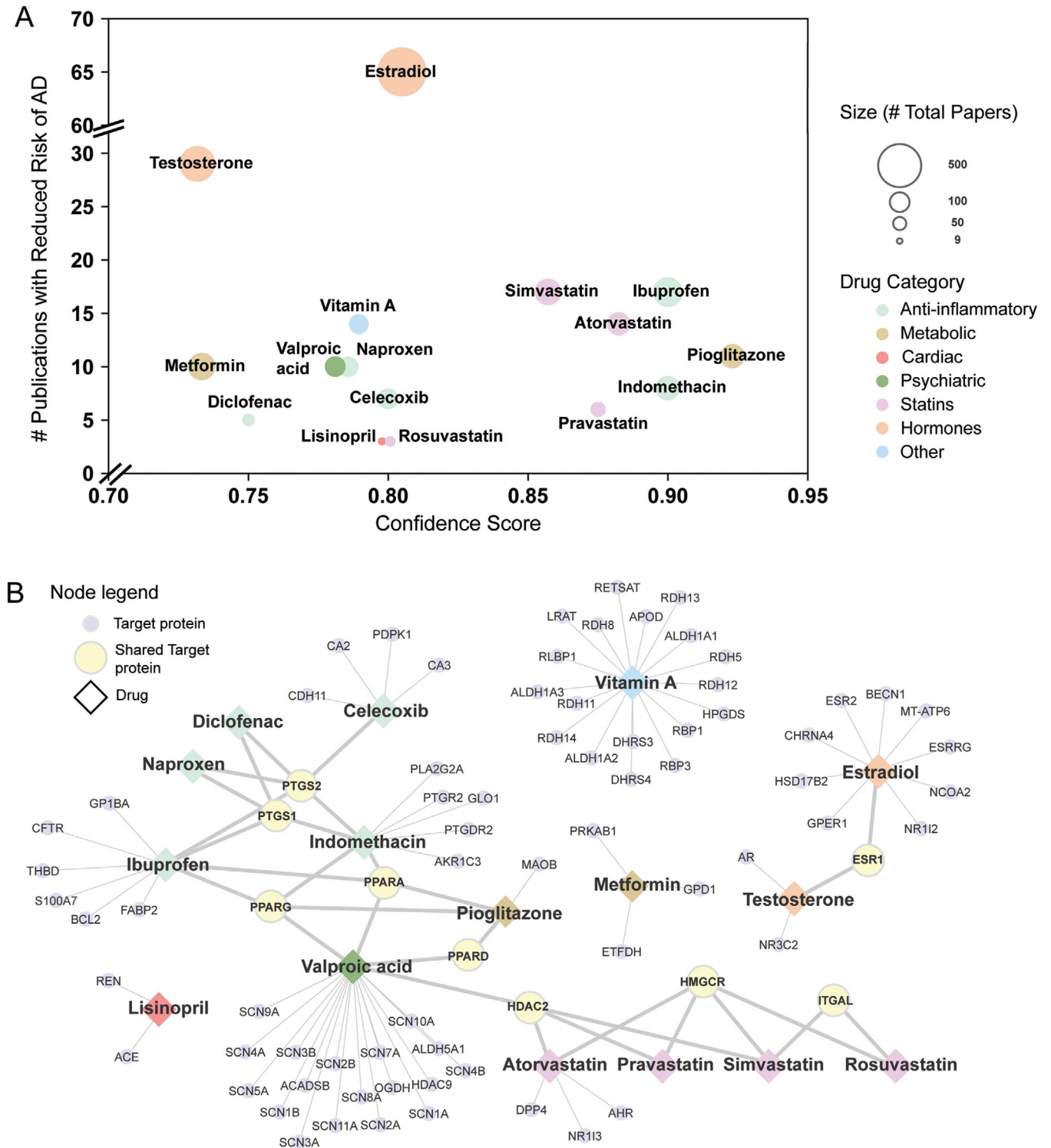
FIGURE 4 Drug reducing Alzheimer's disease (AD) risk supported by clinical studies. A: Bubble plot for confidence score and number of publications with reduced AD risk. Bubble size corresponds to the total number of studies reporting drugs and AD. Bubble color corresponds to the category of therapeutic action. B: Drug-target interaction network for selected drugs. Drugs nodes are colored according to drug category and are shaped with a diamond. Target nodes are shaped with circles and yellow targets represent targets shared by multiple therapeutics. Thicker edges are associated to targets shared by multiple drugs. Abbreviations: AD, Alzheimer's disease; CS, confidence score; RS, relevance score; TRAP, targeted-risk-Alzheimer's disease-prevention

greater importance to reduce the national and global burden of AD. With this understanding, the aim of this study was to analyze the current literature of both clinical and pre-clinical studies to identify therapeutics with high relevance and confidence for reducing risk of AD and achieving the NAPA goal of preventing AD by 2025.

The innovative TRAP approach utilized herein synthesized both clinical and preclinical data to identify therapeutics associated with risk factors and through the generation of relevance and confidence scores determined effectiveness to reduce AD risk. TRAP identified specific drugs associated with prevention of AD within classes of lipid and metabolic regulators, anti-inflammatories, psychiatric, and hormone therapies. Expanding upon a recent scoping review[42] that provided broad drug classes that were associated with AD prevention, TRAP identified specific drugs that target AD risk factors coupled with rankings based on relevance and confidence. The selectivity of the TRAP approach for identifying preventive therapeutics is underscored by the detection and subsequent elimination of currently prescribed FDA-approved AD medications (e.g., donepezil, galantamine, rivastigmine, memantine, and idebenone). Importantly, 16 ($\approx$35%) of the 46 promising preventive therapeutics had at least one clinical study supporting its efficacy in AD prevention.

The TRAP strategy relies on the premise that a risk factor is targetable with a specific drug class, whereas AD has a multiplicity of targets resulting from activation of multiple pathways during progression of the disease.[30,43,44] Thus, single-target therapies effective in reducing risk of AD will not necessarily be effective for treatment for AD.[45,46] However, combination therapies tailored to the cascade of risk factors still hold potential. Because risk factor biology is linked to the pathophysiology of AD, combination therapy that targets the preclinical risk factor profile could provide a combinatorial strategy to treat AD. From this analysis, the most impactful risk factors that target biological mechanisms and pathways underlying AD risk include the metabolic, immune, cardiovascular, and endocrine systems.[9,33,47–50]

The analysis of a drug-target interaction network revealed different biological networks of drug action (Figure 4B). On average, identified preventive therapeutics target six proteins, which indicates the efficacy multi-target profile required for AD prevention likely due to the multi-system biology contributing to AD.

The network analysis indicated that while drugs of the same class share targets, drugs belonging to different categories can share the same pathways of actions. For example, all the anti-inflammatory drugs act on proliferator-activated receptor (PPAR) family genes as well as pioglitazone (a drug used to control high blood sugar in patients with type 2 diabetes) and valproic acid (a drug primarily used to treat epilepsy and bipolar disorder). The gene *PPARG*, implicated in the pathology of several diseases including obesity, diabetes, and atherosclerosis, is targeted by anti-inflammatory, metabolic, and psychiatric drugs. Interestingly, valproic acid acts on the gene *HDAC2*, which is also a statin target. Valproic acid is the only therapeutic sharing targets with three different drug categories (anti-inflammatory drugs, statins, and metabolic drugs) and may explain the neuroprotective effect of valproic acid in combination with estrogen.[51]

In contrast, the drug-target network also specified drugs within a class that targeted unique proteins. These findings indicate drugs within a common class also have unique targets. For example, indomethacin is the only anti-inflammatory drug that inhibits *PTGR2*, a gene encoding an enzyme involved in the metabolism of prostaglandins; *GLO1*, a gene associated with hyperglycemia; and *AKR1C3*, a gene encoding enzymes catalyzing the conversion of aldehydes and ketones to their corresponding alcohols by utilizing NADH and/or NADPH as cofactors. Another example is ibuprofen, which specifically acts on *FABP*, a gene known to play a role in the intracellular transport of long-chain fatty acids; thrombomodulin (*THBG*), a gene known to be the cause of thromboembolic disease; and *BCL2*, which encodes an integral outer mitochondrial membrane protein that blocks apoptotic cell death.

The common versus drug-specific pathways of actions warrant further investigation for three main reasons. First, the efficacy of drugs within the same category could vary in preventing AD.[33,50] Second, to achieve a precision and personalized preventive medicine some drugs could be more effective in specific phenotypic and genotypic subpopulations. Third, given the superior efficacy that could be achieved with a poly-pharmacological approach, system biology analyses are required to gain insights into biological pathways and to achieve predictive validity of combinatorial therapeutics.

Limitations include the analysis of studies without accounting for sample sizes, which limit the ability to draw conclusions about large mixed populations. Additionally, reports highlighting drug classes instead of individual drugs were not included in the analysis. TRAP analysis did not identify any therapeutics passing the TRAP thresholding system that indicated elevated AD risk. This underscores both (1) the lack of drug studies conducted to assess increased AD risk, and (2) the lack of a common and well-defined language to report studies with a negative finding. As expected, most published studies were designed to assess a therapeutic effect on reducing AD risk rather than increasing risk. An important aspect that is not included in the TRAP calculation is the inclusion of demographic data (age, sex, ethnicity, genotype, disease stage, socioeconomic status) to stratify efficacy of each therapeutic for AD prevention in a given population. However, future studies will investigate preventative therapeutic efficacy based on the above factors that could advance precision therapeutic approaches for prevention and delay of AD. To this end, our current pipeline can be modified and extended to incorporate precision medicine publications to stratify the TRAP analytic approach based on demographic factors.

To our knowledge, this is the first analysis of currently available literature to explore and rank specific therapeutics for AD prevention with a computational pipeline that provides a curated list of the most promising candidate drugs. The TRAP pipeline is composed of two novel scoring strategies, a Relevance and a Confidence Score. First, to select drugs for study analysis, we developed a RS to assign points to a single drug-associated publication that evaluates drug-AD relationships through text-mining. Second, we developed a CS to rank and quantify the impact of drugs on AD risk prevention. This relies on a Bayesian statistic to assign a score capturing the magnitude of reduced or elevated AD risk across all publications for drugs passing relevance

thresholding. The TRAP strategy identifies relevant risk factors for AD and supports therapeutic targeting of biological mechanisms and pathways underlying AD risk factors. Incorporation of therapeutics that reduce risk of AD into clinical care decision-making could impact the course of disease. Outcomes of our analyses indicate early interventions that target pathways associated with increased risk of AD support the goal of effectively preventing AD by 2025.

CONFLICTS OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.