PREVENTION AND REVERSAL OF ALZHEIMER'S DISEASE

by

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PREFACE

Why did we write this monograph, what are its contents, what is new, who is the intended audience, and how will readers benefit from it?

Motivation

Non-communicable diseases have overtaken communicable diseases as the leading cause of global mortality. There are myriad reasons for this trend. As this monograph shows, the main reasons center around the implementation and inadequate regulation of modern technology in our economy.

Far more attention is given to "treatment" of these diseases than to prevention. Discovery of new treatments for serious diseases, while both interesting and challenging, is presently insufficient to reverse or eliminate most non-communicable diseases. Eliminating the actionable foundational causes of these diseases is at least as important as applying new treatments, if there is to be any hope for full or partial reversal of non-communicable diseases.

Toward that end, the first author developed a holistic medical principle that would form the bedrock of a healing protocol for diseases: ***At the present time, removal of cause is a necessary, but not necessarily sufficient, condition for restorative treatment to be effective*** (where "removal" encompasses "neutralization" in those cases where actual "removal" is not possible, and "restoration" encompasses restoration of health to the organ/tissue as well as restoration of function). To prevent disease, the actionable foundational causes that underlie the disease symptoms need to be identified and removed as comprehensively, thoroughly, and rapidly as possible. To reverse disease (if irreversible damage has not been done and genetic predisposition is not a dominant factor), the preventive steps above need to be implemented as well. If the preventive protocols are inadequate for reversing disease progression, they need to be augmented by treatments. The first step in either disease prevention or reversal is to identify the full spectrum of potential foundational causes, or contributing factors, for the disease(s) of interest.

It also became evident that much of the information required to identify and eliminate these foundational causes of disease ***is in the literature already***, but is not being extracted and exploited adequately. There is little financial incentive for much of the researcher and clinician community to focus on eliminating causes relative to instituting new treatments. Additionally, the biomedical literatures for diseases such as Alzheimer's Disease (AD) are large, and extracting these AD foundational causes comprehensively from the literatures is a complex text mining problem.

About five years ago, the first author started a series of proof-of-principle demonstrations to show that foundational causes (and treatments) could be identified comprehensively and efficiently for single diseases using a novel text mining approach. The initial application focused on preventing and treating chronic kidney disease (CKD). The next application broadened the perspective by identifying potential contributing factors to ~4000 diseases that had a threshold level of commonality; i.e., those contributing factors/causes that could be viewed as "pervasive". The book that resulted from this comprehensive study provided insights not possible from examining one disease only.

Based on the insights and lessons learned from these two initial studies, it was decided to initiate a larger detailed study on a single disease. AD was selected because of 1) its debilitating nature, 2) projected increased prevalence due to an aging population, and 3) potentially increased future incidence because of the poorly regulated introduction of new technologies that have exhibited adverse effects on some AD surrogate endpoints. The study focusing on identifying potential AD foundational contributing factors is the subject of the present monograph. A monograph was selected as the communication vehicle

rather than a series of journal papers, since separate journal publications would have fragmented the text mining and biomedical results, and would have greatly decremented the value of an integrated interdisciplinary presentation. Producing a monograph allowed a full exposition and integration of the study's results and conclusions, not constrained by journal limitations.

Contents

The overall theme of this monograph is preventing and reversing AD based on the following holistic medical principle: ***At the present time, removal of cause is a necessary, but not necessarily sufficient, condition for restorative treatment to be effective***. The specific focus of this monograph is identifying, categorizing, and analyzing the foundational (tangible actionable) causes of AD, allowing these actionable causes to then be eliminated.

These AD foundational causes are based on analysis of many thousands of biomedical journal articles from the premier medical literature. The AD foundational causes are categorized and analyzed by discipline, as well as by the underlying main sources of these causes.

There is a lengthy section describing the text mining/information technology advances that allowed the AD foundational causes to be extracted efficiently from the large numbers of biomedical journal articles retrieved.

Novelty

While the individual direct AD foundational causes identified in this monograph are "known", in the sense that they exist scattered throughout the published literature, they have not been integrated previously to the extent they are integrated in this monograph. The new "insights" in this monograph are:

1) the sheer number of AD potential foundational causes that are possible;

2) the sheer number of potential foundational causes that have to be eliminated for any person to prevent or reverse AD (assuming irreversible damage has not been done or overwhelming genetic predisposition is not operable);

3) the sheer number of potential combinations of AD foundational causes that have to be identified and researched (many of whose individual components have not yet been identified); and

4) the depth to which each potential AD foundational cause must be eliminated for AD prevention or reversal to occur.

Most papers addressing chronic disease take the form: here's a symptom(s); here's what my drug can do to suppress that symptom(s); and here are some of the other symptoms that can arise as a result of my drug. They are using a 22-caliber handgun for a problem that requires a howitzer!

Audience

There are two communities to whom this monograph is targeted. First is the "AD prevention and reversal" community. This encompasses the public health community, the AD research community, medical practitioners involved clinically with AD prevention and reversal, and individuals interested in what the present approach has to offer (they should heed the warnings in the Disclaimer). The AD foundational cause taxonomies and discussions in Chapters 3 and 8 should be of particular interest to this community.

Second is the text mining and information technology community. This would cover the full spectrum of researchers interested in extraction of useful information from any type of text, since the techniques developed in this monograph can be readily adapted to extracting useful information from myriad types of text. The concepts, algorithms, and discussions in Chapters 2 and 7 should be of special interest to this community.

Benefits

The interested reader will gain a deeper understanding of the main causative factors that drive AD, and will also gain an understanding of the broad spectrum of rigorous actions required to prevent and/or reverse AD. The reader will be able to see why there are no "magic bullets" to prevent or reverse AD, and will be able to understand why motivation, discipline, and hard work are required to achieve, or regain, good health. Finally, the motivated reader will see that much of what is required to reverse AD may potentially ***be available in the here and now***, for selected individuals!

Ronald N. Kostoff, 15 April 2017, Gainesville, VA

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EXECUTIVE SUMMARY

ES-1. Overview

Recent small-scale clinical results by Dr. Dale Bredesen (UCLA) have shown that reversal of cognitive decline in patients with early Alzheimer's Disease (AD) or its precursors, MCI (mild cognitive impairment) and SCI (subjective cognitive impairment), is obtainable today [1, 2]. These results were generated by 1) eliminating a modest number of actionable foundational causes/contributing factors (tangible causes over which one has some control, such as poor diet, lack of exercise, use of recreational drugs, etc) in selected patients, 2) increasing health-promoting practices (e.g., adequate sleep, adequate exercise, stress-reduction practices, etc), and 3) providing myriad supplements to bring selected metabolic parameters into targeted ranges [1, 2].

His approach is founded on the assumptions that AD/dementia symptoms 1) are driven mainly by external factors, and 2) can be prevented/reversed by elimination of these external factors (excluding those cases where genetic deficiencies are overwhelming or irreversible damage has been done), possibly supplemented by other therapies. If assumptions 1 and 2 are correct, then the *effectiveness of this approach will be limited by the comprehensiveness of external factors that have been identified, addressed, and eliminated*.

Our goal is to overcome these limitations by identifying as many of these external factors as possible. Towards that end, we have developed a novel information technology approach that selects those biomedical literature articles identifying potential AD/dementia foundational contributing factors. The approach is based on the following holistic medical principle: ***At the present time, removal of cause is a necessary, but not necessarily sufficient, condition for restorative treatment to be effective***.

To prevent AD (or any chronic disease), the foundational causes that underlie the AD symptoms need to be identified and removed as comprehensively, thoroughly, and rapidly as possible. To reverse AD (if irreversible damage has not been done and strong genetic predisposition is not a dominant factor), the preventive steps above need to be implemented, and treatments to reverse AD progression (if necessary) need to be applied.

The first step in either AD prevention or reversal protocols is to identify the full spectrum of potential foundational causes (or contributing factors) for AD. These contributions are either direct (the biomedical literature source article states the factor(s) contributes to AD/dementia) or indirect (the theme of the biomedical literature source article is AD/dementia, and the article states the factor(s) contributes to a surrogate endpoint of AD/dementia (e.g., tau hyperphosphorylation, neurofibrillary tangles, cognitive decline, amyloid-beta peptide (Abeta) generation)).

ES-2. General Results

We have applied our novel methodology to the Medline database, and identified ~400-600 potential contributing factors (the exact number depending on how these contributing factors are aggregated) to AD/dementia. This represents an order of magnitude more AD potential actionable contributing factors than we have seen in any AD/dementia article in the published literature. We have generated a hierarchical taxonomy consisting of five broad categories at the top level (Lifestyle, Iatrogenic, Biotoxic, Occupational/Environmental, Psychosocial/Socioeconomic) to categorize these potential AD foundational causes. These categories and their sub-categories cover a far wider range of potential AD causes than those used by Bredesen in his study, or any other published study related to potential AD contributing factors. We have also shown the linkages between AD contributing factors and

their impacts on four discrete areas relevant to the disease: 1) cellular-level mechanisms; 2) biomarkers; 3) performance; and 4) AD precursor diseases.

Because of potential synergies among these myriad factors, we believe as many potential AD contributing factors as possible (applicable to any individual) must be eliminated as thoroughly and rapidly as possible in order to achieve maximal results. We do not exclude supplements or drug (or other) therapies in conjunction with comprehensive potential AD cause elimination. We hypothesize that the need for these other therapies may be reduced, or perhaps even eliminated, if comprehensive potential AD cause elimination is successful. In other words, we do not exclude the possibility that the metabolic deficiencies addressed by Bredesen through providing supplements could be reduced or eliminated by removing a wider range of potential AD contributing factors!

ES-3. Specific Results

A. **Lifestyle** AD contributing factors include:

-excessive fat, salt, sugar, refined carbohydrates, calories, and meat, along with high temperature cooking;

-deficient vitamin and mineral-laden fruits, vegetables, and fatty fish;

-sedentary lifestyle and cognitive inactivity;

-inadequate sleep;

-substance abuse (cocaine, amphetamines/MDMA, phencyclidine, opioids, excessive smoking and alcohol).

B. **Iatrogenic** AD contributing factors include: drug side-effects, radiotherapy side effects, surgical complications, and diagnostics side-effects.

Drugs that produce AD-related side-effects include: anti-neoplastic agents, cardiovascular agents, the massive category of central nervous system agents, hematologic agents, steroids/hormones, antihypertensive agents, and gastrointestinal agents.

Radiotherapy involving the brain region was a contributing factor to cognition problems and AD.

Surgeries that produce AD-related side-effects tend to involve vessel occlusion, cerebral ischemia, broader cardiac surgery, estrogen depletion, and myriad forms of dialysis. Since inhalation anesthesia seems to be a strong AD contributing factor, almost any major surgery employing this type of anesthesia would have to involve some potential risk for AD.

Diagnostics that could have been assigned to this category were placed in other more phenomenon-based categories; e.g., dental x-rays were placed under Radiation, and other diagnostic procedures requiring sedation were placed under Anesthetics. More broadly, reference [3] implies that people who experience high doses of ionizing radiation to the brain (such as from CT scans in that general region) can end up with cognitive dysfunction.

C. **Biotoxic** contributing factors reflect mainly the biological substances to which we are exposed naturally, but sometimes accidentally, and sometimes by design. This category is divided into five sub-categories: Mycotoxins; Exotoxins; Bacteria/Fungi/Parasites; Viruses; Other. Biotoxins contributing to AD include:

-some mycotoxins (e.g., ochratoxin A, Fumonisin B1, macrocyclic trichothecenes, etc);

-many exotoxins (e.g., excitotoxins, phosphatase inhibitors, excitatory amino acids, cyanobacteria, saporins, mitochondrial inhibitors);

-large numbers of bacteria, fungi, and parasites;

-large numbers of viruses;

-plant-based contributing factors (e.g., 12-myristate 13-acetate, Forskolin, arecoline hydrobromide, quisqualate, etc);

-a very substantial number of endogenous substances that were administered exogenously (e.g., 27-hydroxycholesterol, acetylcholinesterase, Bradykinin, CD40, etc).

D. **Occupational/Environmental** contributing factors include:

-Industrial and Household Chemicals

--hydrocarbons (e.g. methylcholanthrene, polycyclic aromatic hydrocarbons, diesel fuel, kerosene, etc,);

--solvents (e.g. petroleum-based solvents, chlorinated solvents, organic solvents, etc);

--many other chemicals that emphasize chlorine, bromine, nitrogen, sodium, sulfur, and carbon compounds.

-Materials

--heavy metals (e.g., aluminum, arsenic, cadmium, cobalt, copper, iron, lead, manganese, mercury, selenium, zinc, manganese, etc);

--particulates (e.g., air pollution, surgical smoke, dust, etc);

--nanoparticles (e.g., iron nanoparticles, titanium dioxide nanoparticles, CdSe quantum dots, diesel exhaust nanoparticles, alumina nanoparticles, manganese oxide nanoparticles, copper nanoparticles, silicon dioxide nanoparticles, zinc oxide nanoparticles, silver nanoparticles, and nickel nanoparticles, etc).

-Agricultural Chemicals

--pesticides/herbicides/insecticides (e.g. Organochlorine Pesticides, Organophosphate Pesticides, 2,4,5-trichlorophenoxyacetic acid, 2,4-Dichlorophenoxyacetic Acid, Agent Orange, Aldrin, Alkylphenolpolyethoxylates, APEOs, Arsenic, Beta-hexachlorocyclohexane/beta-HCH, Bipyridyles, Carbamates, Carbofuran, Chlorfenvinphos, Chlorpyrifos/CPF, Cycloheximide, Cypermethrin, Deltamethrin, Dichlorodiphenyldichloroethylene/DDE, Dichlorodiphenyltrichloroethane/DDT, Dichlorodiphenyldichloroethane/DDD, Dieldrin, Dimethyl parathion, Endosulfan, Famoxadone, Fenamidone, Glyphosate, Hexachlorobenzene, Hexachlorocyclohexane/HCH, Imidacloprid, Lindane, Maneb, Methamidophos, Methyl parathion, Neonicotinoids, Nonylphenol, Octylphenol, Paraquat, Parathion, Pyraclostrobin, Pyrethroids, Trans-nonachlor, Trichlorfon/TCF, Trifloxystrobin, etc).

-Electromagnetic Radiation

--ionizing (e.g., gamma radiation (dental X-rays, gamma rays, etc), particle radiation (56Fe-particle radiation, cosmic radiation, HZE particle radiation), radionuclide pollutants (uranium, cesium, cobalt, radon), etc);

--non-ionizing non-visible (e.g., electromagnetic fields at myriad frequencies, such as extremely low frequency/ELF-EMF, 900 MHz radiofrequency (RF), electromagnetic pulse/EMP, electroconvulsive shock/ECS, UV irradiation, etc);

--non-ionizing visible (UV irradiation, photolysis of 1-(2-nitrophenyl)ethyl sulfate, etc).

-Sound (e.g. short-lasting impulse noise, chronic noise exposure, night-time aircraft noise, ultrasound sonication, etc).

-Temperature (e.g. cold water hypothermia, cold water stress, heat shock, heat stress, heating, hyperthermia, etc.).

-Force (e.g. blasts, blast traumatic brain injury, hippocampal injury, accumulated mechanical stress, spinal cord injury, frequent strong Valsalva maneuvers, long hours of repetitive heavy lifting, sequences of blows during the playing of a wind instrument, forceful and repetitive cough, bearing-down efforts during parturition, history of head trauma, etc).

E. **Psychosocial/Socioeconomic** contributing factors include:

-Psychological

--chronic stress (e.g., repeated stress, chronic mild stress, chronic psychological stress, multiple chronic stresses, behavioral stress, childhood trauma, bereavement, chronic restraint stress, high job stress, etc);

--low mental activity (e.g., low cognitively engaging activity, low purposeful activities, low leisure activities/low hobbies, low music/drawing/meditation, low reading/arts/crafts, etc).

-Sociological

--social isolation (e.g., isolation, loneliness, living alone, unmarried, maternal separation, low social activity index, low social support at work, constricted life space, etc);

--low education (e.g., illiteracy, etc).

Genetic causes were not addressed in this monograph. The main focus of the monograph is on potential AD foundational causes that are somewhat actionable (action could, at least in theory, be taken to attenuate, neutralize, or eliminate them). It is difficult to modify a person's genetic endowment presently, although that may not be true in the future. Genetic manipulation is in its infancy, and may some day be the treatment of choice for genetically-based diseases.

ES-4. Underlying Sources of AD Foundational Causes

There appear to be five main underlying sources of the ~400-600 potential AD foundational causes: Direct Technology, Indirect Technology, Inadequate Regulation, Individual Choice, Poverty.

A. Direct Technology (the degree of direct impact of technology on the foundational cause) plays a strong role in Lifestyle, Iatrogenic, and Occupational/ Environmental AD foundational causes. In addition, through its impact on the immune and other critical systems, modern technology may play a role

in whether exposure to bacteria and viruses results in AD and its associated symptoms. Modern technology impacts the growing, processing, and preparation of foods, and many of the adverse effects identified in the present study can be traced back to the use (misuse) of technology in the food cycle. The Iatrogenic adverse effects of modern technology result mainly from the high-technology-based drugs, surgery, diagnostics, and therapy that characterize much of modern medicine today. The Occupational/ Environmental adverse effects result mainly from the employment of modern technology in 1) commerce, 2) the environment, and 3) the workplace.

B. Indirect Technology reflects those adverse health-impacting behaviors enabled by Direct Technology. One example is reduced labor because of modern technology, leading to today's highly damaging sedentary lifestyle that contributes to myriad diseases, including AD. Another example is large numbers of people being able to live in inhospitable northern climates because of modern transportation, food logistics, clothing, and shelter. This results in less exposure to sunlight and less Vitamin D production, contributing to diseases (such as AD) related in part to Vitamin D deficiency.

C. Inadequate Regulation is coupled strongly to the introduction of high technology in all aspects of life. Many of the problems with foods derive from relatively unregulated chemicals, materials, and other contaminants entering the food supply during agriculture and animal husbandry. Many of the Occupational/Environmental exposures arise from relatively unregulated harmful substances entering the workplace and the environment, especially in less developed countries, but in more developed countries as well. Many of the Iatrogenic problems could be traced to drugs, diagnostics, therapies, and other procedures entering practice with insufficient front-end long-term testing, and inadequate evaluation of side-effects.

Two major aspects of Inadequate Regulation revolve around insufficient safety: inadequate safety data gathering, and inadequate safety testing. Much of the adverse impact data gathering tends to be from passive surveillance systems, where response rates can be an order of magnitude (or more) less than real-world incidence rates. Pre-market testing, in many cases, suffers from inadequate sample sizes, unrepresentative samples, insufficient long-term testing, and insufficient combination testing to identify potential synergistic effects. Insufficient long-term testing on humans is particularly troubling, since many serious diseases such as AD may have decadal latency periods from specific toxic stimuli. Transgenerational effects cannot be excluded without appropriate long-term testing. Additionally, results from animal testing (which could be long-term from the perspective of many short-lived animals used in testing) do not necessarily translate to human outcomes.

D. Individual Choice reflects decisions by people to choose unhealthy diets, sedentary activities, recreational drugs, elective drugs and surgery, unhealthy occupations, unhealthy residential environments, unhealthy relationships, etc. There is the unwritten corollary assumption that people have adequate knowledge about the consequences of these choices, and there are no other major factors that limit their choices. For many people, this is a highly unrealistic assumption. They have very limited knowledge about the consequences of these choices, either through

1) accurate information not being available, or

2) apathy in searching out this information, or, as implied in [4, 5],

3) being provided incorrect information.

E. Poverty limits individual choices about diet, occupations, and environment. Poverty plays strong direct and indirect roles in malnutrition and the resulting diseases of deficiency. By limiting access

to modern medicine and modern technology, poverty avoids some of the adverse impacts ascribed to modern technology presented above, but at the same time, denies many of the benefits available from modern medicine and modern technology.

ES-5. Near-Term Implementation of Findings

To gain operational experience with exploiting the findings in this monograph, clinical trials should be started in the near future. Given the limitations in knowing exposures to many potential AD contributing factors outlined above, these trials could start with incorporating the "low-hanging fruit" contributing factors that have been identified in the present study. These are potential AD contributing factors that could be estimated or measured relatively easily. Initial elimination of these contributing factors would include:

1) curbing the dietary excesses identified and removing the dietary deficiencies identified:

-reducing the amounts of fat, salt, sugar, refined carbohydrates, calories, and meat strongly, along with reducing high cooking temperatures;

-increasing the amounts of vitamin and mineral-laden fruits, vegetables, and fatty fish substantially, along with increasing sun exposure for enhanced Vitamin D;

2) eliminating food additives to the extent knowable and possible, including those dietary excesses that derive from food additives (excessive fat, sugar, salt);

3) reversing the sedentary behavior patterns identified, and increasing physical and mental activity;

4) removing the foundational impediments to better sleep;

5) eliminating the use of "recreational" drugs, including smoking and excessive alcohol;

6) eliminating the use of elective (not absolutely necessary) medicinal drugs shown to be potential AD contributing factors;

7) eliminating any elective (not absolutely necessary) diagnostic or surgical procedures that involve inhalational anesthetics or high doses of ionizing radiation in head region (e.g., CT scans);

8) minimizing exposures to some hydrocarbons such as diesel exhaust, kerosene, polycyclic aromatic hydrocarbons (including those found in smoke), etc;

9) minimizing exposures to some solvents, especially petroleum-based solvents, chlorinated solvents, and organic solvents;

10) minimizing exposures to pesticides, herbicides, insecticides, and fungicides, both inhalation and ingestion exposures;

11) minimizing exposures to heavy metals in food, water, and air;

12) minimizing exposures to particulates, especially air pollution;

13) minimizing exposures to ionizing radiation, non-ionizing non-visible radiation (e.g., cell phones, cell towers, WiFi, smart meters, etc), non-ionizing visible radiation (e.g., excessive UV radiation), sound

radiation (e.g., high noise levels), extreme temperature fields (e.g., cold water hypothermia/stress, heat shock/hyperthermia), and extreme force fields (e.g., high impacts, especially to head region);

14) minimizing chronic stress (mental/emotional/psychological), increasing mental and meaningful leisure-time activities;

15) minimizing social isolation.

ES-6. References - Executive Summary

[1] Bredesen DE. Reversal of cognitive decline: A novel therapeutic program. Aging. 2014;6(9):707-17.

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[4] Kostoff RN. Pervasive Causes of Disease. Georgia Institute of Technology. 2015. PDF. http://hdl.handle.net/1853/53714

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Chapter 1

INTRODUCTION

1A. Overview

Alzheimer's Disease (AD) is a brain disease, and the most common form of dementia. Currently, it affects those 65 years old and above overwhelmingly; incidence increases with age. The prevalence of AD in the USA was approximately 4.7 million people in 2010, and is projected to increase to 5.8 million in 2020, 8.4 million in 2030, and 11.6 million in 2040 [1].

These projections may be strong under-estimates. AD has an environmental component, and there have been many high-technology additions to the environment in the past few decades (e.g., wireless radiation, vaccines, agricultural chemicals, etc, have expanded greatly). Because of latency delays, inadequate time has elapsed to show linkages between these environmental additions and changes in the incidence of AD in human populations. As will be shown in the present study, the impact of, e.g., recent environmental and dietary additions on AD surrogate endpoints offers the possibility of extrapolation to increased incidence and prevalence of AD in the future.

The mainstream medical approach to treating AD has been centered around drug therapy mainly. How effective has it been? Bredesen states: "In the case of Alzheimer's disease, there is not a single therapeutic that exerts anything beyond a marginal, un-sustained symptomatic effect, with little or no effect on disease progression. Furthermore, in the past decade alone, hundreds of clinical trials have been conducted for AD, at an aggregate cost of billions of dollars, without success. This has led some to question whether the approach taken to drug development for AD is an optimal one [2]." Bredesen is an AD researcher who has shown that "reversal of cognitive decline in patients with early Alzheimer's disease or its precursors, MCI (mild cognitive impairment) and SCI (subjective cognitive impairment)" is obtainable today [2]. Basing his approach on optimizing metabolic parameters, Bredesen used a combination of 1) eliminating potential AD contributing factors, 2) substituting positive health practices, and 3) adding dietary supplements to achieve his AD/MCI/SCI reversal results.

His approach can be viewed as one "footprint" of a more general holistic medical principle for preventing or reversing disease developed by the first author over the time period 2012-2017: ***At the present time, removal of cause is a necessary, but not necessarily sufficient, condition for restorative treatment of disease to be effective***. To prevent AD, or any disease, the foundational causes that underlie the disease symptoms need to be identified and removed as comprehensively, thoroughly, and rapidly as possible. To reverse AD (if irreversible damage has not been done and strong genetic predisposition is not a dominant factor), the preventive steps above need to be implemented, and treatments to reverse progression (if necessary) need to be applied. The first step in both AD prevention and reversal protocols is to identify the full spectrum of potential AD foundational causes/contributing factors. The remainder of the monograph takes this first step, and addresses the full spectrum of AD actionable contributing factors.

1B. Structure of Monograph

Chapter 6 contains the Background for the present study. Chapter 2 presents a summary of the methodology used to obtain the results; the detailed methodology can be found in Chapter 7. Chapter 3 presents a summary of the findings; the detailed findings can be found in Chapter 8. Chapter 4 presents the discussion and conclusions, and Chapter 5 contains suggested further research. Chapter 9 presents the most highly cited AD/dementia papers, and implications of the patterns in those papers. The references for each chapter will be presented at the end of each chapter.

1C. References - Chapter 1

[1] Alzheimer's Association. 2016 Alzheimer's Disease Facts And Figures. http://www.alz.org/documents_custom/2016-facts-and-figures.pdf.

[2] Bredesen DE. Reversal of cognitive decline: A novel therapeutic program. Aging. 2014;6(9):707-17.

Chapter 2

SUMMARY METHODOLOGY

2A. Overview

The methodology employed in this monograph identifies actionable foundational causes (tangible items over which we have some control, such as smoking, food additives, pesticides, etc) linked directly to AD, or indirectly through surrogate endpoints for AD (*surrogate endpoints are early/intermediate markers thought to predict longer-term clinical benefit, and are used by the FDA to accelerate drug approval* [1]).

Why is the surrogate endpoint concept used as part of the present study? Direct links between potential contributing factors and AD are established through satisfying conditions such as Koch's Postulates, Bradford Hill criteria, or other causation criteria. However, for diseases that emerge late in life, such as AD, linking potential causes/contributing factors to the disease directly could require many decades to validate potential causes that occur early in life. Therefore, to avoid the enhanced risk of populations being exposed to potentially harmful substances for many decades while waiting for definitive links between the potential causes and AD to be demonstrated, identifying links between the potentially harmful substances and shorter-term/intermediate markers of AD (surrogate endpoints) could lead to precautionary risk mitigation.

2B. Approach

Two overlapping approaches were used to identify potential AD contributing factors. First, a complex query (see Chapter 7 for full query) focused on potential causes linked directly to AD (e.g., "increased risk for AD"), or linked to its surrogate endpoints (e.g., "produced hyperphosphorylated tau", "accelerated neurofibrillary tangles", "caused cognitive decline", "induced amyloid beta", etc), was applied to the ~100,000 Medline articles that had Alzheimer* as a Title or MeSH term. The ~5,000 most recently published articles were read by the first three authors to identify potential AD contributing factors.

Second, cause-related MeSH and text terms (e.g., "exposed", "induced", etc) were generated (see Chapter 7 for these full queries) that would link to MeSH and text representations of potential AD actionable foundational causes in the ~100,000 Medline articles (e.g., "nerve agent *exposure*", "smoking-*induced*"). The potential AD foundational causes ("nerve agent", "smoking") would then be separated from the cause-related linking terms ("*exposure*", *"-induced*"). Both factors that linked directly to AD (e.g., "risk factor for AD") and to surrogate endpoints (e.g., "risk factor for tau hyperphosphorylation") were included. Surrogate endpoints for AD additional to those used in the complex query of the previous paragraph were identified over the course of the study (e.g., "impaired BBB integrity", "induced neurotoxicity", "produced cholinergic hypofunction and tissue lesions"), and could be useful for future studies of this type.

2C. References - Chapter 2

[1] Accelerated Approval. US FDA. 2014.
http://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm.

Chapter 3

SUMMARY RESULTS

3A. Overview

A hierarchical taxonomy consisting of six broad categories at the top level (Lifestyle, Iatrogenic, Biotoxic, Occupational/Environmental, Psychosocial/Socioeconomic, and Genetics) was generated to categorize the potential AD foundational causes. Contents of the first five categories will be summarized in the present chapter, and will be analyzed in more detail in Chapter 8.

AD genetic causes were not addressed in the findings because the main focus of this monograph is on AD foundational causes that are (by definition) somewhat actionable (action could, at least in theory, be taken to attenuate, neutralize, or eliminate these types of causes). It is difficult to modify a person's genetic endowment at the present time, although that may not be true in the future. Genetic manipulation is in its infancy, and may someday be the treatment of choice for genetically-based diseases.

The Psychosocial/Socioeconomic top-level category has reasonable overlap with the Lifestyle category. It has two major components: "causes" over which the individual has some control and are therefore "actionable" (e.g., low hobby time, low reading time, low music time, unmarried, urban living, etc), and causes over which the individual has little, if any, control (e.g., bereavement, early life stress, chronic unpredictable stress, etc). A potential AD cause like "high job strain" could be in either category. It is Lifestyle to the extent that the job is an individual choice, and one could always leave. But, that line of reasoning could be extended to other categories. Many of the Iatrogenic adverse effects result from one's choosing to 1) take drugs electively or 2) undergo certain types of elective surgeries. They could be categorized Lifestyle as well. It was decided to treat Psychosocial/Socioeconomic as a separate category.

3B. Under-Reporting of AD Foundational Causes

Chapter 9 of reference [1], and reference [2], contain many caveats showing why the numbers of AD foundational causes presented here may be vast under-representations of the numbers of AD operational foundational causes. Summarily, many adverse events are not reported and published in the literature (e.g., see references 70-125 of reference [1]), or, if they are reported and published, many are not accessed due to inadequate search algorithms. The under-reporting occurs at the patient, doctor, researcher, journal, corporate, and Federal agency levels, mainly because of myriad incentives (and few disincentives) for under-reporting. See Chapter 9 of reference [1], or reference [2], for further examples.

Over-reporting cannot be excluded as well. As is also shown in Chapter 9 of reference [1], and reference [2], there are strong publication pressures (especially in academia), and, depending on the nature of the foundational cause, a finding not warranted by the data could be rushed into publication.

3C. Top-Level Taxonomy of AD Foundational Causes

Table 3-1 reflects the top-level categories of the AD foundational causes taxonomy. It is followed by a more detailed description of the contents in each of the categories listed in Table 3-1. The three columns in Table 3-1 reflect categorization by type of foundational cause (Lifestyle, Iatrogenic, Biotoxic Agents, Occupational/Environmental Exposures, Psychosocial/Socioeconomic, and Genetics); category assignments are not unique. The findings in the first five categories will now be summarized by sub-category; more detailed findings, categorizations, and supporting reference links are shown in Chapter 8.

TABLE 3-1 Taxonomy of AD Foundational Causes

CATEGORY	SUB-CATEGORY	SUB-SUB-CATEGORY
I. Lifestyle	I-A. Diet	I-A1. Dietary Excesses
		I-A2. Dietary Deficiencies
		I-A3. Food Additives
	I-B. Activity	
	I-C. Substance Abuse	
II. Iatrogenic	II-A. Drugs	
	II-B. Radiotherapy	
	II-C. Surgery/Invasive Procedures	
	II-D. Diagnostic Agents/Procedures	
III. Biotoxic Agents	III-A. Mycotoxins	
	III-B. Exotoxins	
	III-C. Bacteria/Fungi/Parasites	
	III-D. Viruses	
	III-E. Other	
IV. Occupational/ Environmental Exposures	IV-A. Chemicals/ Materials	IV-A1. Industrial/Household Chemicals/Materials
		IV-A2. Agricultural Chemicals
		IV-A3. Materials
	IV-B. Physical/ Mechanical	IV-B1. Electromagnetic Radiation
		IV-B2. Sound
		IV-B3. Temperature
		IV-B4. Force/Pressure/Physical Trauma
		IV-B5. Other
V. Psychosocial/	V-A. Psychological	
	V-B. Sociological	

Socioeconomic	V-C. Economic
VI. Genetics	VI-A. Polymorphism/Genotypes/Haplotypes
	VI-B. Mutations
	VI-C. Linkages
	VI-D. Risk Alleles
	VI-E. Genotoxicity
	VI-F. Familial
	VI-G. Congenital

I. Lifestyle

Lifestyle includes choices mainly under individual control, and is divided arbitrarily into Diet, Activity, Substance Abuse, Other.

I-A. Diet

Poor diet reflects the adverse effects of excesses and deficiencies of dietary components. It has been used to induce myriad diseases in test animals, and it was a critical disease factor from many epidemiological and case studies.

I-A1. Dietary Excesses

Dietary excesses include high-calories, high-fat, high-sugar, high-salt, high-meet, high-refined carbohydrates, high advanced glycation end products (AGEs); high-cholesterol; high-iron; high arachidonic acid; high methionine; high copper; high zinc; high unfermented soy, and high-temperature cooking that results in harmful products (e.g., AGEs, nitrosamines, polycyclic aromatic hydrocarbons, and acrylamides).

I-A2. Dietary Deficiencies

Many deficiencies listed in the literature may be symptoms of metabolic problems, not foundational causes in the present sense. Thus, a Vitamin A deficiency may be caused by 1) insufficient Vitamin A intake (foundational cause), or 2) a metabolic problem that results in reduced Vitamin A levels (symptom).

Dietary deficiencies include **low**: vitamins, especially Vitamins B (B2, B6, B12, folate/folic acid, thiamine), C, D, E; minerals, especially potassium, iron, zinc, magnesium, calcium, selenium; calories (starvation, malnutrition, early life nutrient restriction); water (dehydration); glucose; glutathione; linoleic acid; docosahexaenoic acid; tryptophan; alcohol (nondrinkers); flavonoids/flavanols (cocoa, coffee, acacetin, aminogenistein, apigenin, kaempferol, 7,8-Dihydroxyflavone, anthocyanins, atriplex laciniata L, curcumin, cyanidin, datiscetin, delphinidin, EGCG, epicatechin, Epimedium brevicornum, fisetin,

genistein, ginkgo, glycitein, icariin, isoscutellarein 7-O-[6'''-O-acetyl-beta-D-allopyranosyl-(12)]-beta-D-glucopyranoside, isovitexin, morin, myricetin, nobiletin, pelargonidin, phloridzin, rutin, salvigenin, Scutellaria baicalensis Georgi, Sideritis flavonoids, vitexin, xanthomicrol, luteolin, morin, PD98059, quercetin, taxifolin, β-naphthoflavone); fruit (blackberries, blueberries, strawberries, raspberries, cherries, oranges, plums, prunes, red grapes, pomegranates, date palm fruits); vegetables, especially cruciferous, dark and green leafy; fatty fish.

A very clear message about the dietary contribution to AD can be extracted from the above picture of dietary excesses and deficiencies. From the macro perspective, the amounts of fat, salt, sugar, refined carbohydrates, calories, and meat need to be reduced strongly, along with cooking at high temperatures, and the amounts of vitamin and mineral-laden fruits, vegetables, and fatty fish need to be increased substantially to reduce the risk of AD and perhaps contribute to reversal of AD.

I-A3. Food Additives

Many food additives are accompanied by adverse effects, and these effects may be under-diagnosed and under-researched. Many of the excesses and deficiencies mentioned above are the result of substances being added to, or removed from, the fresh whole food.

Additives include cysteine, diacetyl, and monosodium glutamate. Depending on how one defines 'food additives', those additives with the widest impacts tend to include the major items listed under excesses above, such as fat, sugar, and salt. These components are typically added to foods for taste enhancement, not nutritional improvement.

I-B. Activity

The main sub-categories of Activity are exercise, sedentary lifestyle, and sleep. The sedentary lifestyle, including low exercise, low physical activity, low daily gardening, low walking, chronic immobilization was mentioned quite often, and cognitive inactivity also received some mention. The resultant low cardiovascular fitness was also emphasized.

Circadian disruption and poor sleep/sleep deprivation were also mentioned, although the main foundational components of poor sleep would be 1) choosing to sleep less or 2) not practicing good sleep-preparation habits. Other contributing factors to poor sleep, such as excessive pain, anxiety, etc, may be less under one's control, and are not regarded as foundational under the present definition.

I-C. Substance Abuse

Substance abuse includes 'recreational' drugs of all types (cocaine, methamphetamine, etc), and especially excessive cigarette smoking and alcohol. The main substance abuse contributing factors were 1) recreational drugs (especially cocaine, amphetamines/3,4-Methylenedioxyamphetamine [MDMA - Ecstacy], phencyclidine, opioids) and 2) excessive smoking and alcohol. The bulk of the studies identified mainly the recreational drugs' contributions to AD surrogate endpoints, such as neurodegeneration markers and cognitive dysfunction.

The individual AD foundational causes identified with Lifestyle are usually studied in isolation, and synergistic effects are typically not identified. Given the number of Lifestyle component combinations that could potentially be synergistic, and adding in

1) the foundational causes from the remaining categories (identified in Table 8-3) to the potential combinations, and

2) potential foundational causes that surface only when operating in synergy but which have not yet been identified in Table 8-3 as individual foundational causes,

it is clear that only the tip of AD foundational causes iceberg is being identified in this study.

II. Iatrogenic

Iatrogenic reflects diseases, symptoms, and injuries resulting from medical treatment, and is divided into four sub-categories: Drugs; Radiotherapy; Surgeries/Invasive Procedures; Diagnostic Agents/Procedures. Iatrogenic is a substantial category, due mainly to the large numbers of drugs and surgeries that have side-effects and complications. The main categories are presented in this section, and more detailed drugs and surgeries are presented in Table 8-3. While the drug categories have some overlap, each drug in Table 8-3 is listed in one category only for purposes of brevity when populating the drug categories,

The more frequently drugs, radiotherapy, surgeries, or diagnostics are used, the more opportunity for side-effects and complications, and the more opportunity for publications describing these side-effects and complications. This study does not provide an indication of how often such side-effects and complications would occur as a percentage of use.

II-A. Drugs

There were eighteen major drug categories identified in Table 8-3. Only those with substantial entries are discussed in Chapter 8, including anti-neoplastic agents, cardiovascular agents, the massive category of central nervous system agents, hematologic agents, steroids/hormones, antihypertensive agents, and gastrointestinal agents.

Table 8-3 does not show the effect of drug-drug combinations, or drug-other toxic agent combinations. The effects of these combinations could be important, but might not surface in some types of studies.

A study on drug-drug combinations concluded that, of approximately 11,000 drug products on the US market, trillions of clinical trials would be required to provide an evidentiary basis of safety for all combinations of ten drugs [3] . Even for all combinations of only three drugs, approximately one million clinical trials would be required to evaluate safety, or lack thereof, for all these possible three drug combinations. These numbers go far beyond what is practical in real-world laboratory, clinical, and field studies.

Thus, there are many ways that 1) a drug shown to contribute to AD or its surrogate endpoints in isolation, when combined with two other drugs not shown to contribute to AD or its surrogate endpoints in isolation, could in aggregate have a much stronger contribution to AD or its surrogate endpoints, and/or 2) three drugs that have been shown to have a modest contribution to AD in isolation, when combined, could in aggregate have a much stronger contribution to AD, and/or 3) three drugs that have been shown to have negligible contribution to AD in isolation, when combined, could in aggregate have a strong contribution to AD. Even if there are small numbers for any one combination of three drugs, when they are aggregated over the one million potential combinations, this could add up to a large number of strong contributions. This effect might not surface in any epidemiological study because 1) it would fall beneath the statistical radar screen, 2) temporal variation in the combinations would be difficult to assess, and 3) the numbers of clinical trials required to assess the impact of drug combinations are astronomical and

would be impractical. For combinations of drugs larger than three, which increase for people as they age [3], the numbers of combinations and clinical trials to demonstrate safety increase rapidly.

II-B. Radiotherapy

Radiotherapy that involved the brain region was a contributing factor to cognition problems and AD.

II-C. Surgery/Invasive Procedures

The sub-categorization for II-C is not unique. Some procedures could be assigned to multiple categories. Surgeries/invasive procedures that contribute to AD tend to involve vessel occlusion, cerebral ischemia, broader cardiac surgery, estrogen depletion, and myriad forms of dialysis. Since inhalation anesthesia seems to be a strong contributing factor, almost any major surgery employing this type of anesthesia would have to involve some potential risk for AD. As in the case of drugs, these absolute numbers of complications from all surgical and invasive procedures must be considered in light of the numbers of procedures performed.

II-D. Diagnostic Agents/Procedures

Items that could have been assigned to this category were placed in other more phenomenon-based categories. For example, dental x-rays were placed under Radiation, and other diagnostic procedures requiring sedation were placed under under Anesthetics. More broadly, people who experience high doses of ionizing radiation to the brain (such as from CT scans in that general region) can end up with cognitive dysfunction [4].

III. Biotoxic Agents

Biotoxic Agents reflect mainly the biological substances to which we are exposed naturally, but sometimes accidentally, and sometimes by design. This category is divided into five sub-categories: Mycotoxins; Exotoxins; Bacteria/Fungi/Parasites; Viruses; Other. Biotoxins contributing to AD include some mycotoxins, but mainly exotoxins, bacteria, and viruses.

III-A. Mycotoxins

Only a few mycotoxins were identified, including ochratoxin A, Fumonisin B1, and macrocyclic trichothecenes.

III-B. Exotoxins

Many exotoxins were identified, including excitotoxins (kainic acid/kainate, quisqualic acid, ibotenic acid, domoic acid, quinolinic acid/quinolinate), phosphatase inhibitors (okadaic acid), excitatory amino acids, malonate, annonaceaeous acetogenins, cyanobacteria (beta-N-methylamino-L-alanine/BMAA, saxitoxin, anatoxin-a, blue-green algae, microcystin), diphtheria toxin, pseudomonas aeruginosa exotoxin Y, saporins (192 IgG-saporin, p75-saporin), cycad plant (cycasin/methylazoxymethanol), glutamate/glutamine synthetase, mitochondrial inhibitors (rotenone, 3-NPA, antimycin, KCN, oligomycin). Some substances in the Other category could have been assigned to the Exotoxin category.

III-C. Bacteria/Fungi/Parasites

Myriad bacteria/fungi/parasites are contained in this sub-category. The bacteria/bacterial infections include bacterial endotoxins, bacterial lipopolysaccharide, gram-negative bacterium, spirochetes, Chlamydophyla pneumoniae, Helicobacter pylori, Escherichia coli, Treponema pallidum, Tannerella forsythia, Treponema denticola, T. socranskii, T. pectinovorum, T. medium, T. amylovorum, T. maltophilum, Fusobacterium nucleatum, Prevotella intermedia, Chlamydia pneumoniae, Porphyromonas gingivalis, propionibacterium acnes, Treponemas, T. lecithinolyticum, and Borrelia burgdorferi. Bacteria are somewhat ubiquitous, so the flexibility of cause removal for items in this sub-category is much less than for items in the Lifestyle and Iatrogenic categories.

The fungi/fungal infections include Cryptococcus, Coccidioides, Aspergillus, Histoplasma, Blastomyces, C. famata, C. parapsilosis, C. glabrata, C. krusei, Candida albicans, Candida ortholopsis, Candida tropicalis, Cladosporium, Malassezia globosa, Malassezia restricta, Neosartorya hiratsukae, Phoma, Sacharomyces cerevisae, and Sclerotinia borealis.

The parasites include Trypanosoma brucei rhodesiense, Trypanosoma brucei gambiense, Acanthamoeba, Balamuthia mandrillaris, Toxoplasma gondii, Taenia solium, Toxocara canis, T. cati, Toxocara ova, and Leishmania amazonensis.

III-D. Viruses

Myriad viruses are contained in this sub-category, and are shown in detail in Chapter 8.

III-E. Other

The category named Other contains myriad substances, which are listed in detail in Chapter 8. It includes some plant-based contributing factors (e.g., 12-myristate 13-acetate, Forskolin, arecoline hydrobromide, quisqualate, etc), and a very substantial number of endogenous substances that were administered exogenously (e.g., 27-hydroxycholesterol, acetylcholinesterase, Bradykinin, CD40, etc).

Ordinarily, endogenous substances are not foundational causes, but intermediate causes, since their harmful effects typically are driven by other foundational causes. However, for consistency, if an endogenous substance was administered exogenously for purposes of experimentation or trial, it was considered as an exotoxin or other foundational cause for the purposes of this monograph. Thus, amyloid beta, an endogenous substance, could be viewed as an endotoxin when internal processes are being discussed, but also as an exotoxin when administered in laboratory experiments.

IV. Occupational/Environmental Exposures

Occupational/Environmental Exposures are those typically man-made substances and radiations to which we are exposed in our jobs and larger environment. This category is divided into chemicals/materials and physical/mechanical, and the further divisions of these major categories are also shown. This category is also massive, due mainly to the substantial numbers of chemicals and materials in our larger environment.

IV-A. Chemicals/Materials

IV-A1. Industrial and Household Chemicals/Materials

This sub-category, which includes hydrocarbons, solvents, chemical compounds, and Other, is very broad. There is overlap among the next level taxonomy elements; for example, some of the solvents are hydrocarbons and some of the chemical compounds are hydrocarbons.

The hydrocarbons sub-category includes, e.g., methylcholanthrene, polycyclic aromatic hydrocarbons, diesel fuel, kerosene, etc.

The solvents sub-category includes, e.g., petroleum-based solvents (mineral turpentine, diesel fuel, fuel oil, kerosene, etc), chlorinated solvents (trichloroethylene, perchlorethylene, trichloroethane, dichloromethane, benzene), organic solvents (benzene, toluene, phenols, alcohols, ketones, methylmethacrylate), dimethyl sulfoxide/DMSO, etc. The impacts from the members of this sub-category, as reported in the references selected, tended to focus on performance and disease. This was due to a number of epidemiology studies of occupational impacts, which tend to focus on higher level impacts.

The chemical compounds/Other sub-categories include a full spectrum of chemical compounds covering myriad sub-categories, especially chlorine, bromine, nitrogen, sodium, sulfur, and carbon compounds. Members of these sub-categories include, e.g., Neurotoxins (6-hydroxydopamine/6-OHDA, 5,6-dihydroxytryptamine/5,6-DHT, -5,7-dihydroxytryptamine/5,7-DHT, Type-2 Alkenes/Reactive aldehydes (Acrolein, 4-Hydroxynonenal/HNE, Acrylamide, Methyl glyoxal), Nitrosamine/N-nitrosodiethylamine, Adenosine, 3', 5'-cyclic monophosphate/cAMP, Carbon tetrachloride, Chemical warfare agents/nerve agents (organophosphates, soman, sarin, ethyl S-2-di-isopropylaminoethyl-phosphonothiolate, VX, tabun), Cyanide (Potassium cyanide, Sodium cyanide), Formaldehyde, Hydrogen peroxide/H2O2, Lipophilic chemicals (persistent organic pollutants, bisphenol A, phthalates, low molecular weight hydrocarbons, polynuclear aromatic hydrocarbons, endocrine disruptors), Sulfur dioxide/SO2, Phthalates (Di-(2-ethylhexyl)-phthalate/DEHP, mono-2-ethylhexyl phthalate/MEHP, DEHP metabolites), Brominated flame retardants (hexabromocyclo-dodecane/HBCD, tetrabromobisphenol-Al/TBBPA, decabromodiphenyl ether/DBDE, polybrominated diphenyl ethers/PBDEs), Ammonia, Hypochlorous acid/HOCl, Methanol, Peroxynitrite, Sodium azide, Acetaldehyde, 3-Bromopyruvate, Vehicular emission oxides (nitrogen dioxide/NO2, carbon monoxide/CO), Sodium fluoride, Membrane-mimicking detergents (sodium dodecyl sulfate, lithium dodecyl sulfate), Nitric oxide donors (sodium nitroprusside, DETA NONOate), Amorphous aluminosilicates, Sodium nitrite, Tert-butyl hydroperoxide/t-BHP, Alloxan, Ammonium chloride, Anionic dyes (Congo Red, Thiazine Red, Thioflavin S), Aroclor 1254, Cobalt chloride, Magnesium chloride, 2,2'-azobis(2-methylpropionamidine) dihydrochloride/AAPH, Methylglyoxal/Glyoxal, Disuccinimidyl suberate, Naphthazarin/5,8-dihydroxy-1,4-naphthoquinone/ 5,8-dihydroxy-1,4-naphthalenedione, Pyrithiamine, Pyrogallol, Glyceraldehyde-3-phosphate/GAPDH, Ethylcholine mustard aziridinium ion/AF64A, 1-methyl-4-phenylpyridinium ion, 2,2'-dithiodipyridine, Aftin-4, Kaolin, Ozone, 2;3;7;8-tetrachlorodibenzo-p-dioxin.

IV-A2. Agricultural Chemicals

This sub-category emphasizes pesticides, herbicides, insecticides, and fungicides, and includes, e.g., Organochlorine Pesticides, Organophosphate Pesticides, 2,4,5-trichlorophenoxyacetic acid, 2,4-Dichlorophenoxyacetic Acid, Agent Orange, Aldrin, Alkylphenolpolyethoxylates, APEOs, Arsenic, Beta-hexachlorocyclohexane/beta-HCH, Bipyridyles, Carbamates, Carbofuran, Chlorfenvinphos, Chlorpyrifos/CPF, Cycloheximide, Cypermethrin, Deltamethrin, Dichlorodiphenyldichloroethylene/DDE, Dichlorodiphenyltrichloroethane/DDT, Dichlorodiphenyldichloroethane/DDD, Dieldrin, Dimethyl parathion, Endosulfan, Famoxadone, Fenamidone, Glyphosate, Hexachlorobenzene, Hexachlorocyclohexane/HCH, Imidacloprid, Lindane, Maneb, Methamidophos, Methyl parathion, Neonicotinoids, Nonylphenol, Octylphenol, Paraquat, Parathion, Pyraclostrobin, Pyrethroids, Trans-nonachlor, Trichlorfon/TCF, Trifloxystrobin, etc. These chemicals impact the larger population through the food supply, and have devastating effects on the agricultural workforce. Given the ubiquitous

nature of agricultural chemicals and industrial/household chemicals in daily life, eliminating them will be challenging.

IV-A3. Materials

The materials/particulates that constitute this category are broadly-based, and in many cases have become part of the average lifestyle. Some examples include:

-heavy metals (e.g., aluminum, arsenic, cadmium, cobalt, copper, iron, lead, manganese, mercury, selenium, zinc, manganese, etc)

-particulates (e.g., air pollution, surgical smoke, dust, etc)

-nanoparticles (e.g., iron nanoparticles, titanium dioxide nanoparticles, CdSe quantum dots, diesel exhaust nanoparticles, alumina nanoparticles, manganese oxide nanoparticles, copper nanoparticles, silicon dioxide nanoparticles, zinc oxide nanoparticles, silver nanoparticles, and nickel nanoparticles, etc)

IV-B. Physical/Mechanical

This sub-category includes ionizing radiation, non-ionizing non-visible radiation, non-ionizing visible radiation, sound radiation, temperature fields, and force fields.

IV-B1. Electromagnetic Radiation

IV-B1a. Ionizing

The ionizing radiation component includes, e.g., gamma radiation (dental X-rays, gamma rays, etc), particle radiation (56Fe-particle radiation, cosmic radiation, HZE particle radiation), radionuclide pollutants (uranium, cesium, cobalt, radon).

IV-B1b. Non-Ionizing

IV-B1b1. Non-Visible

The non-ionizing non-visible radiation component includes, e.g., electromagnetic fields at myriad frequencies, such as extremely low frequency/ELF-EMF, 900 MHz radiofrequency (RF), electromagnetic pulse/EMP, electroconvulsive shock/ECS, UV irradiation, etc.

IV-B1b2. Visible

The non-ionizing visible radiation component includes, e.g., UV irradiation, photolysis of 1-(2-nitrophenyl)ethyl sulfate, etc.

IV-B2. Sound

The sound radiation component includes, e.g., short-lasting impulse noise, chronic noise exposure, night-time aircraft noise, ultrasound sonication, etc.

IV-B3. Temperature; Heat/Cold

The thermal component includes, e.g., cold water hypothermia, cold water stress, heat shock, heat stress, heating, hyperthermia, etc.

IV-B4. Force/Pressure/Physical Trauma

The physical force component includes, e.g., blasts, blast traumatic brain injury, hippocampal injury, accumulated mechanical stress, spinal cord injury, frequent strong Valsalva maneuvers, long hours of repetitive heavy lifting, sequences of blows during the playing of a wind instrument, forceful and repetitive cough, bearing-down efforts during parturition, history of head trauma, etc.

The main components of this sub-category, the different types of physical fields with which we interact (electromagnetic, sound, temperature, pressure, force) are ubiquitous. Avoiding exposure to these emissions/interactions would require a major change in lifestyle (and possibly location) for most people.

IV-C. Other

The 'Other' category is small, and contains adverse effects from over- and under-exposure to oxygen.

V. Psychosocial/Socioeconomic

Psychosocial/Socioeconomic are those foundational causes that reflect personal problems, social interactions, larger societal interactions, and economic relationships. Psychological and sociological stress were major causative factors; economic types of stress seemed to play less of a direct role.

V-A. Psychological

This sub-category includes, e.g., chronic stress (repeated stress, chronic mild stress, chronic psychological stress, multiple chronic stresses, behavioral stress, childhood trauma, bereavement, chronic restraint stress, high job stress), low mental activity (low cognitively engaging activity, low purposeful activities, low leisure activities/low hobbies, low music/drawing/meditation/reading/arts/crafts), etc.

V-B. Sociological

This sub-category includes, e.g., social isolation (isolation, loneliness, living alone, unmarried, maternal separation, low social activity index, low social support at work, constricted life space), low education (illiteracy), etc.

V-C. Economic

This sub-category includes, e.g., economic stress (childhood socioeconomic circumstance), etc.

3D. References - Chapter 3

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Chapter 4

DISCUSSION AND CONCLUSIONS

4A. Contributing Factors Identified

Approximately 400-600 AD foundational causes are identified in this monograph (depending on how one aggregates). Given the myriad disincentives for reporting adverse medical events [1, 2], this number should be viewed as a 'floor'.

These foundational causes are divided into six traditional categories for clarity of presentation (Lifestyle, Iatrogenic, Biotoxic Agents, Occupational/ Environmental Exposures, Psychosocial/Socioeconomic, Genetics). The latter category, Genetics, was not addressed in the findings because the main focus of this monograph is on foundational causes that are (by definition) somewhat actionable (action could, at least in theory, be taken to attenuate, neutralize, or eliminate them). It is difficult to modify a person's genetic endowment at the present time, although that may not be true in the future.

4A1. Latent Variables

To gain an understanding of the deeper commonality among these foundational causes, they can be re-categorized manually according to a few main latent variables [1]: Direct Technology, Indirect Technology, Inadequate Regulation, Individual Choice, Poverty. Each of these five major themes (latent variables) will be discussed now.

4A1a. Direct Technology

Direct Technology (the degree of direct impact of technology on the foundational cause) plays a strong role in Lifestyle, Iatrogenic, and Occupational/ Environmental foundational causes. In addition, through its impact on the immune and other critical systems, modern technology may play a role in whether exposure to bacteria and viruses results in symptoms and diseases. Modern technology impacts the growing, processing, and preparation of foods, and many of the adverse effects identified in the present study can be traced back to the use (mis-use) of technology in the food cycle. The Iatrogenic adverse effects of modern technology result mainly from the high-technology-based drugs, surgery, diagnostics, and therapy that characterize much of modern medicine today. The Occupational/Environmental adverse effects result mainly from the employment of modern technology in 1) commerce, 2) the environment, and 3) the workplace.

4A1b. Indirect Technology

Indirect Technology reflects those adverse health-impacting behaviors enabled by Direct Technology. One example is reduced labor because of modern technology, leading to today's highly damaging sedentary lifestyle that contributes to myriad diseases, including AD. Another example is large numbers of people being able to live in inhospitable northern climates because of modern transportation,

food logistics, clothing, and shelter. This results in less exposure to sunlight and less Vitamin D production, contributing to diseases (such as AD) related in part to Vitamin D deficiency.

4A1c, Inadequate Regulation

Inadequate Regulation is coupled strongly to the introduction of high technology in all aspects of life. Many of the problems with foods derive from relatively unregulated chemicals, materials, and other contaminants entering the food supply during agriculture and animal husbandry. Many of the Occupational/ Environmental exposures arise from relatively unregulated harmful substances entering the workplace and the environment, especially in less developed countries, but in more developed countries as well. Many of the Iatrogenic problems could be traced to drugs, diagnostics, therapies, and other procedures entering practice with insufficient front-end long-term testing, and inadequate evaluation of side-effects.

Two major aspects of Inadequate Regulation revolve around insufficient safety: inadequate safety data gathering, and inadequate safety testing. Much of the adverse impact data gathering tends to be from passive surveillance systems, where response rates can be an order of magnitude (or more) less than real-world incidence rates. Pre-market testing, in many cases, suffers from inadequate sample sizes, unrepresentative samples, insufficient long-term testing, and insufficient combination testing to identify potential synergistic effects. Insufficient long-term testing on humans is particularly troubling, since many serious diseases such as AD may have decadal latency periods from specific toxic stimuli. Transgenerational effects could not be excluded without appropriate long-term testing. Additionally, results from animal testing (which could be long-term from the perspective of many short-lived animals used in testing) do not necessarily translate to human outcomes.

4A1d. Individual Choice

Individual Choice reflects decisions by people to choose unhealthy diets, sedentary activities, recreational drugs, elective drugs and surgery, unhealthy occupations, unhealthy residential environments, unhealthy relationships, etc. There is the unwritten corollary assumption that people have adequate knowledge about the consequences of these choices, and there are no other major factors that limit their choices. For many people, this is a highly unrealistic assumption. They have very limited knowledge about the consequences of these choices, either through

1) accurate information not being available, or

2) apathy in searching out this information, or,

3) being provided incorrect information [1, 2].

4A1e. Poverty

Poverty limits individual choices about diet, occupations, and environment. Poverty plays a strong role in malnutrition and the diseases of deficiency resulting therefrom, directly and indirectly. By limiting access to modern medicine and modern technology, poverty avoids some of the adverse impacts

ascribed to modern technology presented in this monograph, but at the same time, denies many of the benefits available from modern medicine and modern technology.

4B. Synergies/Combination Effects/Additional Contributing Factors

4B1. Under-Reporting of Combinations of Potential Contributing Factors

Many, if not most, people are exposed to at least tens of the ~400-600 potential foundational causes identified in this monograph, and perhaps tens more of the foundational causes that remain under-reported. Given the potential synergistic effects of these causes acting in concert, whereby the potential damage from the combinations exceeds the damage of the causes acting in isolation, the opportunity for developing AD is significant.

However, while ~400-600 potential foundational causes appears to be a large number, it may be the tip of the iceberg of the real number of potential foundational causes. If two or more substances do not show an adverse effect for AD when each is studied in isolation, then they would probably not be examined in combination in the lab or clinic, even though some could produce an adverse effect in combination. So, a large number of combinations would have to be examined, to cover both 1) the case where each member of the combination showed no adverse effect when studied in isolation, and 2) the case where each member of the combination would have a very slight effect on AD when studied in isolation, but the combination would produce a large effect. While some of these combinations would have been reported in the present study, those reported would probably be a very small fraction of all potential combinations.

The targeted literature studies in particular tend to select substances of interest for the experiments, then look for biomarkers of interest. Unless there is good reason to select a combination for study, it probably would not get chosen.

4B2. Numerical Estimates of Potential Combinations

The reason few combinations are selected for study derives from combinatorics. Consider the number of possible combinations of two and three items. For n variables, and possible combinations of a subset of n consisting of r variables, the number of combinations is: $C(n,r)=n!/(r!*(n-r)!)$, where [!] denotes the factorial function. For large n, and r small compared to n, $C(n,r)\sim=n^r/r!$ For large n, C becomes a large number. How large? Consider the following.

It would be useful to identify those substances that, in isolation or in combination, could potentially impact AD or its surrogate endpoints, but have not been studied yet. There are many tens of thousands of items that could be potential candidates for study. Is there any way to narrow those down?

Reference [1] considered ~4,000 diseases, and identified factors that contributed to 1) any of these diseases and 2) a threshold number of diseases. In reference [1], on the order of 800 substances that contributed to at least a threshold number of the ~4,000 diseases were identified. These 800 pervasive causes constituted about ten percent of the total number of causes (90% of which impacted less than the threshold number of diseases) identified for the ~4,000 diseases. The total number of causes identified

for all diseases (~8,000) might be a good starting point for identifying additional potential AD causes. Why is this a reasonable assumption?

The various systems in the body are inter-related. The immune system, neural system, endocrine system, circulatory system, etc, are linked. There are research disciplines devoted to study of these linked systems (e.g., neuroimmunology, neuroimmunoendocrinology, etc). Most of the ~8,000 causes identified in reference [1] impacted one or more of these inter-related systems. Many of the studies focused on the impact of the test substance on (typically) one system only. It would be reasonable to expect that a substance impacting one of the systems above would have some level of impact on the other systems above, with some impacts being more significant than others.

Thus, the ~8,000 potential causes identified in reference [1], minus those that were identified in the present AD study, would be candidates for evaluation as potential AD causes. Subtracting the ~500 AD causes identified in the present study from the ~8,000 causes leaves on the order of ~7,500 items to be examined in isolation. Assume there were another 500 items evaluated for potential impacts on AD in other studies but were shown not to have an effect (in isolation, although we may want to examine them as part of a combination). We are then left with on the order of 1) ~7,500 substances to study in combination, and 2) ~7,000 of the initial ~7,500 substances to study in isolation. This would include the case where the ~500 identified contributing factors in isolation could have a stronger effect in combination, for those cases where the combinations have not been studied.

The numbers of combinations of two and three for 7,500 test items, C(7500,2), C(7500,3), are, according to the formula above for small r:

C(7500,2)=~28 million

C(7500,3)=~70 billion

These numbers are astronomical in any of the cases shown. Research on each of these combinations is a major resource and time effort, in the lab and/or in the field/clinic. There's no way all the combinations, or even the most relevant ones, can be run. Unfortunately, the combinations of potentially toxic stimuli mirror the real world, not the potentially toxic stimuli acting in isolation. And, which combinations are important to a specific individual would be a function of that person's unique characteristics, such as genetic makeup.

4B3. Synergy Effects on Dose Rates

Dose rates may also be affected by synergy. When two or more items with adverse health effects (in isolation) are combined, smaller doses of each in combination can produce an equal or greater adverse health effect (this synergy is also true for the case of positive health effects).

As an example, assume hypothetically that heavy cell tower radiofrequency (RF) exposure could be a strong contributing factor to AD, and high-fat diet could be a strong contributor. If people are exposed simultaneously to cell towers and fat-containing diets, then perhaps only modest levels of cell tower exposure and modest fat diets could in combination have an adverse effect equivalent to that from

high levels of exposure of each in isolation. Thus, if the initial tests in isolation were at low doses of the stimuli, the results could be misleading. So, each of the combination experiments would have to cover a wide parametric range to be credible.

These conclusions reflect the challenge of preventing or reversing not only AD, but all other chronic diseases that have a wide spectrum of causative factors. The only glimmer of hope for true prevention or reversal is that, for any complex system characterized by many variables, there are typically a few main variables that drive performance and need to be addressed with high priority. That may explain why Dale Bredesen was able to get positive results for his treatment of AD/MCI [3] and Terri Wahls was able to reverse her multiple sclerosis (as summarized in Chapter 9, sub-section D of [1]). Unfortunately, given the rapidly increasing number of potentially harmful exposures to advanced and untested technologies in our biosphere, identifying and eliminating these hazards may become increasingly difficult. This is especially true for those diseases with long latency periods (like AD).

4C. Health Policy

4C1. Health Policy Framework

While the main objective of this monograph is identification of potential contributing factors to AD, some brief statements about the health policy that could exploit these findings might prove useful. The health policy that derives from the above findings would contain two main components: persuasion and mandates. Persuasion would be applied to influence Lifestyle/Individual Choice, which is the "low-hanging fruit" of foundational causes. Mandates would be applied to alter Inadequate Regulation, the next level up on the "fruit tree". Effective persuasion and mandates depend strongly on the most scientifically accurate biomedical information being placed in the biomedical literature, and then communicated to the public in a straight-forward manner.

This monograph has taken a large step in identifying the voluminous potential AD foundational causes that need to be eliminated for AD prevention or possible AD reversal. A better resourced study would be able to 1) sample more Abstracts for analysis, and 2) examine phrases further down the frequency spectrum, to identify additional potential foundational causes for AD.

However, while the addition of more AD foundational causes obtainable with an expanded study would provide a more complete picture of such causes, the elimination of the specific and categorical causes identified in this monograph may be adequate to prevent or (alone or in concert with treatments) reduce/halt/reverse AD progression in selected cases.

4C2. Health Policy Implementation

4C2a. Eliminating Potential AD Contributing Factors

There are three key issues in implementing elimination of any potential AD contributing factor for any person. First, what is the exposure level (duration, strength) of this individual to a given contributing factor, and is this exposure level in the toxic range? For some types of contributing factors, exposures can be estimated readily. These types of contributing factors include some aspects of diet,

some drugs, and perhaps some occupational exposures. For most contributing factors for most people, the exposure levels at both any point in time and as a function of time are unknown. To obtain that data, myriad exposure meters measuring radiation (ionizing, non-ionizing), chemicals ingested, inhaled, entering the body through the skin, etc, would be required on a continual basis. For the foreseeable future, many exposures relevant to AD contributing factors will be unknown because of the absence of these critical measurement systems on a continuing basis.

Second, assuming a particular individual's exposure to a given contributing factor is known and potentially harmful, its elimination needs to be placed in some priority order. If one examines the research papers on potential causes, almost every researcher believes his/her findings are a critical contribution to AD. Not many, if any, papers emphasize prioritization among potential contributing factors.

Third, assuming a particular individual's exposure to a given contributing factor is known and harmful, and its priority for elimination is known and high, then determination of the individual's motivation to eliminate the potential contributing factor is required. Having motivation to eliminate contributing factors to which one is effectively "addicted" may be the most difficult step in the above process.

A parallel issue is understanding what is meant in practice by "elimination". What is the speed, breadth, and depth with which a potential contributing factor has to be removed for it to be considered "eliminated", in order to halt/reverse the progression of AD or any disease? For example, does a poor diet have to be improved by 50% to be effective in disease reversal? 90%? In the multiple sclerosis reversal study summarized in Chapter 9, sub-section D of [1], Dr. Terri Wahls was shown to have reversed her MS. Dr. Wahls' symptom removal and especially damage reversal were not effective until her diet achieved near-"pristine" status. There is no reason to believe that:

1) similar dietary improvement would not be required to reverse AD (for those cases where the damage may not yet be irreversible or genetic predisposition is not overly dominant), or

2) similar improvement in other types of cause removal would not be required to reverse AD.

The degree of cause removal required for reversal (with or without the requirement for additional treatments) would probably be different among patients. The major roadblock would be individual choice. It would require high discipline and compliance on the part of the patient. For those patients who are willing to do whatever it takes to reverse AD (like Dr. Wahls' motivations to reverse multiple sclerosis), and who have no intrinsic limitations based on strong genetic predisposition or irreversible damage, the findings in this monograph offer a starting point for an effective protocol.

4D. References - Chapter 4

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Chapter 5

SUGGESTED FURTHER RESEARCH

5A. Additional AD Contributing Factors

The present study, while more comprehensive than any of its predecessors with respect to identifying potential contributing factors for AD based on the premier biomedical literature, has identified only the tip of the iceberg of potential AD contributing factors. As shown in Chapter 4, section 4B, many other potentially toxic stimuli, and their combinations, have yet to be addressed. As shown in [1], the adverse effects of many potentially toxic stimuli have not entered the biomedical literature for myriad reasons. Many of the AD studies on potential contributing factors have been narrowly focused; only a few sub-levels in the taxonomy of impacts in Chapter 8 were targeted in any research project.

One straight-forward way of identifying additional potential AD contributing factors is with use of the discovery component of the literature-related discovery and innovation (LRDI) approach. Some examples of how this could be done were presented in the CKD LRDI study [2]. An adequately resourced study could identify many more of these contributing factors for AD.

5B. Develop Measurement Devices for Potential AD Contributing Factor Exposures

In the brief discussion of health policy implementation above, it was shown that a key deficiency in implementation is lack of knowledge of the myriad toxic stimuli to which one is being exposed continually. What is the full spectrum of potentially toxic chemicals in 1) our drinking water, 2) the air we breathe, 3) the food we eat, 4) contact with our skin, and what is the full spectrum of ionizing and non-ionizing, visible and non-visible, radiations to which we are exposed as a function of time? To answer these questions, we need devices that can measure the full range of these toxic stimuli and are convenient and portable. Producing such devices would require an extensive research and development effort, especially devices in a form that people would be motivated to wear and use.

5C. Institute Clinical Trials Removing Potential AD Contributing Factors

Finally, to gain operational experience with exploiting the findings in the present monograph, clinical trials should be started in the near future. Given the limitations in knowing exposures to many contributing factors outlined above, these trials could start with incorporating the "low-hanging fruit" contributing factors that have been identified in the present study. These would include:

1) curbing the dietary excesses identified and removing the dietary deficiencies identified;

2) eliminating food additives to the extent knowable and possible, including those dietary excesses that derive from food additives (excessive fat, sugar salt);

3) reversing the sedentary behavior patterns identified;

4) removing the foundational impediments to better sleep;

5) eliminating the use of 'recreational' drugs, including smoking and excessive alcohol;

6) eliminating the use of medicinal drugs shown to be potential contributing factors, unless where these drugs are absolutely necessary;

7) eliminating any elective (not absolutely necessary) diagnostic or surgical procedures that involve inhalational anesthetics or high doses of ionizing radiation in head region (e.g., CT scans);

8) minimizing exposures to some hydrocarbons such as diesel exhaust, kerosene, polycyclic aromatic hydrocarbons (including those found in smoke), etc;

9) minimizing exposures to some solvents, especially petroleum-based solvents, chlorinated solvents, and organic solvents;

10) minimizing exposures to pesticides, herbicides, insecticides, and fungicides, both inhalation and ingestion exposures;

11) minimizing exposures to heavy metals in food, in water, and in the air;

12) minimizing exposure to particulates, especially air pollution;

13) minimizing exposures to ionizing radiation, non-ionizing non-visible radiation (such as cell phones, cell towers, WiFi, smart meters, etc), non-ionizing visible radiation (such as excessive UV radiation), sound radiation (high noise levels), temperature fields (such as cold water hypothermia/stress, heat shock/hyperthermia), and force fields (high impacts, especially to head region);

14) minimizing chronic stress (mental/emotional/psychological), increasing mental activities;

15) minimizing social isolation.

Most of the other sub-category members in Table 8-3 are unknown to the average person (both in name and level of exposure), and would require (mainly) portable instrumentation to determine exposure levels and potential concerns.

5D. References - Chapter 5

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Chapter 6

BACKGROUND

6A. Overview

Alzheimer's Disease (AD) is a brain disease, and the most common form of dementia [1-3]. Presently, it affects overwhelmingly those 65 years old and above; incidence increases with age. According to reference [4], 'A growing number of studies indicate that the age-specific risk of Alzheimer's and other dementias in the United States and other higher-income Western countries may have declined in the past 25 years, though results are mixed. These declines have largely been attributed to increasing levels of education and improved control of cardiovascular risk factors.' That positive assessment of declining incidence was questioned somewhat in a recent comprehensive meta-analysis [5]: "We found no evidence to suggest that the current assumption of constant age-specific prevalence of dementia over time is ill-founded". The prevalence of AD in the USA was approximately 4.7 million people in 2010, and is projected to increase to 5.8 million in 2020, 8.4 million in 2030, and 11.6 million in 2040 [4].

Thus, these studies referenced conclude that age-adjusted AD *incidence* is either declining slightly or remaining approximately level. Projected *prevalence* is increasing rapidly, since the number of elderly is projected to increase rapidly.

The incidence projections may be highly misleading. They are based mainly on extrapolations from the past, estimating the adverse effects of established technologies. The main body of the present monograph identifies many new technologies that could potentially contribute to AD. The growth in implementation of technologies (over the last couple of decades) potentially contributing to AD (or many other chronic diseases) portends ominously for the future. These new technologies have not been operational for sufficient time to display direct impacts on AD (or myriad other chronic diseases) in humans, because of potential decadal latency periods before serious diseases emerge.

Thus, the appropriate future projection of AD incidence and prevalence should consist of superposition of 1) declining/flat incidence trend line due to past personal health advances and 2) increasing incidence due to implementation of new harmful technologies with decadal latency periods. The Precautionary Principle dictates that the impacts of these newer technologies on surrogate endpoints be considered when developing future incidence projections, especially in the longer-term.

Additional details on AD can be found in the following books [6-15] and review articles [16-21].

This Background section consists of two parts: studies to identify a broad spectrum of causes for AD, and text mining approaches for identifying potential contributing factors to disease.

6B. AD Contributing Factors Studies

As shown in Chapter 8, there are many published studies focusing on identifying one or a few contributing factors to AD. There are many fewer studies identifying a broad spectrum of AD

contributing factors, as was done in the present monograph. The focus in the present section is to summarize the results from credible broad spectrum or meta analysis studies indentifying myriad AD contributing factors.

Hazar et al [22] concluded: "Diabetes mellitus (DM) type 2, smoking, physical inactivity, overweight and obesity were significantly associated with increased risk of AD". Grant [23-24] focused on dietary factors, and concluded that advanced glycation end products associated with high-temperature cooking, meat consumption, eggs, high-fat dairy, and low 25-hydroxyvitamin D concentrations are associated with increased risk of AD. Li et al [25] concluded: "Patients with MCI with APOEepsilon4, abnormal CSF tau level, hippocampal and medial temporal lobe atrophy, entorhinal atrophy, depression, diabetes, hypertension, older age, female gender, lower MMSE score and higher ADAS-cog score, had a high risk for the progression to AD". Xu et al [26] concluded that hyperhomocysteine, depression, frailty, carotid atherosclerosis, hypertension, low diastolic blood pressure, type 2 diabetes mellitus (Asian population), low education, and high body mass index (BMI) in mid-life increased AD risk. Barnes and Yaffe [27] concluded that up to half the worldwide cases of AD can be attributed to seven "modifiable" risk factors: diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity, low educational attainment, and physical inactivity. Meng et al [28] concluded that high blood pressure, hypercholesterolemia, obesity, diabetes mellitus in midlife, smoking, and hyperhomocysteinemia are AD risk factors. Srisuwan [29] concluded that reducing dementia risk through "modifiable" risk factors requires cognitive activity, higher education, mentally demanding occupations, participation in mentally challenging leisure activities, more active socially, low saturated fat diet, high fruit and vegetable diet, smoking cessation, prevention of head injury with loss of consciousness, reduce high blood pressure, especially at midlife, reduce diabetes, reduce high serum cholesterol especially at midlife, and reduce depression.

There is a thread of common risk factors running through the above full spectrum surveys and meta-analyses. These include hypertension, diabetes, obesity, smoking, depression, physical inactivity, low education, and cognitive inactivity. Quasi-common risk factors include high meat diet, high saturated fat diet, high cholesterol, and hyperhomocysteine.

Superficially, this is a relatively low number of "modifiable" risk factors (the authors of these review articles view them as "modifiable"). However, this "low number" is deceptive. If we view the foundational causes as independent variables (those over which we have direct control, at least in theory), there are very few that have been identified in the studies above. These include smoking, physical activity, cognitive activity, educational level, and the dietary factors of high fat, high meat, low fruit and vegetables.

The non-foundational risk factors/contributing factors are in fact dependent variables, and include hypertension, diabetes, obesity, depression, hypercholesterolemia, and hyperhomocysteinemia. As shown in Chapter 8, there are many hundreds of foundational causes/contributing factors for AD that can be identified from the published literature alone.

As was shown in the precursor study identifying foundational causes for chronic kidney disease (CKD) [30], there were also many hundreds of potential CKD foundational causes that could be

identified. Additionally, in the first author's book on pervasive causes of disease [31], it was shown that there are many chronic diseases for which hundreds of potential foundational causes could be identified. It is reasonable to assume that hundreds of potential foundational causes could be identified for each of the above dependent variables/diseases (hypertension, diabetes, obesity, depression, hypercholesterolemia, and hyperhomocysteinemia). The surveys above, while valuable in their own right, do not work in the actionable coordinate system of foundational contributing factors, and cannot lead to a protocol whereby action could be taken to prevent or reverse AD in selected cases. The approach in the present monograph does indeed lead to such an actionable protocol!

6C. Text Mining to Identify Contributing Factors to Disease

6C1. Overview

The two main literature-based approaches for identifying potential contributing factors to AD (or any other disease) are "direct" and "indirect", where "direct" can be viewed as analogous to Innovation, and "indirect" can be viewed as analogous to Discovery [30]. The direct approach identifies contributing factors that appear in the same article as AD (e.g., smoking increases the risk for AD) and link directly to AD. The indirect approach identifies potential contributing factors to some disease/symptom other than AD, then links this disease/symptom to AD (e.g., high-salt diet increases the risk for hypertension, hypertension is strongly linked to AD).

The bulk of the present monograph focuses on direct contributing factors to AD, and includes conceptual discussion, but not examples, of indirect contributing factors. The latter are of two types: 1) linkages between a potential contributing factor and a disease/symptom where AD is mentioned in the article as being related to the disease/symptom, and 2) linkages between a potential contributing factor and a disease/symptom where AD is not mentioned in the article. Case 1) is, e.g., typical of surrogate endpoint papers. In case 2), identifying another article where the disease/symptom is linked to AD is required to close the loop. Case 2) is usually described in the text-mining literature as literature-based discovery or literature-related discovery. Case 1) could also be viewed as "soft" discovery, and case 2) as "hard" discovery [30]. Case 2) examples are not provided in the present monograph because of length considerations, but, based on past experience, voluminous discoveries of potential contributing factors for disease are possible (e.g., [30]).

6C2. Literature Survey

The published text mining approach related most closely to that used in the present monograph can be found in [30-31]. In the more recent of these two [31], three approaches were used to develop queries for identifying foundational causes for *all* diseases. The first approach used MeSH Qualifiers relevant to identifying foundational causes of disease (e.g., *adverse effects, toxicity, pathogenicity, poisoning*) to retrieve records from Pubmed for analysis. The second approach used generic MeSH terms related relatively unambiguously to foundational causes (e.g., *"Drug-Related Side Effects AND Adverse Reactions"; Abnormalities, Drug Induced; Air Pollutants, Occupational; Amphetamine Related Disorders; Carcinogens; Chemical Warfare Agents; Chemically-Induced Disorders*, etc) to retrieve the records from Pubmed for analysis. The third approach used text terms (applied to the Title field) to

retrieve the records from Pubmed for analysis. This Title query consisted of two parts: standalone terms (e.g., *cardiotoxic*, genotoxic*, mutagenic, adverse-outcome, adverse-metabolic-effect**, etc) and terms that are intersected with diseases (e.g., (*expos* OR induc*) AND (cancer* OR dermatitis*)).

Other text mining approaches have been developed for generating literature-based discovery. They have been used mainly for identifying potential new treatments for disease, but the approaches used for identification of new treatments could be easily modified for identification of potential new foundational causes as well (e.g., [30]). In the past decade, a number of these semantic relation-based approaches have been promulgated.

Cohen et al [32] use semantic indexing to identify empirically sequences of relationships known as 'discovery patterns', such as "drug x INHIBITS substance y, substance y CAUSES disease z" that link pharmaceutical substances to diseases they are known to treat. These sequences are derived from semantic predications extracted from the biomedical literature, and subsequently utilized to direct the search for known treatments for a held out set of diseases. Hu et al [33] present a biomedical semantic-based association rule system that significantly reduces spurious/useless/biologically irrelevant connections (the B terms in the ABC approach) through semantic filtering. Miller et al [34] advance the hypothesis of "cortisol as part of a mechanistic link elucidating the observed correlation between decreased testosterone in aging men and diminished sleep quality". Hristovski et al [35] overview myriad approaches to literature-based discovery, emphasizing semantic relations, especially 'discovery patterns'. Sang et al [36] develop a supervised learning based approach to generate hypotheses from biomedical literature, splitting the traditional processing of hypothesis generation with classic ABC model into AB model and BC model. Cameron et al [37] implement a context-driven, automatic subgraph creation method that captures multifaceted complex associations between biomedical concepts; given a pair of concepts, the method automatically generates a ranked list of subgraphs, which provide informative and potentially unknown associations between such concepts. Kastrin et al [38] mimic the process of literature-based discovery as a classification problem on a graph of MeSH terms, using unsupervised and supervised link prediction methods for predicting previously unknown connections between biomedical concepts.

These approaches achieve neither the breadth nor the volume of Innovation and Discovery found in references [30-31, 39].

Other information technology approaches have been used to identify potential risk factors/contributing factors for specific diseases. They differ from the Discovery approaches above because of their focus on identifying the direct causes of disease as defined above. Examples of these information technology approaches include training neural networks to identify risk factors for specific diseases/ conditions [40-43], machine learning-based methods to quantify risk factors for diseases/conditions [44-45], data based clustering and rule based prediction to identify risk factors for diseases/conditions [46-48], Bayesian networks to identify risk factors [49-54], association rules to identify risk factors [55-57], decision trees to identify risk factors [58-62], and text/data mining approaches [63-65]. Additionally, there is a substantial literature on information technology approaches for identifying adverse events resulting from drugs and surgery [66-78].

6D. Foundational Cause Definition

The myriad causes of AD reported in this monograph are termed "foundational". A foundational cause is a tangible stimulus or behavior that can contribute to a symptom. Thus, excesses of calcium, water, exercise, drugs, environmental exposures, etc, can contribute to a symptom(s), and severe deficiencies of calcium, water, or exercise can contribute to a symptom(s) as well. Abuse, poverty, educational status, etc, can contribute to symptoms, even though categorizations into excesses and deficiencies may be less applicable.

A symptom(s)/disease(s) is the result of imbalance between the strength of the toxic stimuli and the person's innate ability to neutralize the effects of the toxic stimuli, including the genetic factors that were not included in this monograph. The two are not independent; the toxic stimuli can affect the capabilities of the defensive system to neutralize incoming toxic stimuli. Thus, the incoming toxic stimuli can be viewed as a "signature" of individual toxic stimuli, with different weightings assigned to each toxic stimulus, and the defense can also be viewed as a "signature", with different weightings assigned to the health of the body's defensive mechanisms. Whether a symptom will materialize as a result of one or more toxic stimuli depends on whether the defensive "signature" is able to neutralize the "signature" of the incoming toxic stimuli.

Thus, not every person who eats a high-fat diet or undergoes surgery with inhalation anesthetics develops AD, but some (more than expected randomly) do. There were a number of cases in the literature where relatively few people were reported to have adverse reactions to a given toxic stimulus. Identifying the offensive-defensive "signature" relationships that allow toxic stimuli to translate into symptoms (within the context of understanding genetic polymorphisms and the resulting variations in biological pathways) will play a significant role in explaining why some people develop a disease and others do not when exposed to the same agent. Understanding the complex web of gene-environment interactions is the central challenge of modern medicine; our identification of myriad individual toxic stimuli and defensive system deficiencies is the first step in this long journey.

For purposes of this monograph, we term a toxic stimulus a (foundational) cause if

1) the research author stated/implied/inferred the toxic stimulus was a cause and

2) the information presented supported the research author's conclusion.

We recognize, however, that this toxic stimulus was in all probability one component of a more complex offensive-defensive "signature" imbalance that resulted in the symptom(s) of interest.

6E. References - Chapter 6

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Chapter 7

DETAILED METHODOLOGY

7A. Methodology for Identifying AD Foundational Causes

7A1. Overview

This study focuses on identifying direct (and some indirect) AD foundational causes. It extrapolates and extends the identification techniques used in the chronic kidney disease (CKD) study [1] and in the eBook on identifying foundational causes for "all" diseases [2]. In the CKD study, approximately 900 direct and indirect potential foundational causes of CKD were identified (as well as direct and indirect treatments), and in the eBook, approximately 800 potential pervasive foundational causes of disease were identified ('pervasive' meant that the foundational cause listed contributed to some threshold number of different diseases).

The present study had two main components, with a different approach and different search engine for each component. The earlier component involved 1) using a novel targeted query to retrieve records with high probability of containing AD foundational causes, and then 2) performing a visual inspection (reading) of the retrieved records. The later component involved retrieving all the records in the AD core literature, then using advanced text mining techniques to extract phrases from text fields (and MeSH terms from the MeSH field) that had high probability of being foundational causes.

7A2. Database/Search Engine Selection

The first step in designing and developing a specific query for retrieving records is identifying the databases(s) and search engine(s) that will be used in the retrieval process, since the query format has to be tailored to the database and search engine characteristics. Medline was selected as the database to be used, since it is the main repository of records from the premier biomedical journals. The Thomson Reuters version of the Medline search engine was used for the initial visual inspection component of the AD study, since the Thomson search engine had the proximity search capability compatible with query terms. The Pubmed version of the Medline search engine was used for the later "streamlined" component of the AD study, since the phrase extraction approach did not require proximity searching.

7A3. Visual Inspection Component

To define candidate query terms, an AD core literature consisting of about 100,000 Medline records was downloaded and examined. The higher frequency MeSH terms associated with the AD core literature records were examined manually, and those MeSH terms that appeared to relate to foundational causes were evaluated for relevance. Nominally, ten records that contained each candidate causes MeSH term were examined, and if relevance was about 70% or beyond, the MeSH term was selected. In borderline cases, more MeSH terms were sampled until definitive conclusions could be drawn. Relevant does not mean unanimity or consensus was achieved for causes. Non-agreement with the majority could have been attributable to poor research, research with a pre-determined agenda (e.g., [1, 2]), or selection of a "window" in parameter space different from where the cause was operable. But, if cause was found

operable in a few of the sampled papers for a given MeSH term, the term was deemed sufficiently important to select for the query.

These higher frequency MeSH terms were then matrixed with all MeSH terms in the retrieval. Lower frequency MeSH term candidates were identified through strong co-occurrence with the higher frequency terms, and the lower frequency terms were subsequently validated. Then, a separate database was generated consisting of all the records that included these high and low frequency selected MeSH terms. In this new database, the higher frequency Abstract phrases were examined, and those that appeared to relate to potential causes were evaluated for relevance. A similar procedure to that used for causes MeSH term selection was followed. The higher frequency Abstract phrases, and some generic Abstract phrases related to causes (e.g., expos*, induc*, etc), were matrixed with all Abstract phrases to identify lower frequency phrase candidates through strong co-occurrence.

Eventually, all the MeSH terms were read and examined, and a few low frequency terms that were missed with the co-occurrence procedure were added to the list. The same was not possible with the Abstract phrases. While there were thousands of MeSH terms (readable, although visually intensive), there were millions of Abstract phrases.

As stated in the Introduction, only foundational causes were evaluated in this study. There were six main types of foundational causes: Lifestyle, Iatrogenic, Biotoxic, Occupational/Environmental, Psychosocial/Socioeconomic, and Genetics. Since the purpose of this study is to identify specific causes to eliminate in order to prevent/halt/reverse AD, and since relatively little can be done at this time to alter the genetics foundational causes, the genetics causes were not included in the final queries.

The overall query structure was of the generic form [Cause][Produces][Symptom]. Two of the three would be specified in the query, directly or implicitly, and the retrieval would provide the third. Examples from causes query:

a. Cause near Produces: steroid-induc* or diet-induc* OR antibiotic near/1 cause*. These are generic or specific members of classes of potential causes in proximity to Produces-type terms. The classes tend to be drugs, diets, chemicals, radiation sources, etc. The Produces-type terms are necessary since drugs, diets, etc can be either beneficial or harmful, depending on circumstances (e.g., a chemotherapeutic drug can be helpful for treating cancer, but may also produce cognitive decline).

b. Produces near Symptom: cause* near/5 "cognitive decline" NOT "cognitive decline cause*"

c. Cause near Symptom: *Bacterium or pentachloro* in Title, with either Symptom in Title or in MeSH. If Abstracts are searched, stronger proximity conditions are required; e.g., *Bacterium near/5 Symptom. Unlike case a) above, in this case the causes are specific members of classes of potential causes that usually don't have beneficial effects, and therefore don't require proximity to causes-like terms; the causative nature is implied by the substance.

Note on the above. The model used was [cause-produce-symptom], but a somewhat broader form could be: [cause-produce-adverse effects], of which Symptom is one way of describing an adverse effect.

Thus, "toxic*" or "adverse effect*", or "harm*" in the Title by itself, along with the Symptom in the Title or MeSH tends to be accompanied by the cause and the effect it has.

Additionally, many research articles addressing causes use the language [cause-activates/inhibits/blocks-signaling pathway(s)] (e.g., "MicroRNA-222 promotes tumorigenesis via targeting DKK2 and activating the Wnt/beta-catenin signaling pathway"). The signaling pathways were not used as part of the queries in this study, but a future more comprehensive and well-resourced study could include the signaling pathways in the queries; their incorporation would be straight-forward. Many research papers, especially at the more fundamental biological level, may not mention diseases or symptoms, but are written in the language of effects on signaling pathways, and these papers could be accessed by the appropriately-written queries. To close the loop in this case, the link between altered signalling pathway and either AD or its surrogate endpoints would have to be established.

The final query used is shown in section 7A - Appendix 1. The Thomson Medline AD core literature (from 1994-2014) consisted of 76663 records, and intersection of the query terms with this literature yielded 10,733 records. The most recent 5,000 were inspected visually, and the relevant foundational causes were extracted.

7A4. Streamlined Component

7A4a. Overview

An AD core literature consisting of 99,610 records was downloaded from Pubmed on 25 April 2015. Three streamlined sub-components were applied to this downloaded literature to extract AD foundational causes.

The first sub-component used only MeSH Qualifiers to filter downloaded records and extract potential foundational causes. The second sub-component used MeSH terms (relatively unambiguously related to foundational causes) to filter downloaded records and extract potential foundational causes. The third sub-component used text terms (applied to the Title and Abstract fields) to filter downloaded records and extract potential foundational causes. The results of the Visual Inspection component and the Streamlined component were integrated to produce the final AD foundational causes, as shown in the taxonomy of Table 8-3.

7A4b. MeSH-Based Approach

7A4b1. MeSH Qualifiers Approach

An offshoot of the MeSH Qualifier concept was used for identifying foundational causes. MeSH Headings have a number of Qualifiers associated with them to allow focus on items of interest. Thus, the MeSH term Cadmium/toxicity allows records to be retrieved related to the toxicity of Cadmium. These MeSH Qualifiers may be perceived as linking terms to the MeSH Headings, allowing for "surgical" extraction of MeSH Headings that meet desired criteria. Thus, if MeSH Qualifiers strongly related to foundational causes can be identified, they can be used to identify MeSH Headings that are potential foundational causes of disease.

There were 83 topical MeSH Qualifiers (in Pubmed) used for indexing and cataloging in conjunction with MeSH Heading descriptors when this concept was developed. All 83 were examined in more or less detail for applicability to identifying foundational causes of disease. For the initial Visual Inspection approach query, three were selected as producing relevant results when used in isolation: *chemically induced, toxicity, poisoning*.

The Streamlined approach was performed one year after the Visual Inspection approach, with one year's experience working with the selected MeSH Qualifiers. The MeSH Qualifiers were re-examined for the Streamlined approach, and four were selected (after extensive validation) as producing highly relevant results when used in isolation: *adverse effects, toxicity, pathogenicity, poisoning*. A few limited combinations of the remaining MeSH Qualifiers were examined for the Streamlined approach, but none were deemed to have sufficient relevance.

All MeSH terms that contained at least one of these Qualifiers were extracted, and the related records examined for potential foundational causes. While this MeSH Qualifier linking approach was developed for, and applied to, potential foundational causes, it can be easily modified for identifying potential treatments, identifying potential biomarkers, identifying potential mechanisms, etc.

7A4b2. MeSH Headings Approach

MeSH Headings related relatively unambiguously to foundational causes were identified two ways. First, results from past studies were examined, especially [1, 2], and relevant MeSH Headings were extracted. Second, a few of the most unambiguous MeSH terms identified from past studies were entered into Pubmed as query terms, and all the MeSH terms in the resultant retrieval (i.e., those that co-occurred with the entry MeSH terms) were examined for relevance. The final list of relevant MeSH terms (7A - Appendix 2) was intersected with the total list of MeSH terms in the retrieved database, and the resulting records were examined for potential AD foundational causes. Again, while this focused MeSH Heading approach was developed for identifying potential foundational causes, it could (with some work) be adapted to identifying potential treatments, potential biomarkers, potential mechanisms, etc.

7A4c. Text-Based Approach

7A4c1. Title Linking Phrases Approach

Because of MeSH terms' limitations (not all Medline records have MeSH descriptors, not all MeSH terms are included in those records that have MeSH terms, not all MeSH descriptors used have appropriate Qualifiers attached. etc), a text-based approach for identifying causes was added to the analysis. Because of 1) the large number of phrases in a record's Abstract compared to the Title, and 2) computer storage and software limitations, the bulk of the analysis was performed on the Title phrases. A more limited analysis was performed on the Abstract phrases, and is shown in Section 7A4c3 - Abstract Linking Phrases Approach.

There were millions of Title phrases that had to be evaluated for potential causes. Only the highest frequency phrases could be inspected visually. To access the lower frequency terms, a number of linking terms were identified.

The linking terms were generated through visually inspecting many records containing foundational causes in the Titles, and identifying those terms that appeared frequently with the foundational causes. These linking terms include: -induced; caused by; induced by; -contaminated; exposure to; exposure(s) [at end of phrase]; exposed to; poisoning [at end]; -exposed [at end]; -related; -associated; -infected; abuse*; toxicity. The phrases that included the linking terms eventually had to be separated from the linking terms to identify the specific foundational causes. Other linking terms were virus* and generic bacterial headings, but these did not have to be separated from the phrases.

7A4c2. Title Dot Product Approach

Finally, potential foundational causes from myriad other sources (including past foundational causes studies, government-approved lists of toxic substances, MeSH-derived causes, etc) were intersected with the full list of Title phrases, and added to the potential foundational causes identified in the Linking Phrases approach.

While the Title phrase linking terms were developed specifically for identifying causes, a similar approach could be used to develop linking terms for identifying potential treatments, potential biomarkers, or potential mechanisms. Moreover, there could be substantial benefits gained by using Abstracts for phrase generation rather than Titles, and even full-text rather than Abstracts. While use of proximity queries with the linking terms in the Title were not required, they would be required for use in Abstracts or full-text. Adding proximity capability would be a minor modification to the form of the query developed below. The major issue would be switching to a database search engine that had the capability of proximity searching.

7A4c3 - Abstract Linking Phrases Approach

Given the size and breadth of Abstracts relative to Titles, most of the linking terms used to extract causes from the Title were relatively inefficient in extracting foundational causes from the Abstract. Variants of induc* and expos* were used to link to potential foundational causes in Abstract records, and these extracted terms received the same treatment as those from the Title.

The myriad potential foundational causes from the Visual Inspection component and the Streamlined component were combined.

7A5 - Validation of Potential Foundational Causes

There were 9427 potential foundational causes that resulted from combination of the above sources. Each of these terms had to be validated before inclusion in the final AD potential foundational causes taxonomy. The validation process was as follows.

The Thomson Medline search engine was the main vehicle used for validation, although in some cases Thomson Science Citation Index Expanded (SCI) had to be used, and in a very few cases, Pubmed was used. A query consisting of two components was entered into the search engine. The first component covered the core AD literature: Alzheimer* OR dementia in Title or MeSH. The second component was the potential foundational cause to be validated (e.g., smoking). The two components

were intersected (e.g., (Alzheimer* OR dementia) AND smoking), and some/all of the records retrieved were read. The evidence for linkages between the potential foundational cause and Alzheimer's Disease directly or surrogate endpoints was evaluated critically. This was a difficult process, compounded by the fact that adverse effects of toxic stimuli may be under-reported/mis-reported [1].

Because of the presence of duplicate terms and concepts, not all the 9427 potential foundational cause terms had to be read with the same level of certainty. Many could be eliminated by inspection, as long as the duplication was perceived.

7A - Appendix 1 - AD Causes Query - Visual Inspection Approach

I. **Core Literature Retrieval Thomson Medline** (76,663 records retrieved - core only)

TOPIC

Alzheimer*

OR

MESH HEADING

Alzheimer Disease

NOT

TOPIC

(streptozotocin OR scopolamine OR colchicine OR LPS-induc* OR polymorphism* OR Abeta-induc* OR "beta-amyloid-induc*" OR "amyloid-beta-induc*" OR "beta-amyloid peptide-induc*" OR "Abeta25-35-induc*" OR "Abeta25-35 peptide-induc*" OR Abeta40-induc* OR nontoxic OR non-toxic)

AND

Remainder of Query Intersected with Core Literature

II. TEXT FIELD TERMS

IIA. NON-LIFESTYLE-SPECIFIC COMPONENT - TOPIC

("2,4,6- triiodobenzoic acid" OR "3-deazaneplanocin A" OR "5AZA" OR "5-aza-deoxycytidine" OR "5-fluorouracil" OR "9-alpha fluorocortisol" OR "9-alpha fluoroprednisolone" OR "9-hydroxy-2-methylellipticinium" OR "acarbose" OR "ACE inhibitor*" OR "acetaminophen" OR "acetazolamide" OR "acetylsalicylic acid" OR "acyclovir" OR "adalimumab" OR "adefovir" OR "adriamycin" OR "alclofenac" OR "aliskiren" OR "alizapride" OR "allopurinol" OR "all-trans-retinoic acid" OR "alpha-mercaptopropionylglycine" OR "amikacin" OR "Aminoglycoside*" OR "Amiodarone" OR "amitriptyline" OR "amlodipine" OR "amoxicillin" OR "amphetamine*" OR "amphotericin b" OR "ampicillin" OR "ampiroxicam" OR "anabolic steroid*" OR "Anaesthetic*" OR "Analgesic*" OR "anasthesia" OR "androgen deprivation therapy" OR "anesthetic*" OR "anthracycline" OR "antiadrenergic agent*" OR "anti-adrenergic agent*" OR "antiadrenergic drug*" OR "anti-adrenergic drug*" OR "antiallergic agent*" OR "Anti-Allergic agent*" OR "antiallergic drug*" OR "Anti-Allergic drug*" OR "antiandrogen* agent*" OR "anti-androgen* agent*" OR "antiandrogen* drug*" OR "anti-androgen* drug*" OR "antianginal agent*" OR "anti-anginal agent*" OR "antianginal drug*" OR "anti-anginal drug*" OR "antiangiogenesis agent*" OR "anti-angiogenesis agent*" OR "antiangiogenesis drug*" OR "anti-angiogenesis drug*" OR "antiarrhythmic agent*" OR "antiarrhythmic drug*" OR "anti-arrythmatic agent*" OR "anti-arrythmatic drug*" OR "antiasthmatic agent*" OR "anti-asthmatic agent*"

OR "antiasthmatic drug*" OR "anti-asthmatic drug*" OR "antibacterial agent*" OR "Anti-bacterial agent*" OR "antibacterial drug*" OR "Anti-bacterial drug*" OR "antibiotic*" OR "antibone-loss agent*" OR "Anti-Bone-Loss agent*" OR "antibone-loss drug*" OR "Anti-Bone-Loss drug*" OR "anticholinergic agent*" OR "anti-cholinergic agent*" OR "anti-cholinergic drug*" OR "anticholinergic* drug*" OR "anticoagulant*" OR "Anti-coagulant*" OR "anticonvulsant*" OR "anti-convulsant*" OR "antidepressant*" OR "anti-depressant*" OR "Antidiabetic agent*" OR "anti-diabetic agent*" OR "Antidiabetic drug*" OR "anti-diabetic drug*" OR "antidiarrheal agent*" OR "anti-diarrheal agent*" OR "antidiarrheal drug*" OR "anti-diarrheal drug*" OR "anti-emetic" OR "antiemetic*" OR "antifungal agent*" OR "anti-fungal agent*" OR "antifungal drug*" OR "anti-fungal drug*" OR "antigonadotropic agent*" OR "anti-gonadotropic agent*" OR "antigonadotropic drug*" OR "anti-gonadotropic drug*" OR "antigout agent*" OR "anti-gout agent*" OR "antigout drug*" OR "anti-gout drug*" OR "antihistamine agent*" OR "anti-histamine agent*" OR "antihistamine drug*" OR "anti-histamine drug*" OR "Antihypertensive agent*" OR "anti-hypertensive agent*" OR "Antihypertensive drug*" OR "anti-hypertensive drug*" OR "antiinfective agent*" OR "Anti-Infective agent*" OR "antiinfective drug*" OR "Anti-Infective drug*" OR "anti-infective*" OR "antiinflammatory agent*" OR "Anti-Inflammatory agent*" OR "antiinflammatory drug*" OR "Anti-Inflammatory drug*" OR "antimalarial agent*" OR "anti-malarial agent*" OR "antimalarial drug*" OR "anti-malarial drug*" OR "antimetabolite agent*" OR "anti-metabolite agent*" OR "antimetabolite drug*" OR "anti-metabolite drug*" OR "antimigraine agent*" OR "anti-migraine agent*" OR "antimigraine drug*" OR "anti-migraine drug*" OR "Antineoplastic Agent*" OR "anti-neoplastic agent*" OR "Antineoplastic drug*" OR "anti-neoplastic drug*" OR "antiparkinson agent*" OR "anti-parkinson agent*" OR "antiparkinson drug*" OR "anti-parkinson drug*" OR "antiplatelet agent*" OR "anti-platelet agent*" OR "antiplatelet drug*" OR "anti-platelet drug*" OR "antipseudomonal agent*" OR "anti-pseudomonal agent*" OR "antipseudomonal drug*" OR "anti-pseudomonal drug*" OR "antipsoriatic agent*" OR "anti-psoriatic agent*" OR "antipsoriatic drug*" OR "anti-psoriatic drug*" OR "Antipsychotic Agent*" OR "Anti-psychotic agent*" OR "Antipsychotic drug*" OR "Anti-psychotic drug*" OR "Antiretroviral Agent*" OR "Anti-retroviral Agent*" OR "Antiretroviral drug*" OR "Antiretroviral drug*" OR "antiretroviral therapy" OR "Antirheumatic Agent*" OR "anti-rheumatic agent*" OR "Antirheumatic drug*" OR "anti-rheumatic drug*" OR "antiseptic agent*" OR "anti-septic agent*" OR "antiseptic drug*" OR "anti-septic drug*" OR "antispasmodic agent*" OR "anti-spasmodic agent*" OR "antispasmodic drug*" OR "anti-spasmodic drug*" OR "anti-thymocyte serum" OR "Antithyroid Agent*" OR "Anti-thyroid Agent*" OR "Antithyroid drug*" OR "Anti-thyroid drug*" OR "antitoxin*" OR "anti-toxin*" OR "antituberculosis agent*" OR "anti-tuberculosis agent*" OR "antituberculosis drug*" OR "anti-tuberculosis drug*" OR "antitussive agent*" OR "anti-tussive agent*" OR "antitussive drug*" OR "anti-tussive drug*" OR "antivenin*" OR "antivertigo agent*" OR "anti-vertigo agent*" OR "antivertigo drug*" OR "anti-vertigo drug*" OR "Antiviral agent*" OR "Anti-viral agent*" OR "Antiviral drug*" OR "Anti-viral drug*" OR "aprotinin" OR "aspirin" OR "AT1 receptor antagonists" OR "atazanavir" OR "atorvastatin" OR "axitinib" OR "azacitadine" OR "azathioprine" OR "azithromycin" OR "Azole*" OR "Barbiturate*" OR "bardoxolone methyl" OR "benfluorex" OR "benoxaprofen" OR "beta-lactam" OR "bevacizumab" OR "bezafibrate" OR "bisacodyl" OR "Bisphosphonate*" OR "Bleomycin" OR "bortezomib" OR "bucillamine" OR "bupivacaine" OR "buspirone" OR "caffeine" OR "calcineurin inhibitor*" OR "calcitriol" OR "Calcium Channel Blocker" OR "Calcium channel blocker*" OR "capecitabine" OR

"captopril" OR "carbamazepine" OR "carbenoxolone" OR "carbimazole" OR "carboplatin" OR "Cardiovascular Agent*" OR "carmustine" OR "C-arylsuccinimides" OR "cediranib" OR "cefdinir" OR "cefoxitin" OR "ceftriaxone" OR "cefuroxime" OR "celecoxib" OR "Central Nervous System Agent*" OR "cephaloridine" OR "cephalosporins" OR "Cephems" OR "cetuximab" OR "chlorambucil" OR "Chloramphenicol" OR "chlormezanone" OR "chloroquine" OR "Chlorpromazine" OR "chlorprothixene" OR "chlorthalidone" OR "cidofovir" OR "cimetidine" OR "ciprofibrate" OR "ciprofloxacin" OR "cisplatin" OR "clarithromycin" OR "clometacin" OR "clomipramine" OR "clopentixol" OR "clopidogrel" OR "cloxacillin" OR "clozapine" OR "colchicine" OR "colistin" OR "contrast medium" OR "coronary artery bypass" OR "corosolic acid" OR "Corticosteroid*" OR "cyclophosphamide" OR "cycloserine" OR "cyclosporine" OR "cytarabine" OR "cytosine arabinoside" OR "dasatinib" OR "daunomycin" OR "daunorubicin" OR "decitabine" OR "deferasirox" OR "deferoxamine" OR "demeclocycline" OR "deoxycorticosterone acetate" OR "desipramine" OR "dexamethasone" OR "dexfenfluramine" OR "dexmethylphenidate" OR "dextran" OR "diaziquone" OR "diclofenac" OR "didecyldimethylammonium chloride" OR "diethyacetylurea" OR "diflunisal" OR "Digitalis" OR "diltiazem" OR "diphenylhydantoin" OR "diphosphonates" OR "dipivalyl adrenaline hydrochloride" OR "dipyrone" OR "disopyramide" OR "Diuretic*" OR "doxepin" OR "doxorubicin" OR "doxycycline" OR "d-penicillamine" OR "dRK6" OR "efavirenz" OR "enoxaparin" OR "epoetin" OR "erythromycin" OR "erythropoietin" OR "esomeprazole" OR "etanercept" OR "ethambutol" OR "ethosuximide" OR "famotidine" OR "fenbufen" OR "fenclofenac" OR "fenfluramine" OR "fenofibrate" OR "fenoldopam" OR "fenoprofen" OR "Fibrate therapy" OR "flubiprofen" OR "flucloxacillin" OR "fluindione" OR "Fluoroquinolones" OR "flupenthixol" OR "fluphenazine" OR "flurbiprofen" OR "flurithromycin" OR "fondaparinux sodium" OR "foscarnet" OR "furantoin" OR "furosemide" OR "fusidic acid" OR "FYX-051" OR "gabapentin" OR "gadodiamide" OR "Gadolinium" OR "gadopentetate dimeglumine" OR "Gastrointestinal Agent*" OR "gatifloxacin" OR "GBCA" OR "GCCA" OR "gefitinib" OR "gemcitabine" OR "gemfibrozil" OR "gentamicin" OR "germicide*" OR "Glucocorticoid*" OR "glycyrrhizinic acid" OR "Haloperidol" OR "Halothane" OR "Hematologic Agent*" OR "heparin" OR "hetastarch" OR "high insulin" OR "hydralazine" OR "hydrochlorothiazide" OR "hydroxychloroquine" OR "hydroxyethylstarch" OR "hydroxymethylglutaryl-CoA reductase inhibitor*" OR "hylan G-F 20" OR "Hypnotic Agent*" OR "iatrogenic" OR "ibuprofen" OR "ifosfamide" OR "IGF-1" OR "iloprost" OR "imatinib" OR "imipramine" OR "imiquimod" OR "Immunosuppressive Agent*" OR "indinavir" OR "indomethacin" OR "infliximab" OR "Interferon*" OR "intravenous immunoglobulin*" OR "Iodine" OR "iodixanol" OR "iohexol" OR "ionizing radiation" OR "iopamidol" OR "ioxilan" OR "iron sucrose" OR "iron-induced" OR "iron-overload" OR "isocarboxazid" OR "isoniazid" OR "isoprenaline" OR "ketamine" OR "Ketoconazole" OR "ketoprofen" OR "ketorolac" OR "lansoprazole" OR "lapatinib" OR "leflunomide" OR "levetiracetam" OR "levofloxacin" OR "Lipid Regulating Agent*" OR "lithium" OR "lopinavir" OR "loratadine" OR "loxapine" OR "mannitol" OR "maprotiline" OR "mefanamic acid" OR "meropenem" OR "mesalamine" OR "mesalazine" OR "mesoridazine" OR "metamizole" OR "metformin" OR "methicillin" OR "methimazole" OR "methocarbamol" OR "methotrexate" OR "methotrimeprazine" OR "methoxyflurance" OR "methyldopa" OR "methylphenidate" OR "methysergide" OR "metolazone" OR "metoprolol" OR "Metronidazole" OR "midecamycin acetate" OR "Mineralcorticoid*" OR "minocycline" OR "mirtazapine" OR "mitomycin" OR "Mood Stabilizer*" OR "morphine" OR "Movement Stabilizer*" OR "moxifloxacin" OR "Muscle Relaxant*" OR "Mustard gas" OR "muzolimine" OR "nafcillin" OR

"naphazoline hydrochloride" OR "naproxen" OR "N-arylsuccinimides" OR "Nasal decongestant*" OR "nelfinavir" OR "neomycin" OR "Niacin" OR "nifedipine" OR "niflumic acid" OR "nimesulide" OR "nitrendipine" OR "nitrofurantoin" OR "nitrogen mustard" OR "Nitroglycerin" OR "nitrosureas" OR "nomifensine" OR "Nonsteroidal anti-inflammatory drug*" OR "norepinephrine" OR "norfloxacin" OR "nortriptyline" OR "NSAID*" OR "NVP-BKM120" OR "ofloxasin" OR "olanzapine" OR "olmetin" OR "olsalazine" OR "omeprazole" OR "orlistat" OR "oxaliplatin" OR "oxymetazoline hydrochloride" OR "oxytetracycline" OR "ozurdex" OR "paliperidone" OR "pamidronate" OR "panitumumab" OR "pantoprazole" OR "papaverine" OR "paracetamol" OR "paroxetine" OR "pazopanib" OR "pefloxacin" OR "Penams" OR "penicillamine" OR "penicillin" OR "pentamidine" OR "pentazocine" OR "pericyazine" OR "perphenazine" OR "phenacetin" OR "phenindione" OR "phenobarbital" OR "phenylbutazone" OR "phenylephrine" OR "phenylpropanolamine" OR "phenytoin" OR "phosphatidylinositol-3-kinase inhibitor*" OR "physostigmine" OR "pimozide" OR "piperacillin" OR "piroxicam" OR "pirprofen" OR "platalet aggregation inhibitor*" OR "polymyxin B" OR "pranlukast" OR "prednisolone" OR "Primaquine" OR "probenecid" OR "procainamide" OR "prochlorperazine" OR "propoxyphene" OR "propylthiouracil" OR "protamine" OR "Proton pump inhibitor*" OR "prulifloxacin" OR "pseudoephedrine hydrochloride" OR "ptu-induced" OR "puromycin" OR "quetiapine" OR "quinacrine" OR "quinidine" OR "quinine" OR "quinolone" OR "rabeprazole" OR "radiofrequency-induced cosmetic volume reduction" OR "ranitidine" OR "rapamycin" OR "rhuepo-induced" OR "rifampicin" OR "rifampin" OR "risperidone" OR "Ritalin" OR "ritodrine hydrochloride" OR "ritonavir" OR "rofecoxib" OR "rosuvastatin" OR "scopolamine" OR "selegiline" OR "sibutramine" OR "simvastatin" OR "sodium barbital" OR "sodium valproate" OR "sorafenib" OR "spirapril" OR "spironolactone" OR "Statin*" OR "Steroid*" OR "Stimulant*" OR "streptomycin" OR "streptozocin" OR "streptozotocin" OR "Succinimide derivative*" OR "sulfadiazine" OR "sulfamethoxazole" OR "sulfasalazine" OR "Sulfonamide*" OR "sulfonylureas" OR "sulfur mustard" OR "sulindac" OR "sulphinpyrazone" OR "sulpiride" OR "sunitinib" OR "superdrol" OR "tacrolimus" OR "Tamoxifen" OR "tazobactam" OR "telazol" OR "telithromycin" OR "tenofovir" OR "testosterone" OR "tetrabenazine" OR "Tetracycline*" OR "tetrahydrozoline hydrochloride" OR "tetrandrine" OR "thiazides" OR "thiopropazate" OR "thioproperazine" OR "Thioridazine" OR "thiothixene" OR "thrombolytic therapy" OR "ticlopidine" OR "tiletamine" OR "tiopronin" OR "tobramicin" OR "triamterene" OR "trichostatin A" OR "Tricyclics" OR "trimethadione" OR "trimethoprim" OR "trimipramine" OR "tripelennamine" OR "valdecoxib" OR "Valproic Acid" OR "valpromide" OR "vancomycin" OR "venlafaxine" OR "verapamil" OR "verteporfin" OR "warfarin" OR "whole-body irradiation" OR "wortmannin" OR "yohimbine" OR "zoledronate" OR "zopiclone" OR "zotepine" OR "zuclopenthixol" OR "4-HNE" OR "7-Ketocholesterol" OR "aflatoxin" OR "Aipysurus laevis venom" OR "amorimia exotropica" OR "anti-mouse-GBM sera" OR "AOPP-modified rat serum albumin" OR "apoferritin" OR "bee sting*" OR "beta-conglycinin" OR "bovine serum albumin" OR "cantharidin" OR "ceramide" OR "citrinin" OR "concanavalin A" OR "connective tissue growth factor" OR "cow milk processing" OR "CTGF" OR "cylindrospermopsin" OR "deoxynivalenol" OR "D-fructofuranosyl" OR "Endotoxin*" OR "Exotoxin*" OR "fumonisin B1" OR "homopolysaccharide" OR "indican" OR "indoxyl sulfate" OR "levan" OR "lipopolysaccharide" OR "lipopolysaccharide-induced" OR "L-NAME" OR "L-NNA" OR "lps-induced" OR "monocrotaline" OR "monosodium urate crystal" OR "mycobacterial infection*" OR "Mycotoxin*" OR "nephritogenoside" OR "NG-nitro-L-arginine methyl ester" OR "Nitroarginine" OR "nivalenol" OR "Nω-nitro-L-arginine"

OR "oak toxicosis" OR "ochratoxin A" OR "Ochratoxin*" OR "O-glycosylated IgA rheumatoid factor" OR "p-Cresyl sulfate" OR "PDGF-BB" OR "penicillic acid" OR "Platelet-derived growth factor-BB" OR "pufferfish tetrodotoxin" OR "quercus calliprinos" OR "scorpion sting*" OR "sea anemone Phyllodiscus semoni" OR "sea snake venom" OR "snake bite" OR "stinging insect venom" OR "tetrodotoxin" OR "Tityus serrulatus scorpion venom" OR "Tricothecene*" OR "U1-70-kDa small nuclear ribonucleoprotein/snRPN70" OR "viper snake venom" OR "vomitoxin" OR "wasp sting*" OR "yew" OR "*Bacteri*" OR "*Chia" OR "*Ococcus" OR "*Omonas" OR "adenine" OR "Aspergillus " OR "Bartonella henselae" OR "beta-hemolysin " OR "Brucella" OR "Burkholderia pseudomallei" OR "C. difficile toxin A" OR "C. difficile toxin B" OR "Campylobacter jejuni" OR "Campylobacter jejuni" OR "Candida albicans" OR "Candida tropicalis" OR "Candidemia" OR "Capillaria hepatica" OR "Chlamydia pneumoniae" OR "Chlamydia" OR "Chlamydophila" OR "Citrobacter rodentium" OR "Clostridium" OR "Corynebacterium diphtheriae" OR "diphtheria toxin" OR "Corynebacterium renale" OR "Dirofilaria immitis" OR "Echinococcus" OR "Ehrlichia canis" OR "Enterococcus faecalis" OR "Escherichia coli" OR "e. coli" OR "falciparum malaria" OR "malaria" OR "Fusarium graminearum" OR "Gemella haemolysans" OR "Haemophilus" OR "Helicobacter pylori" OR "Klebsiella pneumoniae" OR "leprosy" OR "Mycobacterium leprae" OR "Mycobacterium lepromatosis" OR "Leptospirosis" OR "leptospira" OR "marcescens" OR "Mycoplasma" OR "Neisseria" OR "Nematode*" OR "Parasite*" OR "Penicillium aurantiogriseum" OR "Penicillium aurantiogriseum" OR "Plasmodium brasilianum" OR "Propionibacterium acnes" OR "Proteus mirabilis" OR "Pseudomonas aeruginosa" OR "Rickettsia" OR "Rochalimaea" OR "salmonella" OR "Schistosoma haematobium" OR "Schistosoma mansoni" OR "Serratia marcescens" OR "staphylococcal infection*" OR "Staphylococcus aureus" OR "Streptococcus agalactiae" OR "Streptococcus mutans" OR "Streptococcus pyogenes" OR "streptococcal pyrogenic exotoxin B" OR "Thy-1.1 monoclonal antibody" OR "Toxocara canis" OR "Treponema" OR "Trichinella spiralis" OR "Trypanosoma brucei" OR "Tyrophagus putrescentiae" OR "Vibrio" OR "Yersinia" OR "*OBACTER" OR "*nitrophenol*" OR "*benzene" OR "*ethane" OR "*phthalate" OR "*toluene" OR "1,1,1-trichloroethane" OR "12-O-tetradecanoylphorbol-13-acetate " OR "1-methyl-4-phenylpyridinium" OR "2,3,5-triiodobenzoic acid" OR "2,3,7,8-tetrachlorodibenzo-p-dioxin" OR "2-Amino-4-(ethylthio)butyric acid) " OR "acetaldehyde" OR "acrolein" OR "Air pollutant*" OR "air pollution" OR "aldrin" OR "alloxan" OR "alpha-Naphthylisothiocyanate" OR "aluminium" OR "aluminum" OR "ammonium perchlorate" OR "anti-trinitrophenol switch variant mAbs" OR "arsenic" OR "asbestos" OR "asphalt" OR "atrazine" OR "beryllium" OR "Bis(2-ethylhexyl) phthalate" OR "bismuth" OR "bitumen" OR "bromodichloromethane" OR "bromoform" OR "cadmium" OR "carbon tetrachloride" OR "cedar dust" OR "cerium oxide nanoparticles" OR "chloroform" OR "chlorpyrifos" OR "chromic acid " OR "chromium" OR "copper sulphate " OR "copper" OR "cotton pellets" OR "cyromazine" OR "decabrom*" OR "DEHP" OR "diazinon" OR "dibromochloromethane" OR "dichloro*" OR "diesel" OR "diethylene glycol" OR "dimethylnitrosamine " OR "dinitro*" OR "dinitrochlorobenzene" OR "dioxane" OR "dioxin " OR "domestic gas" OR "ethionine " OR "ethylene dibromide " OR "ethylene glycol" OR "fiberglass" OR "fibreglass" OR "fluoro-10-methyl-1-2-benzanthracene " OR "formaldehyde" OR "gasoline" OR "germanium" OR "glycerol" OR "grain dust" OR "halomethane* " OR "hcy-induced " OR "Heavy metal*" OR "Herbicide*" OR "hexabrom*" OR "hexachloro*" OR "hgcl2" OR "homocysteine" OR "house dust mite" OR "Hydrocarbons" OR "Insecticide*" OR "isopropyl alcohol" OR "jatropha curcas phorbol ester" OR "ketones" OR "malathion" OR "maleic vinyl ether anhydride " OR "Maneb" OR

"melamine" OR "menadione sodium bisulfite" OR "mercuric chloride" OR "Mercury" OR "methyl tertiary-butyl ether " OR "methylene chloride" OR "methylglyoxal" OR "multiwalled carbon nanotube*" OR "N,N′-dimethyl-4,4′-bipyridinium dichloride" OR "N,N'-diacetylbenzidine " OR "N-3-5-dichlorophenyl-succinimide" OR "nanocopper" OR "n-methyl-n 1-nitro-n-nitroso guanidine " OR "nonylphenol" OR "octylphenol" OR "oxalates" OR "oxidant-induced" OR "p-Aminophenol" OR "parachloro*" OR "paraphenylenediamine" OR "paraquat " OR "Particulates" OR "pb" OR "pentachloro*" OR "pentachlorophenol" OR "perchloroethylene" OR "perfluor*" OR "perfluoroalkyl chemicals" OR "perfluorooctane sulfonate" OR "perfluorooctanoic acid" OR "Pesticide*" OR "Phenols" OR "phenylenediamine " OR "picric acid" OR "plant growth regulator* " OR "polybrom*" OR "polychlor*" OR "polychlorinated organic compound* " OR "polyfluor*" OR "polymethyl methacrylate " OR "potassium bichromate " OR "pristane" OR "p-xylene" OR "pyrinuron" OR "pyruvaldehyde " OR "silane " OR "silica" OR "silicon dioxide" OR "single wall carbon nanotube*" OR "styrene" OR "tetrabrom*" OR "tetrachloro*" OR "tetrachloroethylene" OR "thioacetamide " OR "titanium dioxide nanoparticles" OR "toluene" OR "trichloro*" OR "trichloroethylene" OR "trimethylpentane" OR "trinitrobenzenesulfonic acid " OR "Trinitrophenol" OR "uranium" OR "uranyl nitrate" OR "vacor" OR "wood dust" OR "wood preservatives" OR "xylene" OR "zinc phosphide" OR "sediment-associated" OR "particle-associated" OR "traffic-related" OR "work-related" OR EMF) near/20 ("poison*" OR "ecotoxologic* effect*" OR "occupation*" OR pollut* OR "*virus*" OR environmental OR "induc*" OR "damage-caus*" OR "drug*-caus*" OR "infect*-caus*" OR "chemotherapy-caus*" OR "treat*-caus*" OR "anesthesia-caus*" OR "chemical*-caus*" OR "cytokine*-caus*" OR "surg*-caus*" OR "radiation-caus*" OR "steroid-caus*" OR "mechanically-caus*" OR "promot* progression" OR "caus* accumulation" OR "caus* * accumulation" OR "progression of" OR expos* OR contamina* OR chemicals OR abuse* OR induc* OR "long-term effect*" OR "inhibit* *protection" OR dysfunction* OR aggregation OR accumulation OR "disease link* to" OR "chemical initiator*" OR "stimulat* microglia" OR "activat* microglia" OR "increas* risk*" OR "increas* the risk*" OR "adverse event*" OR "adverse reaction*" OR "adverse * event*" OR "adverse * reaction" OR "adverse effect*" OR "adverse * effect*" OR hypersensitivity OR aggravat* OR exacerbat* OR detriment* OR "caus* *toxi*" OR "increas* *toxi" OR "produc* *toxi*" OR "enhanc* *toxi*" OR "stimulat* *toxi*" OR "accelerat* *toxi*" OR "caus* degrad*" OR "increas* degrad*" OR "caus* damag*" OR "increas* damag*" OR "caus* * *toxi*" OR "increas* * *toxi" OR "produc* * *toxi*" OR "enhanc* * *toxi*" OR "stimulat* * *toxi*" OR "accelerat* * *toxi*" OR "caus* * degrad*" OR "increas* * degrad*" OR "caus* * damag*" OR "increas* * damag*" OR "*toxi* caus* by" OR "*toxi* increas* by" OR "*toxi* produc* by" OR "*toxi* enhanc* by" OR "*toxi* stimulat* by" OR "*toxi* accelerat* by" OR "damag* caus* by" OR "*damag* increas* by" OR deleterious OR deteriorat* OR trigger* OR worsen* OR harm* OR hazard* OR "side-effect*" OR dangerous OR destructive OR injurious OR unsafe OR "increas* amyloid-beta" OR "increas* beta-amyloid" OR "increas* Abeta" OR "increas* senile plaque*" OR "increas* tau aggregat*" OR "increas* T-tau" OR "increas* P-tau" OR "increas*total tau" OR "increas* phospho-tau" OR "increas* tau protein*" OR "increas* hyperphosphorylated tau" OR "increas* neurofibrillary tangle*" OR "enhanc* amyloid-beta" OR "enhanc* beta-amyloid" OR "enhanc* Abeta" OR "enhanc* senile plaque*" OR "enhanc* tau aggregat*" OR "enhanc* T-tau" OR "enhanc* P-tau" OR "enhanc*total tau" OR "enhanc* phospho-tau" OR "enhanc* tau protein*" OR "enhanc* hyperphosphorylated tau" OR "enhanc* neurofibrillary tangle*" OR "stimulat* amyloid-beta" OR "stimulat* beta-amyloid" OR "stimulat* Abeta"

OR "stimulat* senile plaque*" OR "stimulat* tau aggregat*" OR "stimulat* T-tau" OR "stimulat* P-tau" OR "stimulat*total tau" OR "stimulat* phospho-tau" OR "stimulat* tau protein*" OR "stimulat* hyperphosphorylated tau" OR "stimulat* neurofibrillary tangle*" OR "elevat* amyloid-beta" OR "elevat* beta-amyloid" OR "elevat* Abeta" OR "elevat* senile plaque*" OR "elevat* tau aggregat*" OR "elevat* T-tau" OR "elevat* P-tau" OR "elevat*total tau" OR "elevat* phospho-tau" OR "elevat* tau protein*" OR "elevat* hyperphosphorylated tau" OR "elevat* neurofibrillary tangle*" OR "induc* amyloid-beta" OR "induc* beta-amyloid" OR "induc* Abeta" OR "induc* senile plaque*" OR "induc* tau aggregat*" OR "induc* T-tau" OR "induc* P-tau" OR "induc*total tau" OR "induc* phospho-tau" OR "induc* tau protein*" OR "induc* hyperphosphorylated tau" OR "induc* neurofibrillary tangle*" OR "produc* amyloid-beta" OR "produc* beta-amyloid" OR "produc* Abeta" OR "produc* senile plaque*" OR "produc* tau aggregat*" OR "produc* T-tau" OR "produc* P-tau" OR "produc*total tau" OR "produc* phospho-tau" OR "produc* tau protein*" OR "produc* hyperphosphorylated tau" OR "produc* neurofibrillary tangle*" OR "accelerat* amyloid-beta" OR "accelerat* beta-amyloid" OR "accelerat* Abeta" OR "accelerat* senile plaque*" OR "accelerat* tau aggregat*" OR "accelerat* T-tau" OR "accelerat* P-tau" OR "accelerat*total tau" OR "accelerat* phospho-tau" OR "accelerat* tau protein*" OR "accelerat* hyperphosphorylated tau" OR "accelerat* neurofibrillary tangle*" OR "amyloid-beta induc* by" OR "beta-amyloid induc* by" OR "Abeta induc* by" OR "senile plaque* induc* by" OR "tau aggregat* induc* by" OR "T-tau induc* by" OR "P-tau induc* by" OR "total tau induc* by" OR "phospho-tau induc* by" OR "tau protein* induc* by" OR "hyperphosphorylated tau induc* by" OR "neurofibrillary tangle* induc* by" OR "amyloid-beta produc* by" OR "beta-amyloid produc* by" OR "Abeta produc* by" OR "senile plaque* produc* by" OR "tau aggregat* produc* by" OR "T-tau produc* by" OR "P-tau produc* by" OR "total tau produc* by" OR "phospho-tau produc* by" OR "tau protein* produc* by" OR "hyperphosphorylated tau produc* by" OR "neurofibrillary tangle* produc* by" OR "caus* Alzheimer*" OR "caus* dementia" OR "caus* cognitive decline" OR "caus* brain* decline" OR "caus* functional decline" OR "caus* memory decline" OR "caus* cognitive deficit*" OR "caus* language deficit*" OR "caus* memory deficit*" OR "caus* plasticity deficit*" OR "caus* behavioral deficit*" OR "caus* saccade deficit*" OR "caus* learning deficit*" OR "caus* neuropsychological deficit*" OR "caus* cognitive impair*" OR "caus* vascular impair*" OR "caus* memory impair*" OR "caus* neurogenesis impair*" OR "caus* neuropsychological impair*" OR "caus* mind impair*" OR "caus* functional impair*" OR "caus* learning impair*" OR "caus* executive function impair*" OR "caus* cognitive loss*" OR "caus* neuronal loss*" OR "caus* synaptic loss*" OR "caus* memory loss*" OR "caus* loss of memory" OR "caus* hearing loss*" OR "caus* volume loss*" OR "caus* Impair* face recognition" OR "caus* Impair* reasoning" OR "caus* Impair* judgment" OR "caus* Impair* problem solving" OR "caus* inflamm*" OR "caus* oxidative stress" OR "caus* neuropathology" OR "caus* diabetes" OR "caus* hypertension" OR "caus* high cholesterol" OR "caus* hypercholesterolemia" OR "caus* obesity" OR "caus* metabolic syndrome" OR "induc* Alzheimer*" OR "induc* dementia" OR "induc* cognitive decline" OR "induc* brain* decline" OR "induc* functional decline" OR "induc* memory decline" OR "induc* cognitive deficit*" OR "induc* language deficit*" OR "induc* memory deficit*" OR "induc* plasticity deficit*" OR "induc* behavioral deficit*" OR "induc* saccade deficit*" OR "induc* learning deficit*" OR "induc* neuropsychological deficit*" OR "induc* cognitive impair*" OR "induc* vascular impair*" OR "induc* memory impair*" OR "induc* neurogenesis impair*" OR "induc* neuropsychological impair*" OR "induc* mind impair*" OR "induc* functional impair*" OR

"induc* learning impair*" OR "induc* executive function impair*" OR "induc* cognitive loss*" OR "induc* neuronal loss*" OR "induc* synaptic loss*" OR "induc* memory loss*" OR "induc* loss of memory" OR "induc* hearing loss*" OR "induc* volume loss*" OR "induc* Impair* face recognition" OR "induc* Impair* reasoning" OR "induc* Impair* judgment" OR "induc* Impair* problem solving" OR "induc* inflamm*" OR "induc* oxidative stress" OR "induc* neuropathology" OR "induc* diabetes" OR "induc* hypertension" OR "induc* high cholesterol" OR "induc* hypercholesterolemia" OR "induc* obesity" OR "induc* metabolic syndrome" OR "produc* Alzheimer*" OR "produc* dementia" OR "produc* cognitive decline" OR "produc* brain* decline" OR "produc* functional decline" OR "produc* memory decline" OR "produc* cognitive deficit*" OR "produc* language deficit*" OR "produc* memory deficit*" OR "produc* plasticity deficit*" OR "produc* behavioral deficit*" OR "produc* saccade deficit*" OR "produc* learning deficit*" OR "produc* neuropsychological deficit*" OR "produc* cognitive impair*" OR "produc* vascular impair*" OR "produc* memory impair*" OR "produc* neurogenesis impair*" OR "produc* neuropsychological impair*" OR "produc* mind impair*" OR "produc* functional impair*" OR "produc* learning impair*" OR "produc* executive function impair*" OR "produc* cognitive loss*" OR "produc* neuronal loss*" OR "produc* synaptic loss*" OR "produc* memory loss*" OR "produc* loss of memory" OR "produc* hearing loss*" OR "produc* volume loss*" OR "produc* Impair* face recognition" OR "produc* Impair* reasoning" OR "produc* Impair* judgment" OR "produc* Impair* problem solving" OR "produc* inflamm*" OR "produc* oxidative stress" OR "produc* neuropathology" OR "produc* diabetes" OR "produc* hypertension" OR "produc* high cholesterol" OR "produc* hypercholesterolemia" OR "produc* obesity" OR "produc* metabolic syndrome" OR "increas* Alzheimer*" OR "increas* dementia" OR "increas* cognitive decline" OR "increas* brain* decline" OR "increas* functional decline" OR "increas* memory decline" OR "increas* cognitive deficit*" OR "increas* language deficit*" OR "increas* memory deficit*" OR "increas* plasticity deficit*" OR "increas* behavioral deficit*" OR "increas* saccade deficit*" OR "increas* learning deficit*" OR "increas* neuropsychological deficit*" OR "increas* cognitive impair*" OR "increas* vascular impair*" OR "increas* memory impair*" OR "increas* neurogenesis impair*" OR "increas* neuropsychological impair*" OR "increas* mind impair*" OR "increas* functional impair*" OR "increas* learning impair*" OR "increas* executive function impair*" OR "increas* cognitive loss*" OR "increas* neuronal loss*" OR "increas* synaptic loss*" OR "increas* memory loss*" OR "increas* loss of memory" OR "increas* hearing loss*" OR "increas* volume loss*" OR "increas* Impair* face recognition" OR "increas* Impair* reasoning" OR "increas* Impair* judgment" OR "increas* Impair* problem solving" OR "increas* inflamm*" OR "increas* oxidative stress" OR "increas* neuropathology" OR "increas* diabetes" OR "increas* hypertension" OR "increas* high cholesterol" OR "increas* hypercholesterolemia" OR "increas* obesity" OR "increas* metabolic syndrome" OR "exacerbat* Alzheimer*" OR "exacerbat* dementia" OR "exacerbat* cognitive decline" OR "exacerbat* brain* decline" OR "exacerbat* functional decline" OR "exacerbat* memory decline" OR "exacerbat* cognitive deficit*" OR "exacerbat* language deficit*" OR "exacerbat* memory deficit*" OR "exacerbat* plasticity deficit*" OR "exacerbat* behavioral deficit*" OR "exacerbat* saccade deficit*" OR "exacerbat* learning deficit*" OR "exacerbat* neuropsychological deficit*" OR "exacerbat* cognitive impair*" OR "exacerbat* vascular impair*" OR "exacerbat* memory impair*" OR "exacerbat* neurogenesis impair*" OR "exacerbat* neuropsychological impair*" OR "exacerbat* mind impair*" OR "exacerbat* functional impair*" OR "exacerbat* learning impair*" OR "exacerbat* executive function impair*" OR "exacerbat*

cognitive loss*" OR "exacerbat* neuronal loss*" OR "exacerbat* synaptic loss*" OR "exacerbat* memory loss*" OR "exacerbat* loss of memory" OR "exacerbat* hearing loss*" OR "exacerbat* volume loss*" OR "exacerbat* Impair* face recognition" OR "exacerbat* Impair* reasoning" OR "exacerbat* Impair* judgment" OR "exacerbat* Impair* problem solving" OR "exacerbat* inflamm*" OR "exacerbat* oxidative stress" OR "exacerbat* neuropathology" OR "exacerbat* diabetes" OR "exacerbat* hypertension" OR "exacerbat* high cholesterol" OR "exacerbat* hypercholesterolemia" OR "exacerbat* obesity" OR "exacerbat* metabolic syndrome" OR "trigger* Alzheimer*" OR "trigger* dementia" OR "trigger* cognitive decline" OR "trigger* brain* decline" OR "trigger* functional decline" OR "trigger* memory decline" OR "trigger* cognitive deficit*" OR "trigger* language deficit*" OR "trigger* memory deficit*" OR "trigger* plasticity deficit*" OR "trigger* behavioral deficit*" OR "trigger* saccade deficit*" OR "trigger* learning deficit*" OR "trigger* neuropsychological deficit*" OR "trigger* cognitive impair*" OR "trigger* vascular impair*" OR "trigger* memory impair*" OR "trigger* neurogenesis impair*" OR "trigger* neuropsychological impair*" OR "trigger* mind impair*" OR "trigger* functional impair*" OR "trigger* learning impair*" OR "trigger* executive function impair*" OR "trigger* cognitive loss*" OR "trigger* neuronal loss*" OR "trigger* synaptic loss*" OR "trigger* memory loss*" OR "trigger* loss of memory" OR "trigger* hearing loss*" OR "trigger* volume loss*" OR "trigger* Impair* face recognition" OR "trigger* Impair* reasoning" OR "trigger* Impair* judgment" OR "trigger* Impair* problem solving" OR "trigger* inflamm*" OR "trigger* oxidative stress" OR "trigger* neuropathology" OR "trigger* diabetes" OR "trigger* hypertension" OR "trigger* high cholesterol" OR "trigger* hypercholesterolemia" OR "trigger* obesity" OR "trigger* metabolic syndrome" OR "accelerat* Alzheimer*" OR "accelerat* dementia" OR "accelerat* cognitive decline" OR "accelerat* brain* decline" OR "accelerat* functional decline" OR "accelerat* memory decline" OR "accelerat* cognitive deficit*" OR "accelerat* language deficit*" OR "accelerat* memory deficit*" OR "accelerat* plasticity deficit*" OR "accelerat* behavioral deficit*" OR "accelerat* saccade deficit*" OR "accelerat* learning deficit*" OR "accelerat* neuropsychological deficit*" OR "accelerat* cognitive impair*" OR "accelerat* vascular impair*" OR "accelerat* memory impair*" OR "accelerat* neurogenesis impair*" OR "accelerat* neuropsychological impair*" OR "accelerat* mind impair*" OR "accelerat* functional impair*" OR "accelerat* learning impair*" OR "accelerat* executive function impair*" OR "accelerat* cognitive loss*" OR "accelerat* neuronal loss*" OR "accelerat* synaptic loss*" OR "accelerat* memory loss*" OR "accelerat* loss of memory" OR "accelerat* hearing loss*" OR "accelerat* volume loss*" OR "accelerat* Impair* face recognition" OR "accelerat* Impair* reasoning" OR "accelerat* Impair* judgment" OR "accelerat* Impair* problem solving" OR "accelerat* inflamm*" OR "accelerat* oxidative stress" OR "accelerat* neuropathology" OR "accelerat* diabetes" OR "accelerat* hypertension" OR "accelerat* high cholesterol" OR "accelerat* hypercholesterolemia" OR "accelerat* obesity" OR "accelerat* metabolic syndrome" OR "Alzheimer* * caused by" OR "dementia caused by" OR "cognitive decline caused by" OR "brain* decline caused by" OR "functional decline caused by" OR "memory decline caused by" OR "cognitive deficit* caused by" OR "language deficit* caused by" OR "memory deficit* caused by" OR "plasticity deficit* caused by" OR "behavioral deficit* caused by" OR "saccade deficit* caused by" OR "learning deficit* caused by" OR "neuropsychological deficit* caused by" OR "cognitive impair* caused by" OR "vascular impair* caused by" OR "memory impair* caused by" OR "neurogenesis impair* caused by" OR "neuropsychological impair* caused by" OR "mind impair* caused by" OR "functional impair* caused by" OR "learning impair* caused by" OR "

executive function impair* caused by" OR "cognitive loss* caused by" OR "neuronal loss* caused by" OR "synaptic loss* caused by" OR "memory loss* caused by" OR "loss of memory caused by" OR "hearing loss* caused by" OR "volume loss* caused by" OR "Impair* face recognition caused by" OR "Impair* reasoning caused by" OR "Impair* judgment caused by" OR "Impair* problem solving caused by" OR "inflamm* caused by" OR "oxidative stress caused by" OR "neuropathology caused by" OR "diabetes caused by" OR "hypertension caused by" OR "high cholesterol caused by" OR "hypercholesterolemia caused by" OR "obesity caused by" OR "metabolic syndrome caused by" OR "Alzheimer* * induced by" OR "dementia induced by" OR "cognitive decline induced by" OR "brain* decline induced by" OR "functional decline induced by" OR "memory decline induced by" OR "cognitive deficit* induced by" OR "language deficit* induced by" OR "memory deficit* induced by" OR "plasticity deficit* induced by" OR "behavioral deficit* induced by" OR "saccade deficit* induced by" OR "learning deficit* induced by" OR "neuropsychological deficit* induced by" OR "cognitive impair* induced by" OR "vascular impair* induced by" OR "memory impair* induced by" OR "neurogenesis impair* induced by" OR "neuropsychological impair* induced by" OR "mind impair* induced by" OR "functional impair* induced by" OR "learning impair* induced by" OR " executive function impair* induced by" OR "cognitive loss* induced by" OR "neuronal loss* induced by" OR "synaptic loss* induced by" OR "memory loss* induced by" OR "loss of memory induced by" OR "hearing loss* induced by" OR "volume loss* induced by" OR "Impair* face recognition induced by" OR "Impair* reasoning induced by" OR "Impair* judgment induced by" OR "Impair* problem solving induced by" OR "inflamm* induced by" OR "oxidative stress induced by" OR "neuropathology induced by" OR "diabetes induced by" OR "hypertension induced by" OR "high cholesterol induced by" OR "hypercholesterolemia induced by" OR "obesity induced by" OR "metabolic syndrome induced by")

OR

IIB. LIFESTYLE-SPECIFIC COMPONENT

IIB1. LIFESTYLE-SPECIFIC COMPONENT - TOPIC

("2,3-Pentanedione" OR "acidogenic diet*" OR "acrylamide" OR "activity restriction" OR "acute stress" OR "additives" OR "advanced glycation end product*" OR "Advanced glycosylation end product*" OR "adverse food" OR "alcohol abuse*" OR "alcohol consum*" OR "alcohol intake" OR "alcoholic*" OR "alcohol-induc*" OR "alcoholism" OR "Amanita phalloides" OR "amphetamine*" OR "anabolic steroid*" OR "areca nut chewing" OR arnica OR "aspartame" OR "betel nut chewing" OR "binge eating" OR "biomass fuel for cooking" OR "bitter orange" OR "caffeine" OR "childhood adversity" OR "chinese herb*" OR "chlorogenic acid" OR "cholesterol-induced" OR "cigarette*" OR "cocaine" OR "cola" OR "competitive strength exercise training" OR cortinarius OR "dehydration" OR "depression-caus*" OR "depression-induc*" OR dextrose OR diet* near/1 effect* OR diet*-caus* OR diet*-induc* OR dietborne OR "djenkol beans" OR "early-life abuse" OR "eating fast" OR "effort-reward imbalance" OR "emotional abuse" OR ephedra OR "exercise-caus*" OR "folic acid-induc*" OR "food additive" OR "food poisoning" OR "free-fatty-acid-induced" OR "fructose" OR "germ-free" OR "glucose-induc*" OR "glucose-peaks-short-term" OR "gluten" OR glycerin OR guarana OR "heat stroke" OR "heroin" OR "high home temperature" OR "high insulin" OR "high meat" OR "high selenium diet" OR "high-fat-diet*"

OR "high-glucose-induc*" OR "High-glycemic-load diet*" OR "high-phosphate" OR "high-phosphorous-diet*" OR "high-protein-diet*" OR "high-protein-induc*" OR "high-protein-intake*" OR "high-salt-diet*" OR "high-salt-intake*" OR "high-saturated-fat diet*" OR "high-sodium-diet*" OR "high-sodium-intake*" OR "high-soybean oil" OR "high-sucrose-diet*" OR "high-sugar-diet*" OR "high-tryptophan-diet*" OR "Highway proximity" OR hypothermia OR "hypoxia-induced" OR "insufficient sleep" OR "job strain" OR "laxative abuse" OR "low fiber diet*" OR "low fiber intake" OR "low legumes intake" OR "low manganese intake" OR "low melatonin" OR "low potassium intake" OR "low pulses intake" OR "low-Vitamin D intake" OR "meat" OR "milk processing" OR "morphine" OR mothball* OR "mushrooms" OR noise OR "overfeeding" OR palmitate OR "palmitic acid" OR "parental hypertension" OR "parental occupation*" OR "parental sucrose" OR "persistent organic pollutants" OR "phosphorus additive*" OR "physical inactivity" OR "prenatal hypoxia" OR "preserved food*" OR "preserved meat*" OR "prolonged sitting" OR "psychogenic polydipsia" OR "psychological trauma" OR "refined carbohydrate*" OR "refined cereal*" OR "refined grain*" OR "refined flour" OR "residential remoteness" OR "salt-induced" OR "saturated fat*" OR "sedentary" OR "short sleep duration" OR "sitting time" OR "sleep deprivation" OR "smoking" OR "social environment" OR "sodium additive*" OR "soft drink*" OR "soybean oil heated repeatedly" OR "soy-rich diet" OR "star fruit" OR "sucralose" OR "sunflower oil" OR "tobacco" OR "trans-fat*" OR "water-borne" OR "zinc-deficient diet" OR low near/2 sunlight OR waterborne)

OR

IIB2. LIFESTYLE-SPECIFIC COMPONENT - TITLE

(diet* near/1 effect* OR "adverse food" OR "additives" OR exercise-induc* OR diet*-induc* OR exercise-caus* OR diet*-caus* OR waterborne OR "water-borne" OR dietborne OR "acidogenic diet*" OR "activity restriction" OR "advanced glycation end product*" OR "Advanced glycosylation end product*" OR "alcohol abuse*" OR "alcohol consum*" OR "alcohol intake" OR "alcoholic*" OR "alcohol-induc*" OR "alcoholism" OR "amphetamine*" OR "anabolic steroid*" OR "areca nut chewing" OR "betel nut chewing" OR "binge eating" OR "caffeine" OR "childhood adversity" OR "chinese herb*" OR "cholesterol-induced" OR "cigarette*" OR "cocaine" OR "cola" OR "milk processing" OR "dehydration" OR "depression-induc*" OR "depression-caus*" OR "effort-reward imbalance" OR "emotional abuse" OR "Exercise-induced" OR "folic acid-induc*" OR "free-fatty-acid-induced" OR "fructose" OR "germ-free" OR "glucose-induc*" OR "glucose-peaks-short-term" OR "gluten" OR "heat stroke" OR "heroin" OR "high-fat-diet*" OR "high-glucose-induc*" OR "High-glycemic-load diet*" OR "high home temperature" OR "high insulin" OR "high meat" OR "high-phosphate" OR "high-phosphorous-diet*" OR "high-protein-diet*" OR "high-protein-intake*" OR "high-protein-induc*" OR "high-salt-diet*" OR "high-salt-intake*" OR "high-saturated-fat diet*" OR "high selenium diet" OR "high-sodium-intake*" OR "high-sodium-diet*" OR "high-soybean oil" OR "high-sucrose-diet*" OR "high-tryptophan-diet*" OR "job strain" OR "laxative abuse" OR "psychological trauma" OR "competitive strength exercise training" OR "low fiber diet*" OR "low fiber intake" OR "low legumes intake" OR "low manganese intake" OR "low melatonin" OR "low potassium intake" OR "low pulses intake" OR "low-Vitamin D intake" OR "meat" OR "morphine" OR "mothball abuse" OR "mushrooms" OR "parental sucrose" OR "phosphorus additive*" OR "physical inactivity" OR "refined cereal*" OR

"residential remoteness" OR "salt-induced" OR "sedentary" OR "short sleep duration" OR "sitting time" OR "sleep deprivation" OR "smoking" OR "social environment" OR "sodium additive*" OR "soybean oil heated repeatedly" OR "soy-rich diet" OR "star fruit" OR "stress-induced" OR "sunflower oil" OR "tobacco" OR "overfeeding" OR "zinc-deficient diet" OR "TRANS-FAT*" OR "2,3-Pentanedione" OR "acute stress" OR "biomass fuel for cooking" OR "early-life abuse" OR "Highway proximity" OR "parental occupation*" OR "Sugar" OR "Refined Carbohydrate*" OR "Acrylamide" OR "Aspartame" OR "Sucralose" OR "Preserved Meat*" OR "Refined Flour" OR "Saturated Fat*" OR "Soft Drink*" OR "Preserved Food*" OR "Insufficient Sleep")

OR

III. MESH FIELD TERMS

RUN 3A1 AND 3B1 AS ONE QUERY

IIIA. MESH QUALIFIERS - MESH HEADING

IIIA1. NON-LIFESTYLE-SPECIFIC COMPONENT

(/"chemically induced" OR /toxicity OR /poisoning)

OR

IIIB. MESH GENERIC TERMS - MESH HEADING NO EXPLODE

IIIB1. NON-LIFESTYLE-SPECIFIC COMPONENT - MESH HEADING NO EXPLODE

Abnormalities, Drug-Induced OR Aids Related Opportunistic Infections OR Air Pollutants, Occupational OR Bacterial Infections OR Congenital Abnormalities OR Congenital Disorders Of Glycosylation OR Dermatitis, Occupational OR Drug Eruptions OR Drug Hypersensitivity OR Drug Toxicity OR Environmental Exposure OR Environmental Illness OR Environmental Monitoring OR Environmental Pollutants OR Fossil Fuels OR Hazardous Substances OR Herbicides OR Household Products OR HTLV I Infections OR Iatrogenic Disease OR Inhalation Exposure OR Insecticides OR Marine Toxins OR Maternal Exposure OR Mutagens OR Mycotoxins OR Neurotoxins OR Nonprescription Drugs OR Occupational Diseases OR Occupational Exposure OR Occupations OR Opportunistic Infections OR Organic Chemicals OR Paternal Exposure OR Pesticides OR Plant Poisoning OR Plants, Toxic OR Poisoning OR Poisons OR Prenatal Exposure Delayed Effects OR Simplexvirus OR Soil Pollutants OR Solvents OR Streptococcal Infections OR Vehicle Emissions OR Water Pollutants, Chemical OR Welding

OR

IIIB2. LIFESTYLE-SPECIFIC COMPONENT - MESH HEADING NO EXPLODE

Alcohol Drinking OR Alcoholic Intoxication OR Alcoholism OR Alcohol-Related Disorders OR Amphetamine-Related Disorders OR Amphetamines OR Appetite Depressants OR Carbonated Beverages OR Cocaine OR Cocaine-Related Disorders OR Cola OR Contraceptive Agents OR Contraceptives, Oral OR Cooking And Eating Utensils OR Cosmetics OR Diet, High-Fat OR Fast Foods OR Food Additives OR Food Contamination OR Food Habits OR Food Preservatives OR Fructose OR Glycemic Index OR Glycosylation End Products, Advanced/adverse effects OR Hair Dyes OR Hallucinogens OR Hazardous Substances OR Heat Stroke OR Heroin OR Heroin Dependence OR Laxatives OR Leisure Activities OR Marijuana Abuse OR Methadone OR Mushroom Poisoning OR Narcotics OR Nonprescription Drugs OR Plant Poisoning OR Plants, Toxic OR Prenatal Exposure Delayed Effects OR Smoking OR Sodium Chloride, Dietary OR Sodium, Dietary OR Street Drugs OR Substance-Related Disorders OR Sweetening Agents OR Tattooing OR Tobacco OR Tobacco Smoke Pollution OR Tobacco Use Disorder OR Substance Withdrawal Syndrome OR Obesity OR Meat OR Foodborne Diseases OR Food Handling OR Dietary Fats OR Dietary Carbohydrates OR Plants Genetically Modified OR Sucrose OR Behavior Addictive OR Meat Products OR Poverty OR Maternal Exposure OR Flavoring Agents OR Diet High Fat OR Coffee OR Dairy Products OR Nutrition Disorders OR Prenatal Care OR Child Abuse OR Television OR Hygiene OR Doping In Sports OR Maternal Behavior OR Dietary Sucrose OR Thiamine Deficiency OR Folic Acid Deficiency OR Vitamin D Deficiency OR Cholesterol Dietary OR Lifestyle OR Sedentary Lifestyle OR Eating Disorders OR Sleep Disorders OR Paternal Exposure

OR

MESH TERMS DRUGS

IIIB3a. TITLE

("poison*" OR "ecotoxologic* effect*" OR "occupation*" OR pollut* OR "*virus*" OR environmental OR "induc*" OR "damage-caus*" OR "drug*-caus*" OR "infect*-caus*" OR "chemotherapy-caus*" OR "treat*-caus*" OR "anesthesia-caus*" OR "chemical*-caus*" OR "cytokine*-caus*" OR "surg*-caus*" OR "radiation-caus*" OR "steroid-caus*" OR "mechanically-caus*" OR "promot* progression" OR "caus* accumulation" OR "caus* * accumulation" OR "progression of" OR expos* OR contamina* OR abuse* OR induc* OR "long-term effect*" OR "inhibit* *protection" OR dysfunction* OR aggregation OR accumulation OR "disease link* to" OR "chemical initiator*" OR "stimulat* microglia" OR "activat* microglia" OR "increas* risk*" OR "increas* the risk*" OR "adverse event*" OR "adverse reaction*" OR "adverse * event*" OR "adverse * reaction" OR "adverse effect*" OR "adverse * effect*" OR hypersensitivity OR aggravat* OR exacerbat* OR detriment* OR "caus* *toxi*" OR "increas* *toxi" OR "produc* *toxi*" OR "enhanc* *toxi*" OR "stimulat* *toxi*" OR "accelerat* *toxi*" OR "caus* degrad*" OR "increas* degrad*" OR "caus* damag*" OR "increas* damag*" OR "caus* * *toxi*" OR "increas* * *toxi" OR "produc* * *toxi*" OR "enhanc* * *toxi*" OR "stimulat* * *toxi*" OR "accelerat* * *toxi*" OR "caus* * degrad*" OR "increas* * degrad*" OR "caus* * damag*" OR "increas* * damag*" OR "*toxi* caus* by" OR "*toxi* increas* by" OR "*toxi* produc* by" OR "*toxi* enhanc* by" OR "*toxi* stimulat* by" OR "*toxi* accelerat* by" OR "damag* caus* by" OR "*damag* increas* by" OR deleterious OR deteriorat* OR trigger* OR worsen* OR harm* OR hazard* OR "side-effect*" OR dangerous OR destructive OR injurious OR unsafe)

AND

MESH HEADING NO EXPLODE

Antineoplastic Agents OR Anticoagulants OR Antineoplastic Combined Chemotherapy Protocols OR Anti-Inflammatory Agents, Non-Steroidal OR Hypoglycemic Agents OR Anti-Bacterial Agents OR Antipsychotic Agents OR Immunosuppressive Agents OR Anticonvulsants OR Platelet Aggregation Inhibitors OR Glucocorticoids OR Analgesics, Opioid OR Drug-Related Side Effects and Adverse Reactions OR Warfarin OR Analgesics OR Doxorubicin OR Cisplatin OR Protein Kinase Inhibitors OR Fibrinolytic Agents OR Fluorouracil OR Antirheumatic Agents OR Antihypertensive Agents OR Pyridines OR Cyclophosphamide OR Bone Density Conservation Agents OR Antiviral Agents OR Bleomycin OR Antidepressive Agents OR Serotonin Uptake Inhibitors OR Thiophenes OR Antibiotics, Antineoplastic OR Angiogenesis Inhibitors OR Drug Hypersensitivity OR Proton Pump Inhibitors OR Deoxycytidine OR Ticlopidine OR Organoplatinum Compounds OR Anti-Arrhythmia Agents OR Angiotensin-Converting Enzyme Inhibitors OR Anti-HIV Agents OR Paclitaxel OR Chemotherapy, Adjuvant OR Acetaminophen OR Quinazolines OR Taxoids OR Vasodilator Agents OR Pilocarpine OR Triazoles OR Benzodiazepines OR Anti-Infective Agents OR Estrogens OR Thiazolidinediones OR Antineoplastic Agents, Hormonal OR Antineoplastic Agents, Phytogenic OR Cyclooxygenase 2 Inhibitors OR Anti-Ulcer Agents OR Cyclosporine OR Vasoconstrictor Agents OR Anthracyclines OR Anticarcinogenic Agents OR Convulsants OR Calcium Channel Blockers OR Cardiotonic Agents OR Dermatologic Agents OR Isoproterenol OR Antifungal Agents OR Ribavirin OR Antiparkinson Agents OR Clozapine OR Carboplatin OR Tamoxifen OR Antiretroviral Therapy, Highly Active OR Vincristine OR Cholinesterase Inhibitors OR Antidepressive Agents, Second-Generation OR Antitubercular Agents OR Hypolipidemic Agents OR Antineoplastic Agents, Alkylating OR Gastrointestinal Agents OR Aromatase Inhibitors OR Antithyroid Agents OR Organophosphonates OR Cyclooxygenase Inhibitors OR Antidepressive Agents, Tricyclic OR Antimanic Agents OR Phosphodiesterase 5 Inhibitors OR Dipeptidyl-Peptidase IV Inhibitors OR Anti-Retroviral Agents OR Methyl Ethers OR Chelating Agents OR Anticholesteremic Agents OR Contraceptive Agents, Female OR Anti-Asthmatic Agents OR Dopamine Uptake Inhibitors OR HIV Protease Inhibitors OR N-Methyl-3,4-methylenedioxyamphetamine OR Mycophenolic Acid OR Bronchodilator Agents OR Hydroxychloroquine OR Neurotransmitter Agents OR Anti-Obesity Agents OR Anabolic Agents OR Anesthetics OR Cardiovascular Agents OR Histone Deacetylase Inhibitors OR Alkylating Agents OR Chloroquine OR Antifibrinolytic Agents OR Benzoxazines OR Protease Inhibitors OR Fertility Agents, Female OR Dopamine Agents OR Anti-Infective Agents, Local OR Reverse Transcriptase Inhibitors OR Neuromuscular Agents OR Anti-Allergic Agents OR Monoamine Oxidase Inhibitors OR Neuromuscular Nondepolarizing Agents OR Nootropic Agents OR Photosensitizing Agents OR 5-alpha Reductase Inhibitors OR Sweetening Agents OR Sensory System Agents OR Adrenergic Agents OR Adrenergic Uptake Inhibitors OR Indicators and Reagents OR Antitussive Agents OR Surface-Active Agents OR Antimutagenic Agents

OR

IIIB3b. TOPIC

("increas* amyloid-beta" OR "increas* beta-amyloid" OR "increas* Abeta" OR "increas* senile plaque*" OR "increas* tau aggregat*" OR "increas* T-tau" OR "increas* P-tau" OR "increas*total tau" OR "increas* phospho-tau" OR "increas* tau protein*" OR "increas* hyperphosphorylated tau" OR "increas* neurofibrillary tangle*" OR "enhanc* amyloid-beta" OR "enhanc* beta-amyloid" OR "enhanc* Abeta" OR "enhanc* senile plaque*" OR "enhanc* tau aggregat*" OR "enhanc* T-tau" OR "enhanc* P-tau" OR "enhanc*total tau" OR "enhanc* phospho-tau" OR "enhanc* tau protein*" OR "enhanc* hyperphosphorylated tau" OR "enhanc* neurofibrillary tangle*" OR "stimulat* amyloid-beta" OR "stimulat* beta-amyloid" OR "stimulat* Abeta" OR "stimulat* senile plaque*" OR "stimulat* tau aggregat*" OR "stimulat* T-tau" OR "stimulat* P-tau" OR "stimulat*total tau" OR "stimulat* phospho-tau" OR "stimulat* tau protein*" OR "stimulat* hyperphosphorylated tau" OR "stimulat* neurofibrillary tangle*" OR "elevat* amyloid-beta" OR "elevat* beta-amyloid" OR "elevat* Abeta" OR "elevat* senile plaque*" OR "elevat* tau aggregat*" OR "elevat* T-tau" OR "elevat* P-tau" OR "elevat*total tau" OR "elevat* phospho-tau" OR "elevat* tau protein*" OR "elevat* hyperphosphorylated tau" OR "elevat* neurofibrillary tangle*" OR "induc* amyloid-beta" OR "induc* beta-amyloid" OR "induc* Abeta" OR "induc* senile plaque*" OR "induc* tau aggregat*" OR "induc* T-tau" OR "induc* P-tau" OR "induc*total tau" OR "induc* phospho-tau" OR "induc* tau protein*" OR "induc* hyperphosphorylated tau" OR "induc* neurofibrillary tangle*" OR "produc* amyloid-beta" OR "produc* beta-amyloid" OR "produc* Abeta" OR "produc* senile plaque*" OR "produc* tau aggregat*" OR "produc* T-tau" OR "produc* P-tau" OR "produc*total tau" OR "produc* phospho-tau" OR "produc* tau protein*" OR "produc* hyperphosphorylated tau" OR "produc* neurofibrillary tangle*" OR "accelerat* amyloid-beta" OR "accelerat* beta-amyloid" OR "accelerat* Abeta" OR "accelerat* senile plaque*" OR "accelerat* tau aggregat*" OR "accelerat* T-tau" OR "accelerat* P-tau" OR "accelerat*total tau" OR "accelerat* phospho-tau" OR "accelerat* tau protein*" OR "accelerat* hyperphosphorylated tau" OR "accelerat* neurofibrillary tangle*" OR "amyloid-beta induc* by" OR "beta-amyloid induc* by" OR "Abeta induc* by" OR "senile plaque* induc* by" OR "tau aggregat* induc* by" OR "T-tau induc* by" OR "P-tau induc* by" OR "total tau induc* by" OR "phospho-tau induc* by" OR "tau protein* induc* by" OR "hyperphosphorylated tau induc* by" OR "neurofibrillary tangle* induc* by" OR "amyloid-beta produc* by" OR "beta-amyloid produc* by" OR "Abeta produc* by" OR "senile plaque* produc* by" OR "tau aggregat* produc* by" OR "T-tau produc* by" OR "P-tau produc* by" OR "total tau produc* by" OR "phospho-tau produc* by" OR "tau protein* produc* by" OR "hyperphosphorylated tau produc* by" OR "neurofibrillary tangle* produc* by" OR "caus* Alzheimer*" OR "caus* dementia" OR "caus* cognitive decline" OR "caus* brain* decline" OR "caus* functional decline" OR "caus* memory decline" OR "caus* cognitive deficit*" OR "caus* language deficit*" OR "caus* memory deficit*" OR "caus* plasticity deficit*" OR "caus* behavioral deficit*" OR "caus* saccade deficit*" OR "caus* learning deficit*" OR "caus* neuropsychological deficit*" OR "caus* cognitive impair*" OR "caus* vascular impair*" OR "caus* memory impair*" OR "caus* neurogenesis impair*" OR "caus* neuropsychological impair*" OR "caus* mind impair*" OR "caus* functional impair*" OR "caus* learning impair*" OR "caus* executive function impair*" OR "caus* cognitive loss*" OR "caus* neuronal loss*" OR "caus* synaptic loss*" OR "caus* memory loss*" OR "caus* loss of memory" OR "caus* hearing loss*" OR "caus* volume loss*" OR "caus* Impair* face recognition" OR "caus* Impair* reasoning" OR "caus* Impair* judgment" OR "caus* Impair* problem solving" OR "caus* inflamm*" OR "caus* oxidative stress" OR "caus* neuropathology" OR "caus* diabetes" OR "caus* hypertension" OR "caus* high

cholesterol" OR "caus* hypercholesterolemia" OR "caus* obesity" OR "caus* metabolic syndrome" OR "induc* Alzheimer*" OR "induc* dementia" OR "induc* cognitive decline" OR "induc* brain* decline" OR "induc* functional decline" OR "induc* memory decline" OR "induc* cognitive deficit*" OR "induc* language deficit*" OR "induc* memory deficit*" OR "induc* plasticity deficit*" OR "induc* behavioral deficit*" OR "induc* saccade deficit*" OR "induc* learning deficit*" OR "induc* neuropsychological deficit*" OR "induc* cognitive impair*" OR "induc* vascular impair*" OR "induc* memory impair*" OR "induc* neurogenesis impair*" OR "induc* neuropsychological impair*" OR "induc* mind impair*" OR "induc* functional impair*" OR "induc* learning impair*" OR "induc* executive function impair*" OR "induc* cognitive loss*" OR "induc* neuronal loss*" OR "induc* synaptic loss*" OR "induc* memory loss*" OR "induc* loss of memory" OR "induc* hearing loss*" OR "induc* volume loss*" OR "induc* Impair* face recognition" OR "induc* Impair* reasoning" OR "induc* Impair* judgment" OR "induc* Impair* problem solving" OR "induc* inflamm*" OR "induc* oxidative stress" OR "induc* neuropathology" OR "induc* diabetes" OR "induc* hypertension" OR "induc* high cholesterol" OR "induc* hypercholesterolemia" OR "induc* obesity" OR "induc* metabolic syndrome" OR "produc* Alzheimer*" OR "produc* dementia" OR "produc* cognitive decline" OR "produc* brain* decline" OR "produc* functional decline" OR "produc* memory decline" OR "produc* cognitive deficit*" OR "produc* language deficit*" OR "produc* memory deficit*" OR "produc* plasticity deficit*" OR "produc* behavioral deficit*" OR "produc* saccade deficit*" OR "produc* learning deficit*" OR "produc* neuropsychological deficit*" OR "produc* cognitive impair*" OR "produc* vascular impair*" OR "produc* memory impair*" OR "produc* neurogenesis impair*" OR "produc* neuropsychological impair*" OR "produc* mind impair*" OR "produc* functional impair*" OR "produc* learning impair*" OR "produc* executive function impair*" OR "produc* cognitive loss*" OR "produc* neuronal loss*" OR "produc* synaptic loss*" OR "produc* memory loss*" OR "produc* loss of memory" OR "produc* hearing loss*" OR "produc* volume loss*" OR "produc* Impair* face recognition" OR "produc* Impair* reasoning" OR "produc* Impair* judgment" OR "produc* Impair* problem solving" OR "produc* inflamm*" OR "produc* oxidative stress" OR "produc* neuropathology" OR "produc* diabetes" OR "produc* hypertension" OR "produc* high cholesterol" OR "produc* hypercholesterolemia" OR "produc* obesity" OR "produc* metabolic syndrome" OR "increas* Alzheimer*" OR "increas* dementia" OR "increas* cognitive decline" OR "increas* brain* decline" OR "increas* functional decline" OR "increas* memory decline" OR "increas* cognitive deficit*" OR "increas* language deficit*" OR "increas* memory deficit*" OR "increas* plasticity deficit*" OR "increas* behavioral deficit*" OR "increas* saccade deficit*" OR "increas* learning deficit*" OR "increas* neuropsychological deficit*" OR "increas* cognitive impair*" OR "increas* vascular impair*" OR "increas* memory impair*" OR "increas* neurogenesis impair*" OR "increas* neuropsychological impair*" OR "increas* mind impair*" OR "increas* functional impair*" OR "increas* learning impair*" OR "increas* executive function impair*" OR "increas* cognitive loss*" OR "increas* neuronal loss*" OR "increas* synaptic loss*" OR "increas* memory loss*" OR "increas* loss of memory" OR "increas* hearing loss*" OR "increas* volume loss*" OR "increas* Impair* face recognition" OR "increas* Impair* reasoning" OR "increas* Impair* judgment" OR "increas* Impair* problem solving" OR "increas* inflamm*" OR "increas* oxidative stress" OR "increas* neuropathology" OR "increas* diabetes" OR "increas* hypertension" OR "increas* high cholesterol" OR "increas* hypercholesterolemia" OR "increas* obesity" OR "increas* metabolic syndrome" OR "exacerbat* Alzheimer*" OR "exacerbat*

dementia" OR "exacerbat* cognitive decline" OR "exacerbat* brain* decline" OR "exacerbat* functional decline" OR "exacerbat* memory decline" OR "exacerbat* cognitive deficit*" OR "exacerbat* language deficit*" OR "exacerbat* memory deficit*" OR "exacerbat* plasticity deficit*" OR "exacerbat* behavioral deficit*" OR "exacerbat* saccade deficit*" OR "exacerbat* learning deficit*" OR "exacerbat* neuropsychological deficit*" OR "exacerbat* cognitive impair*" OR "exacerbat* vascular impair*" OR "exacerbat* memory impair*" OR "exacerbat* neurogenesis impair*" OR "exacerbat* neuropsychological impair*" OR "exacerbat* mind impair*" OR "exacerbat* functional impair*" OR "exacerbat* learning impair*" OR "exacerbat* executive function impair*" OR "exacerbat* cognitive loss*" OR "exacerbat* neuronal loss*" OR "exacerbat* synaptic loss*" OR "exacerbat* memory loss*" OR "exacerbat* loss of memory" OR "exacerbat* hearing loss*" OR "exacerbat* volume loss*" OR "exacerbat* Impair* face recognition" OR "exacerbat* Impair* reasoning" OR "exacerbat* Impair* judgment" OR "exacerbat* Impair* problem solving" OR "exacerbat* inflamm*" OR "exacerbat* oxidative stress" OR "exacerbat* neuropathology" OR "exacerbat* diabetes" OR "exacerbat* hypertension" OR "exacerbat* high cholesterol" OR "exacerbat* hypercholesterolemia" OR "exacerbat* obesity" OR "exacerbat* metabolic syndrome" OR "trigger* Alzheimer*" OR "trigger* dementia" OR "trigger* cognitive decline" OR "trigger* brain* decline" OR "trigger* functional decline" OR "trigger* memory decline" OR "trigger* cognitive deficit*" OR "trigger* language deficit*" OR "trigger* memory deficit*" OR "trigger* plasticity deficit*" OR "trigger* behavioral deficit*" OR "trigger* saccade deficit*" OR "trigger* learning deficit*" OR "trigger* neuropsychological deficit*" OR "trigger* cognitive impair*" OR "trigger* vascular impair*" OR "trigger* memory impair*" OR "trigger* neurogenesis impair*" OR "trigger* neuropsychological impair*" OR "trigger* mind impair*" OR "trigger* functional impair*" OR "trigger* learning impair*" OR "trigger* executive function impair*" OR "trigger* cognitive loss*" OR "trigger* neuronal loss*" OR "trigger* synaptic loss*" OR "trigger* memory loss*" OR "trigger* loss of memory" OR "trigger* hearing loss*" OR "trigger* volume loss*" OR "trigger* Impair* face recognition" OR "trigger* Impair* reasoning" OR "trigger* Impair* judgment" OR "trigger* Impair* problem solving" OR "trigger* inflamm*" OR "trigger* oxidative stress" OR "trigger* neuropathology" OR "trigger* diabetes" OR "trigger* hypertension" OR "trigger* high cholesterol" OR "trigger* hypercholesterolemia" OR "trigger* obesity" OR "trigger* metabolic syndrome" OR "accelerat* Alzheimer*" OR "accelerat* dementia" OR "accelerat* cognitive decline" OR "accelerat* brain* decline" OR "accelerat* functional decline" OR "accelerat* memory decline" OR "accelerat* cognitive deficit*" OR "accelerat* language deficit*" OR "accelerat* memory deficit*" OR "accelerat* plasticity deficit*" OR "accelerat* behavioral deficit*" OR "accelerat* saccade deficit*" OR "accelerat* learning deficit*" OR "accelerat* neuropsychological deficit*" OR "accelerat* cognitive impair*" OR "accelerat* vascular impair*" OR "accelerat* memory impair*" OR "accelerat* neurogenesis impair*" OR "accelerat* neuropsychological impair*" OR "accelerat* mind impair*" OR "accelerat* functional impair*" OR "accelerat* learning impair*" OR "accelerat* executive function impair*" OR "accelerat* cognitive loss*" OR "accelerat* neuronal loss*" OR "accelerat* synaptic loss*" OR "accelerat* memory loss*" OR "accelerat* loss of memory" OR "accelerat* hearing loss*" OR "accelerat* volume loss*" OR "accelerat* Impair* face recognition" OR "accelerat* Impair* reasoning" OR "accelerat* Impair* judgment" OR "accelerat* Impair* problem solving" OR "accelerat* inflamm*" OR "accelerat* oxidative stress" OR "accelerat* neuropathology" OR "accelerat* diabetes" OR "accelerat* hypertension" OR "accelerat* high cholesterol" OR "accelerat* hypercholesterolemia" OR

"accelerat* obesity" OR "accelerat* metabolic syndrome" OR "Alzheimer* * caused by" OR "dementia caused by" OR "cognitive decline caused by" OR "brain* decline caused by" OR "functional decline caused by" OR "memory decline caused by" OR "cognitive deficit* caused by" OR "language deficit* caused by" OR "memory deficit* caused by" OR "plasticity deficit* caused by" OR "behavioral deficit* caused by" OR "saccade deficit* caused by" OR "learning deficit* caused by" OR "neuropsychological deficit* caused by" OR "cognitive impair* caused by" OR "vascular impair* caused by" OR "memory impair* caused by" OR "neurogenesis impair* caused by" OR "neuropsychological impair* caused by" OR "mind impair* caused by" OR "functional impair* caused by" OR "learning impair* caused by" OR " executive function impair* caused by" OR "cognitive loss* caused by" OR "neuronal loss* caused by" OR "synaptic loss* caused by" OR "memory loss* caused by" OR "loss of memory caused by" OR "hearing loss* caused by" OR "volume loss* caused by" OR "Impair* face recognition caused by" OR "Impair* reasoning caused by" OR "Impair* judgment caused by" OR "Impair* problem solving caused by" OR "inflamm* caused by" OR "oxidative stress caused by" OR "neuropathology caused by" OR "diabetes caused by" OR "hypertension caused by" OR "high cholesterol caused by" OR "hypercholesterolemia caused by" OR "obesity caused by" OR "metabolic syndrome caused by" OR "Alzheimer* * induced by" OR "dementia induced by" OR "cognitive decline induced by" OR "brain* decline induced by" OR "functional decline induced by" OR "memory decline induced by" OR "cognitive deficit* induced by" OR "language deficit* induced by" OR "memory deficit* induced by" OR "plasticity deficit* induced by" OR "behavioral deficit* induced by" OR "saccade deficit* induced by" OR "learning deficit* induced by" OR "neuropsychological deficit* induced by" OR "cognitive impair* induced by" OR "vascular impair* induced by" OR "memory impair* induced by" OR "neurogenesis impair* induced by" OR "neuropsychological impair* induced by" OR "mind impair* induced by" OR "functional impair* induced by" OR "learning impair* induced by" OR " executive function impair* induced by" OR "cognitive loss* induced by" OR "neuronal loss* induced by" OR "synaptic loss* induced by" OR "memory loss* induced by" OR "loss of memory induced by" OR "hearing loss* induced by" OR "volume loss* induced by" OR "Impair* face recognition induced by" OR "Impair* reasoning induced by" OR "Impair* judgment induced by" OR "Impair* problem solving induced by" OR "inflamm* induced by" OR "oxidative stress induced by" OR "neuropathology induced by" OR "diabetes induced by" OR "hypertension induced by" OR "high cholesterol induced by" OR "hypercholesterolemia induced by" OR "obesity induced by" OR "metabolic syndrome induced by")

AND

MESH HEADING NO EXPLODE

Antineoplastic Agents OR Anticoagulants OR Antineoplastic Combined Chemotherapy Protocols OR Anti-Inflammatory Agents, Non-Steroidal OR Hypoglycemic Agents OR Anti-Bacterial Agents OR Antipsychotic Agents OR Immunosuppressive Agents OR Anticonvulsants OR Platelet Aggregation Inhibitors OR Glucocorticoids OR Analgesics, Opioid OR Drug-Related Side Effects and Adverse Reactions OR Warfarin OR Analgesics OR Doxorubicin OR Cisplatin OR Protein Kinase Inhibitors OR Fibrinolytic Agents OR Fluorouracil OR Antirheumatic Agents OR Antihypertensive Agents OR Pyridines OR Cyclophosphamide OR Bone Density Conservation Agents OR Antiviral Agents OR Bleomycin OR Antidepressive Agents OR Serotonin Uptake Inhibitors OR Thiophenes OR Antibiotics,

Antineoplastic OR Angiogenesis Inhibitors OR Drug Hypersensitivity OR Proton Pump Inhibitors OR Deoxycytidine OR Ticlopidine OR Organoplatinum Compounds OR Anti-Arrhythmia Agents OR Angiotensin-Converting Enzyme Inhibitors OR Anti-HIV Agents OR Paclitaxel OR Chemotherapy, Adjuvant OR Acetaminophen OR Quinazolines OR Taxoids OR Vasodilator Agents OR Pilocarpine OR Triazoles OR Benzodiazepines OR Anti-Infective Agents OR Estrogens OR Thiazolidinediones OR Antineoplastic Agents, Hormonal OR Antineoplastic Agents, Phytogenic OR Cyclooxygenase 2 Inhibitors OR Anti-Ulcer Agents OR Cyclosporine OR Vasoconstrictor Agents OR Anthracyclines OR Anticarcinogenic Agents OR Convulsants OR Calcium Channel Blockers OR Cardiotonic Agents OR Dermatologic Agents OR Isoproterenol OR Antifungal Agents OR Ribavirin OR Antiparkinson Agents OR Clozapine OR Carboplatin OR Tamoxifen OR Antiretroviral Therapy, Highly Active OR Vincristine OR Cholinesterase Inhibitors OR Antidepressive Agents, Second-Generation OR Antitubercular Agents OR Hypolipidemic Agents OR Antineoplastic Agents, Alkylating OR Gastrointestinal Agents OR Aromatase Inhibitors OR Antithyroid Agents OR Organophosphonates OR Cyclooxygenase Inhibitors OR Antidepressive Agents, Tricyclic OR Antimanic Agents OR Phosphodiesterase 5 Inhibitors OR Dipeptidyl-Peptidase IV Inhibitors OR Anti-Retroviral Agents OR Methyl Ethers OR Chelating Agents OR Anticholesteremic Agents OR Contraceptive Agents, Female OR Anti-Asthmatic Agents OR Dopamine Uptake Inhibitors OR HIV Protease Inhibitors OR N-Methyl-3,4-methylenedioxyamphetamine OR Mycophenolic Acid OR Bronchodilator Agents OR Hydroxychloroquine OR Neurotransmitter Agents OR Anti-Obesity Agents OR Anabolic Agents OR Anesthetics OR Cardiovascular Agents OR Histone Deacetylase Inhibitors OR Alkylating Agents OR Chloroquine OR Antifibrinolytic Agents OR Benzoxazines OR Protease Inhibitors OR Fertility Agents, Female OR Dopamine Agents OR Anti-Infective Agents, Local OR Reverse Transcriptase Inhibitors OR Neuromuscular Agents OR Anti-Allergic Agents OR Monoamine Oxidase Inhibitors OR Neuromuscular Nondepolarizing Agents OR Nootropic Agents OR Photosensitizing Agents OR 5-alpha Reductase Inhibitors OR Sweetening Agents OR Sensory System Agents OR Adrenergic Agents OR Adrenergic Uptake Inhibitors OR Indicators and Reagents OR Antitussive Agents OR Surface-Active Agents OR Antimutagenic Agents

OR

MESH TERMS CHEMICALS

IIIB4a - TITLE

("poison*" OR "ecotoxologic* effect*" OR "occupation*" OR pollut* OR "*virus*" OR environmental OR "induc*" OR "damage-caus*" OR "drug*-caus*" OR "infect*-caus*" OR "chemotherapy-caus*" OR "treat*-caus*" OR "anesthesia-caus*" OR "chemical*-caus*" OR "cytokine*-caus*" OR "surg*-caus*" OR "radiation-caus*" OR "steroid-caus*" OR "mechanically-caus*" OR "promot* progression" OR "caus* accumulation" OR "caus* * accumulation" OR "progression of" OR expos* OR contamina* OR chemicals OR abuse* OR induc* OR "long-term effect*" OR "inhibit* *protection" OR dysfunction* OR aggregation OR accumulation OR "disease link* to" OR "chemical initiator*" OR "stimulat* microglia" OR "activat* microglia" OR "increas* risk*" OR "increas* the risk*" OR "adverse event*" OR "adverse reaction*" OR "adverse * event*" OR "adverse * reaction" OR "adverse effect*" OR "adverse * effect*" OR hypersensitivity OR aggravat* OR exacerbat* OR detriment* OR *TOXI* OR "caus* * degrad*" OR

"increas* * degrad*" OR "caus* * damag*" OR "increas* * damag*" OR "*toxi* caus* by" OR "*toxi* increas* by" OR "*toxi* produc* by" OR "*toxi* enhanc* by" OR "*toxi* stimulat* by" OR "*toxi* accelerat* by" OR "damag* caus* by" OR "*damag* increas* by" OR deleterious OR deteriorat* OR trigger* OR worsen* OR harm* OR hazard* OR "side-effect*" OR dangerous OR destructive OR injurious OR unsafe)

AND

MESH HEADING NO EXPLODE

Lipopolysaccharides OR Malondialdehyde OR Neurotoxicity Syndromes OR Carbon Tetrachloride OR Formaldehyde OR 9,10-Dimethyl-1,2-benzanthracene OR Trinitrobenzenesulfonic Acid OR Insecticides OR Endocrine Disruptors OR Diethylnitrosamine OR Hydrogen Peroxide OR Benzhydryl Compounds OR Chemical Warfare Agents OR Asbestos OR Herbicides OR Organometallic Compounds OR Scopolamine Hydrobromide OR Silicon Dioxide OR Polychlorinated Biphenyls OR 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine OR Benzo(a)pyrene OR Fluorocarbons OR Nitrogen Dioxide OR Polycyclic Hydrocarbons, Aromatic OR Tetrachlorodibenzodioxin OR Metals, Heavy OR Hydrocarbons, Chlorinated OR Chemical Industry OR 1,2-Dimethylhydrazine OR Ethylene Glycol OR Nitrosamines OR Benzene OR Fluorides OR Agricultural Workers' Diseases OR Bromodeoxyuridine OR Chromium OR Organophosphorus Compounds OR Organic Chemicals OR Carbon Monoxide OR Benzalkonium Compounds OR Chlorpyrifos OR Organophosphates OR Organophosphate Poisoning OR Volatile Organic Compounds OR Diethylhexyl Phthalate OR Sulfur Dioxide OR Petroleum OR Methylmercury Compounds OR Chlorine OR Dichlorodiphenyl Dichloroethylene OR Hydrocarbons OR Trichloroethylene OR Carbon Tetrachloride Poisoning OR 3,4-Dihydroxyphenylacetic Acid OR Alkanesulfonic Acids OR Plasticizers OR Halogenated Diphenyl Ethers OR Benzene Derivatives OR Dinitrofluorobenzene OR Toluene 2,4-Diisocyanate OR Benzopyrenes OR Cyclohexenes OR Nitrobenzenes OR Plastics OR Trihalomethanes OR Hydrocarbons, Brominated

OR

IIIB4b. TOPIC

("increas* amyloid-beta" OR "increas* beta-amyloid" OR "increas* Abeta" OR "increas* senile plaque*" OR "increas* tau aggregat*" OR "increas* T-tau" OR "increas* P-tau" OR "increas*total tau" OR "increas* phospho-tau" OR "increas* tau protein*" OR "increas* hyperphosphorylated tau" OR "increas* neurofibrillary tangle*" OR "enhanc* amyloid-beta" OR "enhanc* beta-amyloid" OR "enhanc* Abeta" OR "enhanc* senile plaque*" OR "enhanc* tau aggregat*" OR "enhanc* T-tau" OR "enhanc* P-tau" OR "enhanc*total tau" OR "enhanc* phospho-tau" OR "enhanc* tau protein*" OR "enhanc* hyperphosphorylated tau" OR "enhanc* neurofibrillary tangle*" OR "stimulat* amyloid-beta" OR "stimulat* beta-amyloid" OR "stimulat* Abeta" OR "stimulat* senile plaque*" OR "stimulat* tau aggregat*" OR "stimulat* T-tau" OR "stimulat* P-tau" OR "stimulat*total tau" OR "stimulat* phospho-tau" OR "stimulat* tau protein*" OR "stimulat* hyperphosphorylated tau" OR "stimulat* neurofibrillary tangle*" OR "elevat* amyloid-beta" OR "elevat* beta-amyloid" OR "elevat* Abeta" OR "elevat* senile plaque*" OR "elevat* tau aggregat*" OR "elevat* T-tau" OR "elevat* P-tau" OR "elevat*total tau" OR

"elevat* phospho-tau" OR "elevat* tau protein*" OR "elevat* hyperphosphorylated tau" OR "elevat* neurofibrillary tangle*" OR "induc* amyloid-beta" OR "induc* beta-amyloid" OR "induc* Abeta" OR "induc* senile plaque*" OR "induc* tau aggregat*" OR "induc* T-tau" OR "induc* P-tau" OR "induc*total tau" OR "induc* phospho-tau" OR "induc* tau protein*" OR "induc* hyperphosphorylated tau" OR "induc* neurofibrillary tangle*" OR "produc* amyloid-beta" OR "produc* beta-amyloid" OR "produc* Abeta" OR "produc* senile plaque*" OR "produc* tau aggregat*" OR "produc* T-tau" OR "produc* P-tau" OR "produc*total tau" OR "produc* phospho-tau" OR "produc* tau protein*" OR "produc* hyperphosphorylated tau" OR "produc* neurofibrillary tangle*" OR "accelerat* amyloid-beta" OR "accelerat* beta-amyloid" OR "accelerat* Abeta" OR "accelerat* senile plaque*" OR "accelerat* tau aggregat*" OR "accelerat* T-tau" OR "accelerat* P-tau" OR "accelerat*total tau" OR "accelerat* phospho-tau" OR "accelerat* tau protein*" OR "accelerat* hyperphosphorylated tau" OR "accelerat* neurofibrillary tangle*" OR "amyloid-beta induc* by" OR "beta-amyloid induc* by" OR "Abeta induc* by" OR "senile plaque* induc* by" OR "tau aggregat* induc* by" OR "T-tau induc* by" OR "P-tau induc* by" OR "total tau induc* by" OR "phospho-tau induc* by" OR "tau protein* induc* by" OR "hyperphosphorylated tau induc* by" OR "neurofibrillary tangle* induc* by" OR "amyloid-beta produc* by" OR "beta-amyloid produc* by" OR "Abeta produc* by" OR "senile plaque* produc* by" OR "tau aggregat* produc* by" OR "T-tau produc* by" OR "P-tau produc* by" OR "total tau produc* by" OR "phospho-tau produc* by" OR "tau protein* produc* by" OR "hyperphosphorylated tau produc* by" OR "neurofibrillary tangle* produc* by" OR "caus* Alzheimer*" OR "caus* dementia" OR "caus* cognitive decline" OR "caus* brain* decline" OR "caus* functional decline" OR "caus* memory decline" OR "caus* cognitive deficit*" OR "caus* language deficit*" OR "caus* memory deficit*" OR "caus* plasticity deficit*" OR "caus* behavioral deficit*" OR "caus* saccade deficit*" OR "caus* learning deficit*" OR "caus* neuropsychological deficit*" OR "caus* cognitive impair*" OR "caus* vascular impair*" OR "caus* memory impair*" OR "caus* neurogenesis impair*" OR "caus* neuropsychological impair*" OR "caus* mind impair*" OR "caus* functional impair*" OR "caus* learning impair*" OR "caus* executive function impair*" OR "caus* cognitive loss*" OR "caus* neuronal loss*" OR "caus* synaptic loss*" OR "caus* memory loss*" OR "caus* loss of memory" OR "caus* hearing loss*" OR "caus* volume loss*" OR "caus* Impair* face recognition" OR "caus* Impair* reasoning" OR "caus* Impair* judgment" OR "caus* Impair* problem solving" OR "caus* inflamm*" OR "caus* oxidative stress" OR "caus* neuropathology" OR "caus* diabetes" OR "caus* hypertension" OR "caus* high cholesterol" OR "caus* hypercholesterolemia" OR "caus* obesity" OR "caus* metabolic syndrome" OR "induc* Alzheimer*" OR "induc* dementia" OR "induc* cognitive decline" OR "induc* brain* decline" OR "induc* functional decline" OR "induc* memory decline" OR "induc* cognitive deficit*" OR "induc* language deficit*" OR "induc* memory deficit*" OR "induc* plasticity deficit*" OR "induc* behavioral deficit*" OR "induc* saccade deficit*" OR "induc* learning deficit*" OR "induc* neuropsychological deficit*" OR "induc* cognitive impair*" OR "induc* vascular impair*" OR "induc* memory impair*" OR "induc* neurogenesis impair*" OR "induc* neuropsychological impair*" OR "induc* mind impair*" OR "induc* functional impair*" OR "induc* learning impair*" OR "induc* executive function impair*" OR "induc* cognitive loss*" OR "induc* neuronal loss*" OR "induc* synaptic loss*" OR "induc* memory loss*" OR "induc* loss of memory" OR "induc* hearing loss*" OR "induc* volume loss*" OR "induc* Impair* face recognition" OR "induc* Impair* reasoning" OR "induc* Impair* judgment" OR "induc* Impair* problem solving" OR "induc* inflamm*" OR "induc* oxidative stress" OR "induc*

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oxidative stress" OR "exacerbat* neuropathology" OR "exacerbat* diabetes" OR "exacerbat* hypertension" OR "exacerbat* high cholesterol" OR "exacerbat* hypercholesterolemia" OR "exacerbat* obesity" OR "exacerbat* metabolic syndrome" OR "trigger* Alzheimer*" OR "trigger* dementia" OR "trigger* cognitive decline" OR "trigger* brain* decline" OR "trigger* functional decline" OR "trigger* memory decline" OR "trigger* cognitive deficit*" OR "trigger* language deficit*" OR "trigger* memory deficit*" OR "trigger* plasticity deficit*" OR "trigger* behavioral deficit*" OR "trigger* saccade deficit*" OR "trigger* learning deficit*" OR "trigger* neuropsychological deficit*" OR "trigger* cognitive impair*" OR "trigger* vascular impair*" OR "trigger* memory impair*" OR "trigger* neurogenesis impair*" OR "trigger* neuropsychological impair*" OR "trigger* mind impair*" OR "trigger* functional impair*" OR "trigger* learning impair*" OR "trigger* executive function impair*" OR "trigger* cognitive loss*" OR "trigger* neuronal loss*" OR "trigger* synaptic loss*" OR "trigger* memory loss*" OR "trigger* loss of memory" OR "trigger* hearing loss*" OR "trigger* volume loss*" OR "trigger* Impair* face recognition" OR "trigger* Impair* reasoning" OR "trigger* Impair* judgment" OR "trigger* Impair* problem solving" OR "trigger* inflamm*" OR "trigger* oxidative stress" OR "trigger* neuropathology" OR "trigger* diabetes" OR "trigger* hypertension" OR "trigger* high cholesterol" OR "trigger* hypercholesterolemia" OR "trigger* obesity" OR "trigger* metabolic syndrome" OR "accelerat* Alzheimer*" OR "accelerat* dementia" OR "accelerat* cognitive decline" OR "accelerat* brain* decline" OR "accelerat* functional decline" OR "accelerat* memory decline" OR "accelerat* cognitive deficit*" OR "accelerat* language deficit*" OR "accelerat* memory deficit*" OR "accelerat* plasticity deficit*" OR "accelerat* behavioral deficit*" OR "accelerat* saccade deficit*" OR "accelerat* learning deficit*" OR "accelerat* neuropsychological deficit*" OR "accelerat* cognitive impair*" OR "accelerat* vascular impair*" OR "accelerat* memory impair*" OR "accelerat* neurogenesis impair*" OR "accelerat* neuropsychological impair*" OR "accelerat* mind impair*" OR "accelerat* functional impair*" OR "accelerat* learning impair*" OR "accelerat* executive function impair*" OR "accelerat* cognitive loss*" OR "accelerat* neuronal loss*" OR "accelerat* synaptic loss*" OR "accelerat* memory loss*" OR "accelerat* loss of memory" OR "accelerat* hearing loss*" OR "accelerat* volume loss*" OR "accelerat* Impair* face recognition" OR "accelerat* Impair* reasoning" OR "accelerat* Impair* judgment" OR "accelerat* Impair* problem solving" OR "accelerat* inflamm*" OR "accelerat* oxidative stress" OR "accelerat* neuropathology" OR "accelerat* diabetes" OR "accelerat* hypertension" OR "accelerat* high cholesterol" OR "accelerat* hypercholesterolemia" OR "accelerat* obesity" OR "accelerat* metabolic syndrome" OR "Alzheimer* * caused by" OR "dementia caused by" OR "cognitive decline caused by" OR "brain* decline caused by" OR "functional decline caused by" OR "memory decline caused by" OR "cognitive deficit* caused by" OR "language deficit* caused by" OR "memory deficit* caused by" OR "plasticity deficit* caused by" OR "behavioral deficit* caused by" OR "saccade deficit* caused by" OR "learning deficit* caused by" OR "neuropsychological deficit* caused by" OR "cognitive impair* caused by" OR "vascular impair* caused by" OR "memory impair* caused by" OR "neurogenesis impair* caused by" OR "neuropsychological impair* caused by" OR "mind impair* caused by" OR "functional impair* caused by" OR "learning impair* caused by" OR " executive function impair* caused by" OR "cognitive loss* caused by" OR "neuronal loss* caused by" OR "synaptic loss* caused by" OR "memory loss* caused by" OR "loss of memory caused by" OR "hearing loss* caused by" OR "volume loss* caused by" OR "Impair* face recognition caused by" OR "Impair* reasoning caused by" OR "Impair* judgment caused by" OR "Impair* problem solving caused

by" OR "inflamm* caused by" OR "oxidative stress caused by" OR "neuropathology caused by" OR "diabetes caused by" OR "hypertension caused by" OR "high cholesterol caused by" OR "hypercholesterolemia caused by" OR "obesity caused by" OR "metabolic syndrome caused by" OR "Alzheimer* * induced by" OR "dementia induced by" OR "cognitive decline induced by" OR "brain* decline induced by" OR "functional decline induced by" OR "memory decline induced by" OR "cognitive deficit* induced by" OR "language deficit* induced by" OR "memory deficit* induced by" OR "plasticity deficit* induced by" OR "behavioral deficit* induced by" OR "saccade deficit* induced by" OR "learning deficit* induced by" OR "neuropsychological deficit* induced by" OR "cognitive impair* induced by" OR "vascular impair* induced by" OR "memory impair* induced by" OR "neurogenesis impair* induced by" OR "neuropsychological impair* induced by" OR "mind impair* induced by" OR "functional impair* induced by" OR "learning impair* induced by" OR " executive function impair* induced by" OR "cognitive loss* induced by" OR "neuronal loss* induced by" OR "synaptic loss* induced by" OR "memory loss* induced by" OR "loss of memory induced by" OR "hearing loss* induced by" OR "volume loss* induced by" OR "Impair* face recognition induced by" OR "Impair* reasoning induced by" OR "Impair* judgment induced by" OR "Impair* problem solving induced by" OR "inflamm* induced by" OR "oxidative stress induced by" OR "neuropathology induced by" OR "diabetes induced by" OR "hypertension induced by" OR "high cholesterol induced by" OR "hypercholesterolemia induced by" OR "obesity induced by" OR "metabolic syndrome induced by")

AND

MESH HEADING NO EXPLODE

Lipopolysaccharides OR Malondialdehyde OR Neurotoxicity Syndromes OR Carbon Tetrachloride OR Formaldehyde OR 9,10-Dimethyl-1,2-benzanthracene OR Trinitrobenzenesulfonic Acid OR Insecticides OR Endocrine Disruptors OR Diethylnitrosamine OR Hydrogen Peroxide OR Benzhydryl Compounds OR Chemical Warfare Agents OR Asbestos OR Herbicides OR Organometallic Compounds OR Scopolamine Hydrobromide OR Silicon Dioxide OR Polychlorinated Biphenyls OR 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine OR Benzo(a)pyrene OR Fluorocarbons OR Nitrogen Dioxide OR Polycyclic Hydrocarbons, Aromatic OR Tetrachlorodibenzodioxin OR Metals, Heavy OR Hydrocarbons, Chlorinated OR Chemical Industry OR 1,2-Dimethylhydrazine OR Ethylene Glycol OR Nitrosamines OR Benzene OR Fluorides OR Agricultural Workers' Diseases OR Bromodeoxyuridine OR Chromium OR Organophosphorus Compounds OR Organic Chemicals OR Carbon Monoxide OR Benzalkonium Compounds OR Chlorpyrifos OR Organophosphates OR Organophosphate Poisoning OR Volatile Organic Compounds OR Diethylhexyl Phthalate OR Sulfur Dioxide OR Petroleum OR Methylmercury Compounds OR Chlorine OR Dichlorodiphenyl Dichloroethylene OR Hydrocarbons OR Trichloroethylene OR Carbon Tetrachloride Poisoning OR 3,4-Dihydroxyphenylacetic Acid OR Alkanesulfonic Acids OR Plasticizers OR Halogenated Diphenyl Ethers OR Benzene Derivatives OR Dinitrofluorobenzene OR Toluene 2,4-Diisocyanate OR Benzopyrenes OR Cyclohexenes OR Nitrobenzenes OR Plastics OR Trihalomethanes OR Hydrocarbons, Brominated

7A - Appendix 2 - Unambiguous MeSH Terms - Streamlined Approach

("Drug-Related Side Effects AND Adverse Reactions" OR Abnormalities, Drug Induced OR Abnormalities, Radiation-Induced OR Agricultural Workers Diseases OR Aids Related Opportunistic Infections OR Air Pollutants OR Air Pollutants, Occupational OR Air Pollutants, Radioactive OR Air Pollution OR Air Pollution, Indoor OR Air Pollution, Radioactive OR Alcohol Drinking OR Alcohol Related Disorders OR Alcoholic Beverages OR Alcoholic Intoxication OR Alcoholism OR Amphetamine Related Disorders OR Amphetamines OR Arsenic Poisoning OR Asthma, Aspirin-Induced OR Asthma, Exercise-Induced OR Asthma, Occupational OR Behavior, Addictive OR Bullying OR Cadmium Poisoning OR Carbon Monoxide Poisoning OR Carbon Tetrachloride Poisoning OR Carcinogenicity Tests OR Carcinogens OR Carcinogens, Environmental OR Causality OR Cardiomegaly, Exercise-Induced OR Chemical Warfare Agents OR Chemically-Induced Disorders OR Child Abuse OR Child Abuse, Sexual OR Cholesterol, Dietary OR Ciguatera Poisoning OR Cocaine Related Disorders OR Cytomegalovirus Infections OR Dermatitis, Occupational OR Diet, Atherogenic OR Diet, High Fat OR Dietary Carbohydrates OR Dietary Fats OR Dietary Fats, Unsaturated OR Dietary Fiber OR Dietary Sucrose OR Domestic Violence OR Drug Contamination OR Drug Eruptions OR Drug Hypersensitivity OR Drug Overdose OR Drug-Induced Liver Injury OR Dyskinesia, Drug Induced OR Eating Disorders OR Environmental Exposure OR Environmental Illness OR Environmental Pollutants OR Environmental Pollution OR Environmental Pollution OR Escherichia Coli Infections OR Fast Foods OR Fluoride Poisoning OR Food Additives OR Food Contamination OR Food Hypersensitivity OR Foodborne Diseases OR Gas Poisoning OR Hazardous Substances OR Hazardous Waste OR Hearing Loss, Noise Induced OR Heavy Metal Poisoning, Nervous System OR Hepatitis A, Chronic OR Hepatitis B, Chronic OR Hepatitis C, Chronic OR Heroin Dependence OR Herpesviridae Infections OR Htlv I Infections OR Hypersensitivity OR Hypersensitivity, Delayed OR Hypersensitivity, Immediate OR Iatrogenic Disease OR Inhalation Exposure OR Iron Overload OR Lead Poisoning OR Lead Poisoning, Nervous System OR Lead Poisoning, Nervous System, Adult OR Lead Poisoning, Nervous System, Childhood OR Leukemia, Radiation Induced OR Manganese Poisoning OR Marijuana Abuse OR Maternal Exposure OR Mercury Poisoning OR Mercury Poisoning, Nervous System OR Morphine Dependence OR Mptp Poisoning OR Mushroom Poisoning OR Mutagenicity Tests OR Mutagens OR Neoplasms, Radiation Induced OR Neurotoxicity Syndromes OR Occupational Diseases OR Occupational Exposure OR Opioid Related Disorders OR Opportunistic Infections OR Organophosphate Poisoning OR Paternal Exposure OR Plant Poisoning OR Pneumonia, Ventilator-Associated OR Poisoning OR Poisons OR Prenatal Exposure Delayed Effects OR Psychoses, Substance Induced OR Radiation Effects OR Radiation Injuries OR Radioactive Hazard Release OR Radioactive Pollutants OR Respiratory Hypersensitivity OR Salmonella Food Poisoning OR Sedentary Lifestyle OR Shellfish Poisoning OR Sleep Deprivation OR Sleep Disorders OR Sodium Chloride, Dietary OR Sodium, Dietary OR Soil Pollutants OR Soil Pollutants, Radioactive OR Spouse Abuse OR Staphylococcal Food Poisoning OR Staphylococcal Infections OR Streptococcal Infections OR Substance Abuse, Intravenous OR Substance Withdrawal Syndrome OR Substance-Related Disorders OR Teratogens OR Tobacco Smoke Pollution OR Tobacco Use Disorder OR Toxicity Tests, Chronic OR Virus Diseases OR Vitamin D Deficiency OR Water Pollutants OR Water Pollutants, Chemical OR Water Pollutants, Radioactive OR Water Pollution OR Water Pollution, Chemical)

7B. References - Chapter 7

[1] Kostoff RN. Under-reporting of adverse events in the biomedical literature. JDIS. 2016;1(4):10-32. doi:10.20309/jdis.201623

[2] Kostoff RN. Pervasive Causes of Disease. Georgia Institute of Technology. 2015. PDF. http://hdl.handle.net/1853/53714

Chapter 8

DETAILED AD FOUNDATIONAL CAUSES

8A. Taxonomy of AD Causes

Table 3-1 presented a top-level outline of the taxonomy categories to be used for showing the results. Table 8-1 presents this taxonomy with the categories shown at the next level of detail.

Table 8-1 - Detailed Taxonomy of AD Foundational Causes

CODE	CATEGORY
I	LIFESTYLE
I-A	Diet
I-A1	Excesses
I-A2	Deficiencies
I-A3	Food Additives/Pollutants
I-B	Activity
I-B1	Sedentary Lifestyle
I-B2	Sleep
I-C	Substance Abuse
I-C1	Recreational Drugs
I-C2	Smoking
I-C3	Alcohol
I-D	Other
II	IATROGENIC
II-A	Drugs
II-A1	Anti-Neoplastic Agents
II-A2	Anti-Infective Agents
II-A2a	Anti-Bacterial/Anti-Fungal/Anti-Parasitical Agents
II-A2b	Anti-Viral/Anti-Retroviral Agents
II-A3	Anti-Inflammatory Agents
II-A4	Cardiovascular Agents
II-A5	Central Nervous System Agents
II-A5a	Analgesics and Pain Relievers
II-A5b	Movement Stabilizers
II-A5c	Depressants/Anti-Depressants and Stimulants
II-A5d	Mood Stabilizers
II-A6a	Immunosuppressive Agents/Immunosuppression
II-A6b	Immunostimulation Agents

II-A6b1	Vaccines/Vaccination
II-A7	Hematologic Agents
II-A7a	Coagulants
II-A7b	Anti-Coagulants
II-A7c	Other
II-A8	Steroids/Hormones
II-A9	Anti-Hypertensive Agents
II-A10	Gastrointestinal Agents
II-A11	Lipid Regulating Agents
II-A12	Dermatologic Agents
II-A13	Anti-Bone-Loss Agents
II-A14	Anti-Diabetic Agents
II-A15	Anti-Rheumatic Agents
II-A16	Anti-Allergic Agents
II-A17	Anti-Hypotensive Agents
II-A18	Anti-Thyroid Agents
II-B	Radiotherapy
II-C	Surgery/Invasive Treatments
II-C1	Transplantation
II-C2	CardioVascular
II-C3	Orthopedic
II-C4	Gastrointestinal
II-C5	Kidney/Urologic
II-C6	Brain/Neural
II-C7	Dental/Oral/Nose/Ear
II-C8	Gynecologic
II-C9	Respiratory/Thorax
II-C10	Liver/Spleen
II-C11	Ocular
II-C12	Breast
II-C13	Dermal/Tissue/Neck
II-C14	Thyroid
II-C15	Pancreas
II-C16	General
II-C17	Other
II-D	Diagnostic Agents/Procedures
II-D1	Contrast Media
II-D2	Radiation

II-D2a	Ionizing
II-D2b	Non-Ionizing
II-D3	Invasive
II-D4	Other
III	BIOTOXIC AGENTS
III-A	Mycotoxins
III-B	Exotoxins
III-C	Bacteria/Fungi/Parasites
III-D	Viruses
III-E	Other
IV	OCCUPATIONAL/ENVIRONMENTAL EXPOSURES
IV-A	Chemicals/Materials
IV-A1	Industrial/Household Chemicals/Materials
IV-A1a	Hydrocarbons
IV-A1b	Solvents
IV-A1c	Chemical Compounds
IV-A1d	Other
IV-A2	Agricultural Chemicals
IV-A3	Materials
IV-A3a	Heavy Metals
IV-A3b	Particulates
IV-A3c	Nanotechnology
IV-B	Physical/Mechanical
IV-B1	Electromagnetic Radiation
IV-B1a	Ionizing
IV-B1b	Non-Ionizing
IV-B1b1	Non-Visible
IV-B1b2	Visible
IV-B2	Sound
IV-B3	Temperature; Heat/Cold
IV-B4	Force/Pressure/Physical Trauma
IV-C	Other
V	PSYCHOSOCIAL/SOCIOECONOMIC
V-A	Psychological
V-B	Sociological
V-C	Economic
VI	GENETICS (Categories Only)
VI-A	Polymorphism/Genotypes/Haplotypes

VI-B	Mutations
VI-C	Linkages
VI-D	Risk Alleles
VI-E	Genotoxicity
VI-F	Familial
VI-G	Congenital

8B. Effects/Impacts from AD Foundational Causes

Table 8-2 presents a taxonomy of effects/impacts from the AD foundational causes. Its members will be used to identify potential links to effects/impacts of the foundational causes identified in the final results taxonomy of Table 8-3.

Table 8-2 Taxonomy of Effects/Impacts from AD Foundational Causes

CODE	LEVEL
	CELLULAR LEVEL
A1	increase neuroinflammation
A2	increase neurotoxicity
A3	increase neuronal death
A4	increase neurodegeneration
A5	induce DNA damage
A6	damage mitochondria
A7	increase neuronal oxidative stress
	BIOMARKER LEVEL
B1	increase tau pathology/neurofibrillary tangles
B2	increase Abeta generation
B3	increase AGEs
B4	increase insulin resistance
B5	reduce brain volume
B6	produce low tostesterone
B7	produce tissue lesions
B8	induce synaptic/neurotransmission dysfunction
B9	induce hippocampal damage
B10	induce olfactory dysfunction
B11	impair glutamate uptake
B12	compromise BBB integrity
B13	impair glucose homeostasis
B14	impair metal homeostasis
	PERFORMANCE LEVEL
C1	increase memory loss
C2	increase seizures
C3	induce cognitive dysfunction
	DISEASE LEVEL
D1	increase AD risk
D2	increase diabetes risk
D3	induce hypothyroidism
D4	induce metabolic syndrome
D5	increase obesity

These effects/impacts are divided into four categories: Cellular Level, Biomarker Level, Performance Level, Disease Level. Each lowest-level sub-category was obtained by inspecting visually many Abstracts and Titles of records that related cause to effect/impact, and extracting those effects mentioned multiple times.

The lowest-level sub-categories are not orthogonal; there is some partial overlap and redundancy. Much of this is due to the different less-than-precise language of the article authors themselves. For

example, some authors may use neurotoxicity to refer to neural damage, others may use neuro-degeneration or neuronal death or .....

The value of incorporating the members of the above table in the final results is that it conveys (to the research community, the medical clinician community, and the consumer community) how the research is linked either 1) directly to AD, or indirectly to AD through 2) strong disease precursors of AD (e.g., diabetes), or 3) strong behavioral precursors of AD (e.g., cognitive decline), or 4) strong biomarker precursors of AD (e.g., increase tau hyperphosphorylation), or 5) strong cellular precursors of AD (e.g., increase neuronal death). Why is this important?

Consider two potential foundational causes of AD identified in the present study, high-fat diets and wireless radiation. High-fat-diets have been studied for a long time, and there appears to be good evidence that such diets are strong contributors to AD. The long-term data are sufficient to conclude there is a direct link between high-fat diets and AD.

Wireless radiation (e.g., cell phone radiofrequencies or WiFi frequencies) has been in commercial/military use for perhaps thirty years, and in wide-scale use for perhaps ten years. It might take 50-60 years to identify impacts of this radiation on the development of AD. We have a choice. We can wait many decades for the types of conclusive evidence that would satisfy the statisticians, or we can start to take precautions based on the impact of wireless radiation on surrogate endpoints already demonstrated. This is the Precautionary Principle, and the results contained in Table 8-3 provide a starting point for implementation of the Precautionary Principle for prevention and reversal of AD.

8C. Specific Foundational Causes of AD

Table 8-3 shows the AD potential foundational causes in this detailed taxonomic structure. There are four columns listed. The first column on the left (CAT) is the foundational cause category as shown in Table 8-1. The next column is the foundational cause. To keep the volume of results manageable, in some cases only the cause in aggregate was shown, rather than listing all the members (e.g., vegetables). The third column is the effect(s) produced by the foundational cause, and the entry tags are those listed in Table 8-2. The fourth column contains relevant references that confirm the foundational cause.

In most cases, there were multiple papers linking each foundational cause listed either directly to AD or indirectly to one or more surrogate endpoints. Referencing every single relevant paper for every detailed foundational cause would have produced an overly voluminous unreadable table and write-up. In order to balance comprehensiveness with readability, multiple compromises were made.

First, one or two representative papers for each foundational cause were selected and referenced. Second, foundational causes that had relatively minor differences were aggregated. Some were listed separately under a categorical heading, and others were subsumed within the heading. Third, the effects/impacts of the foundational causes were extracted from at least the papers referenced, and sometimes from other relevant papers that were not selected for referencing. Thus, the effects/impacts shown for any potential cause should be viewed as a "floor" of all potential effects, not a "ceiling".

It should also be noted that all the effects/impacts were derived from papers whose central theme was AD/dementia, because of the criteria used to extract these records from Medline. So, a foundational cause that, e.g., "damaged mitochondria" (A6) did so within the overall context of relating to AD or dementia. If the four different levels shown, and the items contained in each level, are viewed as potential "pathways" to AD, then conventional wisdom implies that the more pathways impacted by a potential contributing factor, the greater likelihood that factor would be an important "cause" of AD. However, not only are the numbers of pathways impacted important, but the strength of the contributing factor's impact on each pathway is important. This strength of impact is not shown in the table, reflecting its ambiguity in the literature.

The foundational causes identified are at different levels of importance to AD, and are at different levels of verification/validation. In the Medline literature examined, some foundational causes were identified through: 1) in vitro cell or tissue tests; 2) animal experiments; 3) epidemiological studies; 4) individual case studies; and, 5) trials with large numbers of subjects. Conventional wisdom implies that those foundational causes associated with large numbers of papers published and large numbers of test subjects would have greater credibility. However, as shown in [1-2], there may be (many) important foundational causes being withheld from the literature deliberately, so numbers of papers is not a definitive metric for credibility.

Table 8-3. Foundational Causes of AD

CAT	CAUSE	EFFECTS	REF
I	**LIFESTYLE**		
I-A	**DIET**		
I-A1	EXCESSES		
	High Fat Diet -saturated fat -dairy fat -trans-unsaturated fat -hydrogenated fat -omega-6 PUFAs -n-6/n-3 ratio -maternal high fat diet	A2, B1, B2, C1, C3, D1, D4, D5	[3-12]
	Diabetogenic diet	B2	[13]
	High calorie diet	A1, B1, B12, C3, D1, D5	[14-16]
	High salt diet	B2, C3, D1	[17]
	High carbohydrate diet -refined carbohydrates -sugars (fructose/sucrose/glucose/D-galactose) -gluten -high glycemic index diet	A1, A3, A4, A7, B2, B4, B11, B12, B13, C1, C3, D1, D2	[18-25]
	High advanced glycation end products diet -high temperature food heating -food irradiation -high glucose -high nutrient-bound AGEs -animal foods high in fat and protein	A6, A7, B1, B2, B3, C1, C3, D1, D2	[26-31]
	High cholesterol diet	A1, A4	[32]
	High iron diet -high red meat -high processed meat	A1, C3, D1	[33-35]
	High meat diet	D1	[36]
	High arachidonic acid	B1	[37]
	High methionine diet	A1, A2, A7, B1, B8, B2, C1, C3	[38-40]
	High copper diet	C3, D1	[35, 41]
	High zinc	A3, A7, B1, B2	[42-43]
	High pickle diet	D1	[44]
	High unfermented soy	D1	[45]
I-A2	DEFICIENCIES		
	Vitamin B deficiency -myriad B-Vitamin deficiency -B2/B6/B12 deficiency -folate/folic acid deficiency -thiamine deficiency	A3, A4, A6, A7, B1, B2, C1, C3	[46-49]

	Vitamin C deficiency	A7, C2	[50]
	Vitamin D deficiency	A1, A4, A6, B1, B2, B5, B8, C3, D1	[51-52]
	Vitamin E deficiency	D1	[53]
	Vitamin K deficiency -fluindone	C3	[54]
	Potassium deficiency	A1, A3, A7, B1, B2, C3	[55-56]
	Iron deficiency	C3	[57]
	Zinc deficiency	A3, C3, D1	[58]
	Magnesium deficiency	C3	[59]
	Calcium deficiency	A3, A7	[60]
	Selenium deficiency	B2	[61]
	Starvation	B2	[62]
	Dehydration	B5, D1, D2, D5	[63]
	Malnutrition	D1	[64]
	Early life nutrient restriction	B2, D1	[65]
	Glucose deprivation	A3, B1, B2	[66]
	Glutathione depletion	A1, A2, A4	[67]
	Linoleic acid deficiency	A4, D1	[68]
	Low docosahexaenoic acid	A3	[53]
	Low tryptophan diet	B2	[69]
	Nondrinkers	C3, D1	[70]
	Low cocoa	A1, A7, C3	[71]
	Low coffee	C3, D1	[72]
	Low flavonoids/flavanols: acacetin, aminogenistein, apigenin, kaempferol, 7,8-Dihydroxyflavone, anthocyanins, atriplex laciniata L, blueberries, Curcumin, cyanidin, datiscetin, delphinidin, EGCG, epicatechin, Epimedium brevicornum, fisetin, genistein, Ginkgo, glycitein, icariin, isoscutellarein 7-O-[6'''-O-acetyl-beta-D-allopyranosyl-(12)]-beta-D-glucopyranoside, isovitexin, morin, myricetin, Nobiletin, pelargonidin, phloridzin, rutin, salvigenin, Scutellaria baicalensis Georgi, Sideritis flavonoids, vitexin, xanthomicrol, luteolin, morin, PD98059, quercetin, taxifolin, β-naphthoflavone	A1, A7, B2, C3, D1	[71, 73-74]
	Low fruit: **low**: blackberries, blueberries, strawberries, raspberries, cherries, oranges, plums, prunes, red grapes, pomegranates, date palm fruits	A7, B2, B3, B13, C1, C3, D1	[21, 75-76]
	Low vegetables -cruciferous -dark and green leafy	A7, B13, C3, D1	[8]
	Low fatty fish	B2, C3, D1	[77]

I-A3	FOOD ADDITIVES/POLLUTANTS		
	Industrialized/preserved food	D1	[78]
	Monosodium glutamate	A2, A3, B2, B9	[79]
	Menadione	A3, A7	[80]
	Cysteine	A7	[81]
	Diacetyl	A2, B2	[82]
I-B	**ACTIVITY**		
I-B1	SEDENTARY LIFESTYLE		
	Physical inactivity/low daily gardening, walking	A6, A7, D1	[83-84]
	Chronic immobilization stress	A4, B1, B2, B9, C3	[85]
	Cognitive inactivity	D1	[86]
	Lack of exercise	D1, D2	[23]
	Low cardiovascular fitness	D1	[87]
I-B2	SLEEP		
	Sleep deprivation	C3, D1	[20, 88]
	Circadian disruption	C1, C3	[89-90]
I-C	**SUBSTANCE ABUSE**		
I-C1	RECREATIONAL DRUGS		
	Amphetamine	C3	[91]
	3,4-Methylenedioxyamphetamine; MDMA; Ecstacy	A2, A7, B1, C1, C3	[92]
	Cocaine/opiates	A2, A4	[93-94]
	Phencyclidine	C3	[95]
I-C2	SMOKING		
	Tobacco smoke	A4	[96]
	Ethanol/excess alcohol	A7, B9, C1, C3, D1	[97]
II	**IATROGENIC**		
II-A	**DRUGS**		
II-A1	ANTI-NEOPLASTIC AGENTS		
	Chemotherapy	A2, A4, B9	[98]
	Chemical castration	C3	[99]
	Camptothecin	A2, A3	[100]
	Epoxomicin	A3, A6	[101]
	Staurosporine/Etoposide	A3, A4	[102-103]
	Methylmethane sulfonate	A5	[104]
	Paclitaxel/Doxorubicin	A3, A4, B1	[105]
	Doxycyclin	B2	[106]
	Cyclophosphamide/cytophosphane	A2, A7	[107]
	Letrozole	B9, C1	[108]
	Methotrexate	B9, C1, C3	[109]
	Choline mustard Az/Nitrogen mustard	B9, C1	[110]
	Anastrozole	B2, B9	[111]
	d,l-buthionine-S,R-sulfoximine/BSO	A3, A6, A7, B14	[112]
	Fostriecin/Fos	B1	[113]
	carbobenzoxy-Leu-Leu-leucinal/MG132	A2, A4	[114]
	Streptozocin	B14, D1	[115]

II-A2	ANTI-INFECTIVE AGENTS		
	Chloroquine(CQ); CQ; lysosomotropic agent	B2	[116]
	Ionomycin	A6, B2	[117]
II-A3	ANTI-INFLAMMATORY AGENTS		
	colchicine	A1, A4, C1, D1	[118]
II-A4	CARDIOVASCULAR AGENTS		
	isoproterenol	B1, C1	[119]
	atropine	B2	[120]
	D-ribose	A3, B1, B3	[121]
	Muscarinic receptor antagonists	C1, C3	[122]
II-A5	CENTRAL NERVOUS SYSTEM AGENTS		
II-A5a	Analgesics and Pain Relievers		
	Anesthetics/Opiods -acetaminophen -barbital -barbitone -desflurane -dexmedetomidine -diethylbarbituric acid -diethylmalonyl urea -enflurane -halothane -isoflurane -ketamine -medinal -morphine -nitrous oxide -pentobarbital -propofol -psychotropic drugs -sevoflurane -sodium diethylbarbiturate -veronal	A2, A3, A4, A6, B1, B2, B9, C1, C3, D1	[123-129]
II-A5b	Movement Stabilizers		
	Anticholinergic medications -doxepin -chlorpheniramine -oxybutynin -trihexyphenidyl -propiverine -L-DOPA/dopamine	A3, A7, B1, C3, D1	[130-132]
II-A5C	Depressants/Anti-Depressants and Stimulants		
	selective serotonin re-uptake inhibitors	D1	[133]
	benzodiazepine	D1	[134]
	dizocilpine	C1, C3	[135]
	3-quinuclidinyl benzilate	C3	[136]

II-A5d	Mood Stabilizers		
	-clozapine -methyllycaconitine -dihydro-beta-erythrodine	C1, C3	[137]
	anisomycin	A7, B2	[138]
II-A6	IMMUNE SYSTEM AGENTS		
II-A6a	Immunosuppressive Agents/ Immunosuppression		
	Cyclosporin	B1, C1	[139]
II-A6b	Immunostimulation Agents		
	polyinosinic:polycytidylic acid	B2, C3	[140]
II-A7	Hematologic Agents		
II-A7b	Anti-Coagulants		
	Sulfated glycosaminoglycans -heparin/heparan sulfate -dextran sulfate -pentosan polysulfate -chondroitin sulfate -dermatan sulfate	B1	[141]
II-A7c	Other		
	mitochondrial toxins -1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine/MPTP	A1, A3, A6, A7	[142]
II-A8	Steroids/Hormones		
	Corticosteroids -methylprednisolone -dexamethasone	A1, A3, A4, B1, B5	[143-145]
	Anabolic androgenic steroids -nandrolone -stanozolol	B8, B9, C1, C3	[146]
	Corticosterone	B1, B2, C3	[147]
	Wortmannin	A7, B1	[148]
	17beta-trenbolone	A3, A4, B2	[149]
	Salmon calcitonin	B2	[150]
	Human chorionic gonadotropin	B2	[151-152]
	Corticotrophin releasing factor	B2	[153]
	Sex steroid hormones -transient testosterone treatment -flutamide	B2	[154]
	U18666A	A3, A7, B2	[155]
	Allopregnanolone	B9, C1, C3	[156]
	Medroxy-progesterone acetate	C3, D1	[157]
	Androgen deprivation therapy	D1	[158]
	Postmenopausal hormone therapy	C3	[159]
	Testosterone depletion	A1, D1, D2	[160]
	Leptin deficiency	B1	[161]

	Prenatal sex hormone exposure	D1	[162]
II-A9	ANTI-HYPERTENSIVE AGENTS		
	ACE inhibitor	D1	[163]
	ICI 118,551/Selective beta2AR antagonist	B1, B2, C3	[164]
	Telmisartan/Olmesartan	B2	[165]
	Mecamylamine	C3	[166]
II-A10	GASTROINTESTINAL AGENTS		
	Thiorphan/Phosphoramidon	B2	[167]
	Proton pump inhibitors -omeprazole -pantoprazole -lansoprazole -esomeprazole -rabeprazole	B2, D1	[168-169]
II-A13	ANTI-BONE-LOSS AGENTS		
	PGE2	B2	[170]
II-A14	ANTI-DIABETIC AGENTS		
	Intralipid and insulin	B2	[171]
	Metformin	B2	[172]
II-A16	ANTI-ALLERGIC AGENTS		
	Anticholinergics -first-generation antihistamines -tricyclic antidepressants -bladder antimuscarinics	D1	[173]
II-A18	ANTI-THYROID AGENTS		
	Propythiouracyl	A1, B1, B2, B5, B8, C1	[174]
II-A19	Other		
	Carbachol	B8, B14	[175]
	MDL72974/Mofegiline	A3, A7	[176]
	Pilocarpine	A3, B1, B2	[177]
	Clenbuterol hydrochloride	B2	[178]
	Semagacestat	C3	[179]
II-B	**RADIOTHERAPY**		
	Head radiotherapy	C3, D1	[180-181]
II-C	**SURGERY/ INVASIVE TREATMENTS**		
II-C1	TRANSPLANTATION		
	Liver transplant	B2, C3	[182]
II-C2	CARDIOVASCULAR		
	Cardiac surgery/bypass	A1, B1, B2, C3	[183-185]
II-C5	KIDNEY/UROLOGIC		
	Dialysis	C1, C3	[186-187]
	Gonadectomy	B2	[188]
II-C7	DENTAL/ORAL/NOSE/EAR		
	Olfactory bulbectomy	A4, A6, A7, B2, C1	[189-190]
	Occlusal disharmony	B2	[191]
II-C8	GYNECOLOGIC		

	Hysterectomy/oophorectomy	C3	[192]
	Premature surgical menopause/Premature ovarian failure	C3	[193]
II-C17	OTHER		
	Axotomy	A3, A7	[194]
	Cerebral artery occlusion	A3, A4, A7, B8, C1, C3	[195-198]
	Intermittent hypoxia/ischemia	A3, A4, A7, B2, B12, C1, C3	[199-202]
	Brain embolism	A4, B1, B2, C1, C3	[203-204]
	Aortic coarctation	A1, B2	[205]
	Forebrain lesions	C1, C3	[206-207]
	Adrenalectomy	B2	[208]
	Pituitary hormone injections with Abeta	B2	[209]
	Abdominal surgery	B2, C3	[210]
III	**BIOTOXIC AGENTS**		
III-A	**MYCOTOXINS**		
	Mycotoxins -ochratoxin A/OTA -Fumonisin B1/FB1 -macrocyclic trichothecenes	A2, A3, A4, A7, B1, C1, C3, D1	[211-214]
	3-nitropropionic acid	A6	[215]
III-B	**EXOTOXINS**		
	Excitotoxins -kainic acid/ kainate -quisqualic acid -ibotenic acid -domoic acid -quinolinic acid/quinolinate	A1, A2, A3, A4, B9, C1, C2, C3,	[216-220]
	Phosphatase inhibitor -okadaic acid	B1	[221]
	Excitatory amino acids	D1	[222]
	Malonate	B9	[223]
	Annonaceaeous acetogenins	A2, D1	[224]
	Cyanobacteria -beta-N-methylamino-L-alanine/BMAA -saxitoxin -anatoxin-a -blue-green algae -microcystin	A2, B1, B2, B14	[225-228]
	Diphtheria toxin	B2	[229]
	Pseudomonas aeruginosa exotoxin Y	B1, B12	[230]
	Saporin -192 IgG-saporin -p75-saporin	B1, B2, B13, C3	[231-233]
	Cycad plant -cycasin/methylazoxymethanol	A2, A4, A5	[234]

	Glutamate/Glutamine synthetase	A2, A3, A4, A6, B2	[235-237]
	Mitochondrial inhibitors -rotenone -3-NPA -antimycin -KCN -oligomycin	A6	[238]
III-C	**BACTERIA/FUNGI/PARASITES**		
	Bacteria/bacterial infections -bacterial endotoxins -bacterial lipopolysaccharide -gram-negative bacterium -spirochetes -Chlamydophyla pneumoniae -Helicobacter pylori -Escherichia coli -Treponema pallidum -Tannerella forsythia -Treponema denticola -T. socranskii -T. pectinovorum -T. medium -T. amylovorum -T. maltophilum -Fusobacterium nucleatum -Prevotella intermedia -Chlamydia pneumoniae -Porphyromonas gingivalis -propionibacterium acnes -Treponemas -T. lecithinolyticum -Borrelia burgdorferi Fungi/fungal infection -Cryptococcus -Coccidioides -Aspergillus -Histoplasma -Blastomyces -C. famata -C. parapsilosis -C. glabrata -C. krusei -Candida albicans -Candida ortholopsis -Candida tropicalis -Cladosporium -Malassezia globosa -Malassezia restricta	A1, A4, A7, B1, B2, B3, C3, D1	[239-253]

	-Neosartorya hiratsukae -Phoma -Sacharomyces cerevisae -Sclerotinia borealis Parasites -Trypanosoma brucei rhodesiense -Trypanosoma brucei gambiense -Acanthamoeba -Balamuthia mandrillaris -Toxoplasma gondii -Taenia solium -Toxocara canis -T. cati -Toxocara ova -Leishmania amazonensis		
III-D	**VIRUSES**		
	Viruses/Viral infections/Virulence factors Bornaviridae -Mammalian 1 bornavirus Bunyaviridae -Hantavirus -La Crosse encephalitis virus Coronaviridae -Human coronavirus OC43 -Murine hepatitis virus Flaviviridae -Hepatitis C virus -Japanese encephalitis virus -Murray Valley encephalitis virus -St. Louis encephalitis virus -West Nile virus Hepadnaviridae -Hepatitis B virus Herpesviridae -Cytomegalovirus -Epstein-Barr virus -Herpes simplex virus 1 -Human herpesvirus 6 Orthomyxoviridae -Influenza A virus (H1N1) -Influenza A virus (H3N2) -Influenza A virus (H5N1) Paramyxoviridae -Hendra virus -Measles virus Picornaviridae -Enterovirus 71 -Theiler's murine encephalomyelitis virus	A1, A3, A4, B1, B2, C3, D1	[254-260]

	Polyomaviridae -Simian 40 virus large T antigen Retroviridae -Human immunodeficiency virus 1 -Human T-cell leukemia virus -Moloney murine leukemia virus Rhabdoviridae -Chandipura virus Togaviridae -Chikungunya virus -Eastern equine encephalitis virus -Venezuelan equine encephalitis virus		
III-E	**OTHER**		
	Abeta -amyloid precursor protein -C31 -CT105 -Curli fibrils	A1, A2, A3, A4, A6, B2, B8, B14, C1, C3	[261-271]
	Homocysteine/3-Mercaptopropionic Acid	B8, B12, C1	[272-273]
	Lipopolysaccharide	A7, B3, C1	[274]
	Prions/Prion protein fragment	A2, A3, B14	[275-277]
	Cytokines -CXCL10 -IL-1 beta -IL-10 -interferon-alpha -interferon-gamma -interleukin-6 -interleukin-18 -interleukin-8 -TNF-alpha	A1, A2, A3, A4, B1, B2, B9, C1, C3	[278-288]
	Lipoperoxydation proteins -advanced lipoperoxydation products -oxidized low density lipoprotein	A1, A2, A3	[289-290]
	Trophic factor withdrawal	A3, A4, B2	[291-293]
	Amylin	A1, A2, A4, A6, A7	[294]
	Lysophosphatidic acid	B2	[295]
	S100B	A1, B1, B2	[296]
	3-hydroxykynurenine/3-hydroxyanthranilic acid	A4, A7, B2	[297]
	Abscisic acid	A1	[298]
	Phorbol myristate acetate	A1	[298]
	Acid phosphatase	D1	[299]
	2-deoxy-D-glucose	B2	[300]
	3-methylindole/Skatole	B10	[301]
	alpha-amino-3-hydrozy-5-methyl-4-isoxazole propionic acid/AMPA	A2	[302]
	Asymmetric dimethylarginine	A2, A7, B2, C3	[303-304]

	Dolichyl phosphate	B12	[305]
	N-(2-chloroethyl)-N-ethyl-bromo-benzylamine/dsp4	A1, A3, A4, B2, B13, C1	[306]
	Galanin	C1, C3	[307]
	GW4869/hydrochloride hydrate	B2	[308]
	Cottonseed	B1, B2	[309]
	Homocysteic acid/Homocysteate	A3, A7	[310]
	Isoprostane	B2	[311]
	Lysophosphatidylcholine	A2, A3, A7, B2	[312]
	Saturated non-esterified fatty acids	B2	[313]
	Palmitic acid	A3, C3	[314]
	Oncostatin M	A2, B11	[315]
	S100A9	A1, B2, C3	[316]
	Salsolinol	A2, A3	[317]
	Sulfatide	A3	[318]
	Brefeldin A	A3, A6, A7	[319]
	Thapsigargin	A3, A6, A7	[319]
	GF-109203X	B1	[320]
	Isopropyl-1-beta-D-thiogalactopyranoside	A3, A6, B1	[321]
	C2-ceramide	A3, A7	[322]
	dl-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol/PDMP	B2	[323]
	(1S,2R-d-erythro-2-N-myristoylamino)-1-phenyl-1-propanol/DMAPP	B2	[323]
	alpha7 nAChR subunit alpha7(1-208)	A1, B2, C3	[324]
	Adenosine triphosphate/ATP	B1	[325]
	Recombinant BiP/GRP78	B2	[326]
	Bradykinin	B1, B14	[327]
	CD40/CD40L	B2	[328]
	Collagen	B2	[329]
	Cyclic dipeptides	A3	[330]
	D-serine	A7	[331]
	Elastase	A7, B1	[332]
	4-Hydroxyhexenal/HHE	A3, B11, B13	[333]
	High-mobility group box-1/HMGB1	C3	[334]
	Exogenous amyloidogenic proteins -casein -fibroin -sericin -actin -islet amyloid polypeptide	B2	[335]
	Leukotrienes -Leukotriene B4/LTB4 -Leukotriene D4/LTD4	A1, B2, C1	[336-337]
	Myostatin precursor protein	B2	[338]
	N-acetylcholinesterase	A3, B1	[339]
	Secreted phospholipase A2-IIA/sPLA2-IIA	A1	[340]

	Spermine	A2	[341]
	Xanthine oxidase	A3, A7	[342]
	3-hydroxykynurenine/3-HK	A2, A3, A6	[343]
	Mitochondrial lysates	A1	[344]
	Phytohemagglutinin	A3, B14	[345]
	Angiotensin II	B1, B2, C3	[346]
	3beta-hydroxy-5-oxo-5,6-secocholestan-6-al/ ChSeco	A2, A3, A7, B2	[347]
	Cholesterol oxidation products/oxysterols -27-hydroxycholesterol/27-OHC -24-OH -7beta-hydroxycholesterol -7-ketocholesterol -5,6-alpha cholesterol epoxide -5,6-beta cholesterol epoxide -cholesterol triol -lathosterol -beta cholesterol epoxide -cholesterol triol	A1, A2, A7	[348-349]
	Calyculin A	A2, A7, B1	[350]
	Chromogranin A	A1	[351]
	Forskolin	B1	[352]
	N-methyl-D-aspartate	A3, B9	[353]
	PGJ2	A1, A3, B1	[354-355]
	Quisqualate	A3, B9, C2	[356]
	Tunicamycin	A3, B14	[357]
	2-chloro-2'-deoxyadenosine/2-CDA/ cladribine	B2, C3	[358]
	N-acetylglucosamine	A2, B8, B9	[359]
	Cholinesterase -acetylcholinesterase -butyrylcholinesterase	B2	[360]
	Glycogen synthase kinase 3-beta/GSK3beta	B1	[361]
	HMG-CoA reductase	D1	[362]
	Pam(3)CSK(4)	A1	[363]
	Superoxide dismutase deficiency	A1, A7, B1, B2, B3, C1	[364]
IV	**OCCUPATIONAL/ENVIRONMENTAL EXPOSURES**		
IV-A	**CHEMICALS/MATERIALS**		
IV-A1	INDUSTRIAL/HOUSEHOLD CHEMICALS/MATERIALS		
IV-A1a	Hydrocarbons		
	20-methylcholanthrene/methylcholanthrene	A1	[365]
IV-A1b	Solvents		
	Petroleum-based solvents -Mineral turpentine	D1	[366]

	-Diesel fuel -Fuel oil -Kerosene		
	Chlorinated solvents -Trichloroethylene -Perchlorethylene -Trichloroethane -Dichloromethane -Benzene	C3	[367]
	Dimethyl sulfoxide/DMSO	B1	[368]
	Organic solvents -Benzene -Toluene -Phenols -Alcohols -Ketones -Methylmethacrylate	D1	[369-370]
IV-A1c	Chemical Compounds		
	Neurotoxins -6-hydroxydopamine/6-OHDA -5,6-dihydroxytryptamine/5,6-DHT -5,7-dihydroxytryptamine/5,7-DHT	A3, A7	[371-372]
	Type-2 Alkenes/Reactive aldehydes -Acrolein -4-Hydroxynonenal/HNE -Acrylamide -Methyl glyoxal	A2, A3, A4, A7, B1, B2, B3, B8	[373-378]
	Nitrosamine/N-nitrosodiethylamine	A3, A4, B4, C3	[379]
	Adenosine, 3', 5'-cyclic monophosphate/ cAMP	B2	[380]
	Carbon tetrachloride	A1, A4, A7, B4, B13	[381]
	Chemical warfare agents/nerve agents -organophosphates -soman -sarin -ethyl S-2-di-isopropylaminoethyl-phosphonothiolate -VX -tabun	C1, C3	[382]
	Cyanide -Potassium cyanide -Sodium cyanide	A3, A7	[383-385]
	Formaldehyde	B1, C1	[386]
	Hydrogen Peroxide/H2O2	A2, A3, A6, A7	[387]
	Lipophilic chemicals -persistent organic pollutants -bisphenol A -phthalates	C3, D1	[388]

	-low molecular weight hydrocarbons -polynuclear aromatic hydrocarbons -endocrine disruptors		
	Sulfur dioxide/ SO2	A2, B8, C3	[389]
	Phthalates -Di-(2-ethylhexyl)-phthalate/DEHP -mono-2-ethylhexyl phthalate/MEHP -DEHP metabolites	B1, B4, B14, C3	[390]
	Brominated flame retardants -hexabromocyclo-dodecane/HBCD -tetrabromobisphenol-Al/TBBPA -decabromodiphenyl ether/DBDE -polybrominated diphenyl ethers/PBDEs	A2, A3, A6, A7, B2	[391-392]
	Ammonia	A1, B2, B8	[393-394]
	Hypochlorous acid/HOCl	A2, A6, B13	[395-396]
	Methanol	A3, B1, C1	[397]
	Peroxynitrite	B1	[398]
	Sodium azide	A3, B1, B2	[399]
	Acetaldehyde	A3, A7	[400]
	3-Bromopyruvate	B13, C3	[401]
	Vehicular emission oxides -nitrogen dioxide/NO2 -carbon monoxide/CO	C3, D1	[402]
	Sodium fluoride	C1, C3	[403
	Membrane-mimicking detergents -sodium dodecyl sulfate -lithium dodecyl sulfate	B2	[404-405]
	Nitric oxide donors -sodium nitroprusside -DETA NONOate	B1	[406-407]
	Amorphous aluminosilicates	B2	[408]
	Sodium nitrite	A3, A4, B1, B2, B9, B11, C1	[409]
	Tert-butyl hydroperoxide/t-BHP	A3, A7	[410]
	Alloxan	B1, B2	[411]
	Ammonium chloride	A4, A6	[412]
	Anionic dyes -Congo Red -Thiazine Red -Thioflavin S	B1	[413]
	Aroclor 1254	A3	[414]
	Cobalt chloride	A2, A3, A6, A7, C1, C3	[415]
	Magnesium chloride	B2	[416]
	2,2'-azobis(2-methylpropionamidine) dihydrochloride/AAPH	A7	[417]
	Methylglyoxal/Glyoxal	A1, A2, A7, B12	[378, 418]

	Disuccinimidyl suberate	B2	[419]
	Naphthazarin/5,8-dihydroxy-1,4-naphthoquinone/5,8-dihydroxy-1,4-naphthalenedione	A7	[420]
	Pyrithiamine	B1, B2, C1	[421]
	Pyrogallol	A3, A7	[422]
	Glyceraldehyde-3-phosphate/GAPDH	A3, A6, B2	[423]
IV-A1d	Other		
	Ethylcholine mustard aziridinium ion/ AF64A	B8, C1	[424]
	1-methyl-4-phenylpyridinium ion	A2, A3, A6, A7	[425]
	2,2'-dithiodipyridine	B14	[426]
	Aftin-4	A7, B2, B8, C3	[427]
	Kaolin	B2	[428]
	Ozone	A3, A7, C1, C3	[429]
	2;3;7;8-tetrachlorodibenzo-p-dioxin	A2, D1	[430-431]
IV-A2	AGRICULTURAL CHEMICALS		
	Pesticides/Insecticides/Herbicides/Fungicides -Organochlorine Pesticides -Organophosphate Pesticides -2,4,5-trichlorophenoxyacetic acid -2,4-Dichlorophenoxyacetic Acid -Agent Orange -Aldrin -Alkylphenolpolyethoxylates -APEOs -Arsenic -Beta-hexachlorocyclohexane/beta-HCH -Bipyridyles -Carbamates -Carbofuran -Chlorfenvinphos -Chlorpyrifos/CPF -Cycloheximide -Cypermethrin -Deltamethrin -Dichlorodiphenyldichloroethylene/DDE -Dichlorodiphenyltrichloroethane/DDT -Dichlorodiphenyldichloroethane/DDD -Dieldrin -Dimethyl parathion -Endosulfan -Famoxadone -Fenamidone -Glyphosate -Hexachlorobenzene -Hexachlorocyclohexane/HCH -Imidacloprid -Lindane	A1, A2, A3, A5, A6, A7, B1, B2, B11, B14, C1, C3, D1,	[391, 431-443]

	-Maneb -Methamidophos -Methyl parathion -Neonicotinoids -Nonylphenol -Octylphenol -Paraquat -Parathion -Pyraclostrobin -Pyrethroids -Trans-nonachlor -Trichlorfon/TCF -Trifloxystrobin		
IV-A3	MATERIALS		
IV-A3a	Heavy Metals		
	Heavy Metals -aluminum -arsenic -cadmium -calcium/Ca2/CaCl -calcium ionophore/A-23187/calcimycin -cobalt -copper -iron -lead -manganese -mercury -methylmercury -selenium -tin -zinc	A1, A2, A3, A4, A6, A7, B1, B2, B14, D1	[391, 444-455]
IV-A3b	Particulates		
	Air pollution -fine/ultrafine particles -inhalable dust -surgical smoke	A1, A4, A7, B1, B2, D1	[456-458]
IV-A3c	Nanotechnology		
	Nanoparticles -iron -titanium dioxide -CdSe quantum dots -diesel exhaust -alumina -manganese oxide -copper -silica/silicon dioxide -zinc oxide -silver	A1, A2, A3, A4, A7, B2, B8, B12; B14	[459-462]

	-nickel		
IV-B	Physical/Mechanical		
IV-B1	Electromagnetic Radiation		
IV-B1a	Ionizing		
	Gamma radiation -dental X-ray -gamma rays	A3, B1	[463-464]
	Particle radiation -56Fe-particle radiation -cosmic radiation -HZE particle radiation	B2, B8, B9, B12, C3	[465-466]
	Radionuclide pollutants -uranium -cesium -cobalt -radon	A7, C1, C3, D1	[467-468]
IV-B1b	Non-Ionizing		
IV-B1b1	Non-Visible		
	Electromagnetic fields -extremely low frequency/ELF-EMF -900 MHz/RFEMR -electromagnetic pulse/EMP -electroconvulsive shock/ECS -UV irradiation	B1, B2, B8, B9, C1, C3, D1	469-473]
IV-B1b2	Visible		
	photolysis of 1-(2-nitrophenyl)ethyl sulfate	B2	[474]
IV-B2	SOUND		
	Noise -chronic noise exposure -short-lasting impulse noise -ultrasound sonication	A1, A4, B2, B3, D1	[475-477]
IV-B3	TEMPERATURE; HEAT/COLD		
	Heat stress -heat shock -heating -hyperthermia	A6, A7, B1, B2	[478-481]
	Cold stress -cold water stress -cold water hypothermia	A3, B1, B2, C1, C3	[482]
IV-B4	Force/ Pressure/ Physical Trauma		
	Traumatic brain injury	A4, B2, B9, C1, C3, D1	[483-486]
	Head trauma -history of head trauma -closed head injury -axonal injury	A1, B1, B8, B9, C1, C3, D1	[487-490]

	Spinal cord injury	A1, A4, C3	[491]
	Mechanical stress -Valsalva maneuver -repetitive heavy lifting -repetitive strong cough -accumulated mechanical stress	A1, A3, B1, B2, D1	[492-493]
IV-C	**OTHER**		
	Oxygen alterations -hyperoxia -hypoxia	A1, A3, A4, A7, B2, C3	[494-495]
V	**PSYCHOSOCIAL/SOCIOECONOMIC**		
V-A	**PSYCHOLOGICAL**		
	Chronic stress -repeated stress -chronic mild stress -chronic psychological stress -multiple chronic stresses -behavioral stress -childhood trauma -bereavement -chronic restraint stress -high job stress -low level of job control	A4, A6, A7, B1, B2, B9, C1, C3, D1	[496-503]
	Low mental activity -low cognitively engaging activity -low purposeful activities -low leisure activities/low hobbies --low music/drawing/meditation/reading/arts/crafts	B5, C3, D1	[504-507]
V-B	**SOCIOLOGICAL**		
	Social isolation -isolation -loneliness -living alone -unmarried -maternal separation -low social activity index -low social support at work -constricted life space	A3, B1, B2, B8, C1, C3, D1	[508-513]
	Low education -illiteracy	D1	[514-516]
V-C	**ECONOMIC**		
	Early life socioeconomic circumstances	C3	[517]

8C1. Analysis of Results in Table 8-3

The findings in the Lifestyle, Iatrogenic, Biotoxic Agents, Occupational/ Environmental Exposures, and Psychosocial/Socioeconomic categories will now be examined by sub-category. The sub-category alphanumerical headings correspond to those in Table 8-3.

I. Lifestyle

Lifestyle includes choices mainly under individual control, and is divided arbitrarily into Diet, Activity, Substance Abuse, Other.

I-A. Diet

Poor diet reflects the adverse effects of excesses and deficiencies of dietary components. It has been used to induce myriad diseases in test animals, and it was a critical disease factor from many epidemiological and case studies.

I-A1. Dietary Excesses

Dietary excesses include: high-fat; diabetogenic diet; high-calorie; high-salt; high-carbohydrate; high advanced glycation end products (AGEs); high-cholesterol; high-iron; high-meat; high arachidonic acid; high methionine; high copper; high zinc; high pickle diet; high unfermented soy; and high-temperature cooking that results in harmful products (e.g., AGEs, nitrosamines, polycyclic aromatic hydrocarbons, and acrylamides).

As Table 8-3 shows, high-fat diet (from the specific types of fat listed in the table) had impacts at the cellular, biomarker, performance, and disease categories listed in Table 8-2. These high-fat diets were 1) directly related to AD, 2) indirectly related to AD through their direct impact on other diseases directly related to AD (e.g., metabolic syndrome, diabetes), and 3) indirectly related to AD through their direct impact on the pre-disease surrogate endpoints directly related to AD. High-fats were also a key component of the diabetogenic diet listed in the table.

High-calorie and high-salt diets had both direct and indirect relationships to AD. High-carbohydrate diet, especially refined carbohydrates/sugars, also had full spectrum impacts. They also contributed to the diabetogenic diet.

High-AGEs, high-cholesterol, high-iron, and high-meat diets are intertwined, to a large extent. Meat tends to be high-cholesterol, high-iron, and, especially when cooked at high temperatures, associated with production of high AGEs. Most of the articles related to meat consumption and AD emphasized adverse effects. Unfortunately, in most of these meat studies, especially epidemiological studies on humans, there was no separation of confounding effects.

Most meat available to the American public comes from CAFO (confined animal feeding operations). These animals are raised confined in very close quarters. To reduce infections from such

close confinement, animals are given antibiotics, and to increase growth more rapidly, animals are given synthetic growth hormones. Their feed is grain-based, not the grass they would have if pasture-raised. Would the dementia-related diseases associated with meat consumption in the articles be as copious and serious for pasture/grass-fed animals not raised under confined conditions, and not given antibiotics and synthetic growth hormones?

Most meat eaten is cooked, much of it at high temperatures, usually in the presence of endogenous and exogenous additional fats. High-temperature cooking, especially of animal foods that are high in protein and fat, results in substantial production of AGEs and other harmful substances (e.g., nitrosamines, polycyclic aromatic hydrocarbons, and acrylamides). How are the harmful effects of the cooking separated from the harmful effects of the meat? Separation was not evident in any papers examined. The bulk of the biomedical literature has not demonstrated that meat from 'organic' pasture-raised grass-fed animals not fed antibiotics and growth hormones and not cooked at high temperatures is equally harmful to CAFO meat consumed by the vast majority of the American public, and there is some evidence that a moderate amount of high-quality meat may be beneficial.

Finally, diets high in arachidonic acid, methionine, copper, zinc, pickles, and unfermented soy contribute directly or indirectly to the development of AD.

1A2. Dietary Deficiencies

Many deficiencies listed in the literature may be symptoms of metabolic problems, not foundational causes in the present sense. Thus, a Vitamin A deficiency may be caused by 1) insufficient Vitamin A intake (foundational cause), or 2) some metabolic problem that results in reduced Vitamin A levels (symptom). Dietary deficiencies include **low**: vitamins, especially Vitamins B (B2, B6, B12, folate/folic acid, thiamine), C, D, E; minerals, especially potassium, iron, zinc, magnesium, calcium, selenium; calories (starvation, malnutrition, early life nutrient restriction); water (dehydration); glucose; glutathione; linoleic acid; docosahexaenoic acid; tryptophan; alcohol (nondrinkers); flavonoids/flavanols (cocoa, coffee, acacetin, aminogenistein, apigenin, kaempferol, 7,8-Dihydroxyflavone, anthocyanins, atriplex laciniata L, curcumin, cyanidin, datiscetin, delphinidin, EGCG, epicatechin, Epimedium brevicornum, fisetin, genistein, ginkgo, glycitein, icariin, isoscutellarein 7-O-[6'''-O-acetyl-beta-D-allopyranosyl-(12)]-beta-D-glucopyranoside, isovitexin, morin, myricetin, nobiletin, pelargonidin, phloridzin, rutin, salvigenin, Scutellaria baicalensis Georgi, Sideritis flavonoids, vitexin, xanthomicrol, luteolin, morin, PD98059, quercetin, taxifolin, β-naphthoflavone); fruit (blackberries, blueberries, strawberries, raspberries, cherries, oranges, plums, prunes, red grapes, pomegranates, date palm fruits); vegetables, especially cruciferous, dark and green leafy; fatty fish.

A very clear message about the dietary contribution to AD can be extracted from the above picture of dietary excesses and deficiencies. From the macro perspective, the amounts of fat, salt, sugar, refined carbohydrates, calories, and meat need to be reduced strongly, along with high temperature cooking, and the amounts of vitamin and mineral-laden fruits, vegetables, and fatty fish need to be increased substantially to reduce the risk of AD and perhaps contribute to reversal of AD.

I-A3. Food Additives

Many food additives are accompanied by adverse effects, and these effects may be under-diagnosed and under-researched. Many of the excesses and deficiencies mentioned above are the result of substances being added to, or removed from, the fresh whole food.

Additives include preservatives, monosodium glutamate, menadione, cysteine, diacetylcysteine, and diacetyl. Depending on how one defines "food additives", those additives with the widest impacts tend to include the major items listed under excesses above, such as fat, sugar, and salt. These components are typically added to foods for taste enhancement, not nutritional improvement. The effects of these additives appear to be at the cellular and biomarker levels.

I-B. Activity

The main sub-categories of Activity are exercise, sedentary lifestyle, and sleep.

I-B1. Sedentary Lifestyle/Lack of Exercise

The sedentary lifestyle, including low exercise, low physical activity, low daily gardening, low walking, and chronic immobilization, was mentioned quite often, and cognitive inactivity also received some mention. The resultant low cardiovascular fitness was also emphasized.

Sleep

Circadian disruption and poor sleep/sleep deprivation were also mentioned, although the main foundational components of poor sleep would be 1) choosing to sleep less or 2) not practicing good sleep-preparation habits. Other contributing factors to poor sleep, such as excessive pain, anxiety, etc, may be less under one's control, and are not regarded as foundational under the definition in the present monograph.

I-C. Substance Abuse

Substance abuse includes "recreational" drugs of all types (cocaine, methamphetamine, etc), other substances such as laxatives, common household products not usually identified as recreational drugs (such as mothballs), and especially excessive cigarette smoking and alcohol. The main substance abuse contributing factors to AD for the present study were 1) recreational drugs (especially cocaine, amphetamines/3,4-Methylenedioxyamphetamine (MDMA - Ecstacy), phencyclidine, opioids) and 2) excessive smoking and alcohol. The bulk of the studies showed the recreational drugs' contributions to AD surrogate endpoints, such as neurodegeneration markers and cognitive dysfunction.

Potential Synergies

The individual AD foundational causes identified with Lifestyle are usually studied in isolation, and synergistic effects are typically not identified. Given the number of Lifestyle component combinations that could potentially be synergistic, and adding in

1) the foundational causes from the remaining categories (identified in Table 8-3) to the potential combinations, and

2) potential foundational causes that surface only when operating in synergy but which have not yet been identified in Table 8-3 as individual foundational causes,

it is clear that only the tip of AD foundational causes iceberg is being identified in this study.

II. Iatrogenic

Iatrogenic reflects diseases, symptoms, and injuries resulting from medical treatment, and is divided into four sub-categories: Drugs; Radiotherapy; Surgeries/ Invasive Procedures; Diagnostic Agents/Procedures. Iatrogenic is a substantial category, due mainly to the large numbers of drugs and surgeries that have side-effects and complications. The main categories, along with detailed drugs and surgeries, are presented in Table 8-3.

II-A. Drugs

While the drug categories have some overlap, each drug is listed in one category only in Table 8-3 for purposes of brevity when generating the drug categories. The more frequently a drug is used, or the more frequently surgery or invasive treatments are employed, the more opportunity for side-effects and complications, and the more opportunity for publications describing these side-effects and complications. This study does not provide an indication of how often such side-effects and complications would occur as a percentage of use.

There were eighteen major drug categories identified in Table 8-3, but only those with substantial entries will be discussed in this narrative. These include anti-neoplastic agents, cardiovascular agents, the massive category of central nervous system agents, hematologic agents, steroids/hormones, antihypertensive agents, and gastrointestinal agents.

What the table does not show is the effect of drug-drug combinations, or drug-other agent combinations. The effects of these combinations could be important, but might not surface in some types of studies. A study on drug-drug combinations concluded that, of approximately 11,000 drug products on the US market, trillions of clinical trials would be required to provide an evidentiary basis of safety for all combinations of ten drugs [518]. Even for all combinations of three drugs, the number of clinical trials required to evaluate safety, or lack thereof, would be astronomical.

Thus, there are many ways that 1) a drug that has been shown to contribute to AD in isolation, when combined with two other drugs that have not been shown to contribute to AD in isolation, could in aggregate have a much stronger contribution to AD, and/or 2) three drugs that have been shown to have a modest contribution to AD in isolation, when combined, could in aggregate have a much stronger contribution to AD, and/or 3) three drugs that have been shown to have negligible contribution to AD in isolation, when combined, could in aggregate have a strong contribution to AD. Even if there are small numbers for any one combination of three drugs, when they are aggregated over the total number of potential combinations, this could add up to a large number of strong contributions. This effect might not surface in any epidemiological study because 1) it would fall beneath the statistical radar screen, 2)

temporal variation in the combinations would be difficult to assess, and 3) the numbers of clinical trials required to assess the impact of drug combinations are astronomical and would be impractical. For combinations of drugs larger than three, which increase for people as they age [518], the numbers of combinations and clinical trials to demonstrate safety increase rapidly.

II-A1. Antineoplastic Agents

This is a powerful class of drugs, and they tend to exert toxic/destructive effects on cancer cells. It is therefore unsurprising that these drugs would result in surrogate endpoint effects such as neurotoxicity/neurodegeneration/apoptoses on some healthy cells as well. The types of impacts in Table 8-3 bear this out. Neurotoxic-type effects are seen for many of the agents, as well as the accompanying memory degradation, but direct links to AD are not reported as frequently. The old dictum "absence of evidence is not evidence of absence" should be a warning flag on drawing hard conclusions about direct links.

II-A4. Cardiovascular Agents

The impacts of the four agents/agent classes (isoproterenol, atropine, D-ribose, muscarinic receptor antagonists) presented in Table 8-3 concentrate on the surrogate endpoints, with emphasis on the biomarkers (increase tau, Abeta) and performance (decrease memory, cognition).

II-A5. Central Nervous System Agents

This was by far the largest category of potential contributors to AD. This should not be surprising, since the members of this category act on the central nervous system (and some on the peripheral nervous system as well), and the brain is an integral part of the central nervous system. The impacts of the myriad contributing factors in this category differ somewhat by sub-category.

The analgesics and pain relievers (anesthetics/opiods) sub-category, consisting of acetaminophen, barbital, barbitone, desflurane, dexmedetomidine, diethylbarbituric acid, diethylmalonyl urea, enflurane, halothane, isoflurane, ketamine, medinal, morphine, nitrous oxide, pentobarbital, propofol, psychotropic drugs, sevoflurane, sodium diethylbarbiturate, veronal, affected all four impact areas. There was a substantial literature on the AD-related impacts of these sub-category members. One analytic problem deriving from this observation is that the relationship between the types of surgery to AD is conflated with the relationship between the anesthetic to AD, and it is difficult to separate the two, since anesthetics are used almost universally in surgery, especially major surgery.

The movement stabilizer sub-category, consisting of the anticholinergic medications doxepin, chlorpheniramine, oxybutynin, trihexyphenidyl, propiverine, L-DOPA/dopamine, was less numerous in terms of publications than the anesthetic sub-category, but covered the four impact classes as well.

The depressant/antidepressant sub-category, consisting of selective serotonin re-uptake inhibitors, benzodiazepine, dizocilpine, and 3-quinuclidinyl benzilate, had impact on performance and AD in the references shown. The absence of impact at the cellular and biomarker levels could mean that these

classes of impacts were not the objectives of the research that was conducted, or they were reported in other papers not presented here.

The mood stabilizer sub-category, consisting of clozapine, methyllycaconitine, dihydro-beta-erythrodine, and anisomycin, impacted across the surrogate endpoints.

II-A7. Hematologic Agents

The main component of this category is the anti-coagulant sub-category, consisting mainly of the sulfated glycosaminoglycans heparin/heparan sulfate, dextran sulfate, pentosan polysulfate, chondroitin sulfate, dermatan sulfate, and fluindione.

II-A8. Steroids/Hormones

The substances in this category include corticosteroids (methylprednisolone, dexamethasone), anabolic androgenic steroids (nandrolone, stanozolol), corticosterone, Wortmannin, 17beta-trenbolone, salmon calcitonin, human chorionic gonadotropin, corticotrophin releasing factor, sex steroid hormones (transient testosterone treatment, flutamide), U18666A, allopregnanolone, medroxy-progesterone acetate, androgen deprivation therapy, postmenopausal hormone therapy, testosterone depletion, human chorionic gonadotropin, prenatal sex hormone exposure, and the deficiency of leptin. This class of pharmaceuticals (especially the corticosteroids) is used for a wide spectrum of medical conditions, and the broad scope of potential impacts is concerning. While some of the drugs in the larger Iatrogenic category have rather narrow applications, the long-term effects on neurodegenerative diseases of widely used drugs such as anesthetics and steroids should be cause for serious concern.

II-A9. Antihypertensive Agents

These agents include ACE inhibitors, ICI 118,551/Selective beta2AR antagonists, telmisartan/olmesartan, and Mecamylamine. Some of the anti-hypertensive agents listed are widely used because of the prevalence of hypertension, and their long-term effects need to be examined more closely. The main impacts listed are those on the surrogate endpoints, although the ACE inhibitors are linked to AD. The referenced papers don't report impacts at the cellular level, although, again, that does not imply the absence of such impacts.

II-A10. Gastrointestinal Agents

These agents include thiorphan/phosphoramidon, and the large class of proton pump inhibitors (omeprazole, pantoprazole, lansoprazole, esomeprazole, and rabeprazole). Again, this is disturbing for the long-term, because of the almost common-place used of this family of drugs for digestive problems.

II-B. Radiotherapy

Radiotherapy that involves the head region impacts cognition and AD.

II-C. Surgery/Invasive Treatments

The following categorization is not unique. Some procedures could be assigned to multiple categories. Surgeries/invasive procedures that contribute to AD tend to involve vessel occlusion, cerebral ischemia, broader cardiac surgery, estrogen depletion, and myriad forms of dialysis.

One interesting observation is that the surgery impacts are all on AD surrogate endpoints, not on AD directly, for the references selected. This may be due to personal choice of the authors. Some authors identified a number of surrogate endpoints that were impacted, and referred to the aggregate as Alzheimer's-like. Other authors would refer to the aggregate as Alzheimer's Disease. Since inhalation anesthesia seems to be a strong contributing factor, almost any major surgery employing this type of anesthesia would have to involve some potential risk for AD, either through the surrogate endpoints, or directly.

III. Biotoxic Agents

Biotoxic Agents reflect mainly the biological substances to which we are exposed naturally, but sometimes accidentally, and sometimes by design. This category is divided into five sub-categories: Mycotoxins; Exotoxins; Bacteria/ Fungi/ Parasites; Viruses; Other. Biotoxins contributing to AD include some mycotoxins, but mainly exotoxins, bacteria, and viruses.

III-A. Mycotoxins

Only a few mycotoxins were identified, including ochratoxin A, fumonisin B1, and macrocyclic trichothecenes. Their impacts cover all four levels.

III-B. Exotoxins

Many exotoxins were identified, including excitotoxins (kainic acid/kainate, quisqualic acid, ibotenic acid, domoic acid, quinolinic acid/quinolinate), phosphatase inhibitors (okadaic acid), excitatory amino acids, malonate, annonaceaeous acetogenins, cyanobacteria (beta-N-methylamino-L-alanine/BMAA, saxitoxin, anatoxin-a, blue-green algae, microcystin), diphtheria toxin, pseudomonas aeruginosa exotoxin Y, saporins (192 IgG-saporin, p75-saporin), cycad plant (cycasin/methylazoxymethanol), glutamate/glutamine synthetase, mitochondrial inhibitors (rotenone, 3-NPA, antimycin, KCN, oligomycin). Some substances in the Other category could have been assigned to the Exotoxin category. The impacts were heavily weighted toward the cellular and biomarker levels, less so toward the performance level, and even less toward the disease level.

III-C. Bacteria/Fungi/Parasites

Myriad bacteria, fungi, and parasites (shown in Table 8-3) are dominant in sub-category III-C. The bacteria/bacterial infections include bacterial endotoxins, bacterial lipopolysaccharide, gram-negative bacterium, spirochetes, Chlamydophyla pneumoniae, Helicobacter pylori, Escherichia coli, Treponema pallidum, Tannerella forsythia, Treponema denticola, T. socranskii, T. pectinovorum, T. medium, T. amylovorum, T. maltophilum, Fusobacterium nucleatum, Prevotella intermedia, Chlamydia pneumoniae,

Porphyromonas gingivalis, propionibacterium acnes, Treponemas, T. lecithinolyticum, and Borrelia burgdorferi. Bacteria are somewhat ubiquitous, so the flexibility of cause removal for items in this sub-category is much less than for items in the Lifestyle and Iatrogenic categories.

The fungi/fungal infections include Cryptococcus, Coccidioides, Aspergillus, Histoplasma, Blastomyces, C. famata, C. parapsilosis, C. glabrata, C. krusei, Candida albicans, Candida ortholopsis, Candida tropicalis, Cladosporium, Malassezia globosa, Malassezia restricta, Neosartorya hiratsukae, Phoma, Sacharomyces cerevisae, and Sclerotinia borealis.

The parasites include Trypanosoma brucei rhodesiense, Trypanosoma brucei gambiense, Acanthamoeba, Balamuthia mandrillaris, Toxoplasma gondii, Taenia solium, Toxocara canis, T. cati, Toxocara ova, and Leishmania amazonensis.

III-D. Viruses

Myriad viruses (shown in Table 8-3) are dominant in sub-category III-D. These viruses include Bornaviridae (Mammalian 1 bornavirus), Bunyaviridae (Hantavirus, La Crosse encephalitis virus), Coronaviridae (Human coronavirus OC43, Murine hepatitis virus), Flaviviridae (Hepatitis C virus, Japanese encephalitis virus, Murray Valley encephalitis virus, St. Louis encephalitis virus, West Nile virus), Hepadnaviridae (Hepatitis B virus), Herpesviridae (Cytomegalovirus, Epstein-Barr virus, Herpes simplex virus 1, Human herpesvirus 6), Orthomyxoviridae (Influenza A virus (H1N1), Influenza A virus (H3N2), Influenza A virus (H5N1)), Paramyxoviridae (Hendra virus, Measles virus), Picornaviridae (Enterovirus 71, Theiler's murine encephalomyelitis virus), Polyomaviridae (Simian 40 virus large T antigen), Retroviridae (Human immunodeficiency virus 1, Human T-cell leukemia virus, Moloney murine leukemia virus), Rhabdoviridae (Chandipura virus), Togaviridae (Chikungunya virus, Eastern equine encephalitis virus, Venezuelan equine encephalitis virus).

Based on the volume of records examined in the bacteria/fungi/viruses categories, linkages to tau and Abeta pathologies were mentioned often, as were direct linkages to AD. Neuroinflammation induced by bacterial and viral infections appeared to be responsible for some of the tau pathology.

III-E. Other

The category named Other contains myriad substances, which are listed in Table 8-3. It includes some plant-based contributing factors (e.g., 12-myristate 13-acetate, Forskolin, arecoline hydrobromide, quisqualate, etc), and a very substantial number of endogenous substances that were administered exogenously (e.g., 27-hydroxycholesterol, acetylcholinesterase, Bradykinin, CD40, etc).

Ordinarily, endogenous substances are not foundational causes, but intermediate causes, since their harmful effects typically are driven by other foundational causes. However, for consistency, if an endogenous substance was administered exogenously for purposes of experimentation or trial, it was considered as an exotoxin or other foundational cause for the purposes of this monograph. Thus, amyloid beta, an endogenous substance, could be viewed as an endotoxin when internal processes are being discussed, but also as an exotoxin when administered in laboratory experiments.

Because of the heterogeneity of the myriad substances in this class, specific impact statements need to be tailored to the specific members of this class. However, from an overall perspective, the majority of impacts are at the cellular and biomarker levels, much fewer impacts at the performance level, and very few impacts at the disease level. It should be cautioned again that the absence of impacts reported should not be interpreted as their non-existence. They may not exist, they may exist and were not an objective of the research, or they may exist and were not reported.

IV. Occupational/Environmental Exposures

IV-A. Chemicals/Materials

IV-A1. Industrial and Household Chemicals/Materials

This sub-category is very broad. There is overlap among the next level taxonomy elements; for example, some of the solvents are hydrocarbons and some of the chemical compounds are hydrocarbons.

This sub-category includes hydrocarbons, solvents, chemical compounds, and Other.

The hydrocarbons sub-category includes, e.g., methylcholanthrene, polycyclic aromatic hydrocarbons, diesel fuel, kerosene, etc.

The solvents sub-category includes, e.g., petroleum-based solvents (mineral turpentine, diesel fuel, fuel oil, kerosene, etc), chlorinated solvents (trichloroethylene, perchlorethylene, trichloroethane, dichloromethane, benzene), organic solvents (benzene, toluene, phenols, alcohols, ketones, methylmethacrylate), dimethyl sulfoxide/ DMSO, etc. The impacts from the members of this sub-category, as reported in the references selected, tended to focus on performance and disease. This was due to a number of epidemiology studies of occupational impacts, which tend to focus on higher level impacts.

The chemical compounds/Other sub-categories include a full spectrum of chemical compounds, especially chlorine, bromine, nitrogen, sodium, sulfur, and carbon compounds. Members of these sub-categories include, e.g., Neurotoxins (6-hydroxydopamine/6-OHDA, 5,6-dihydroxytryptamine/ 5,6-DHT, -5,7-dihydroxytryptamine/5,7-DHT, Type-2 Alkenes/Reactive aldehydes (Acrolein, 4-Hydroxynonenal/HNE, Acrylamide, Methyl glyoxal), Nitrosamine/ N-nitrosodiethylamine, Adenosine, 3', 5'-cyclic monophosphate/cAMP, Carbon tetrachloride, Chemical warfare agents/ nerve agents (organophosphates, soman, sarin, ethyl S-2-di-isopropylaminoethyl-phosphonothiolate, VX, tabun), Cyanide (Potassium cyanide, Sodium cyanide), Formaldehyde, Hydrogen Peroxide/H2O2, Lipophilic chemicals (persistent organic pollutants, bisphenol A, phthalates, low molecular weight hydrocarbons, polynuclear aromatic hydrocarbons, endocrine disruptors), Sulfur dioxide/SO2, Phthalates (Di-(2-ethylhexyl)-phthalate/DEHP, mono-2-ethylhexyl phthalate/MEHP, DEHP metabolites), Brominated flame retardants (hexabromocyclo-dodecane/HBCD, tetrabromobisphenol-Al/TBBPA, decabromodiphenyl ether/DBDE, polybrominated diphenyl ethers/PBDEs), Ammonia, Hypochlorous acid/HOCl, Methanol, Peroxynitrite, Sodium azide, Acetaldehyde, 3-Bromopyruvate, Vehicular emission

oxides (nitrogen dioxide/NO2, carbon monoxide/CO), Sodium fluoride, Membrane-mimicking detergents (sodium dodecyl sulfate, lithium dodecyl sulfate), Nitric oxide donors (sodium nitroprusside, DETA NONOate), Amorphous aluminosilicates, Sodium nitrite, Tert-butyl hydroperoxide/t-BHP, Alloxan, Ammonium chloride, Anionic dyes (Congo Red, Thiazine Red, Thioflavin S), Aroclor 1254, Cobalt chloride, Magnesium chloride, 2,2'-azobis(2-methylpropionamidine) dihydrochloride/AAPH, Methylglyoxal/ Glyoxal, Disuccinimidyl suberate, Naphthazarin/5,8-dihydroxy-1,4-naphthoquinone/ 5,8-dihydroxy-1,4-naphthalenedione, Pyrithiamine, Pyrogallol, Glyceraldehyde-3-phosphate/GAPDH, Ethylcholine mustard aziridinium ion/AF64A, 1-methyl-4-phenylpyridinium ion, 2,2'-dithiodipyridine, Aftin-4, Kaolin, Ozone, 2;3;7;8-tetrachlorodibenzo-p-dioxin.

The largest sub-category, by far, is the chemical compounds. This sub-category is associated with roughly even impacts at the cellular, biomarker, and performance levels. There is much less reported direct association at the disease level, for the selected references.

IV-A2. Agricultural Chemicals

This sub-category emphasizes pesticides, herbicides, insecticides, and fungicides, and includes, e.g., Organochlorine pesticides, Organophosphate pesticides, 2,4,5-trichlorophenoxyacetic acid, 2,4-dichlorophenoxyacetic acid, Agent Orange, Aldrin, Alkylphenolpolyethoxylates, APEOs, Arsenic, Beta-hexachlorocyclohexane/beta-HCH, Bipyridyles, Carbamates, Carbofuran, Chlorfenvinphos, Chlorpyrifos/ CPF, Cycloheximide, Cypermethrin, Deltamethrin, Dichlorodiphenyldichloroethylene/DDE, Dichlorodiphenyltrichloroethane/DDT, Dichlorodiphenyldichloroethane/DDD, Dieldrin, Dimethyl parathion, Endosulfan, Famoxadone, Fenamidone, Glyphosate, Hexachlorobenzene, Hexachlorocyclohexane/HCH, Imidacloprid, Lindane, Maneb, Methamidophos, Methyl parathion, Neonicotinoids, Nonylphenol, Octylphenol, Paraquat, Parathion, Pyraclostrobin, Pyrethroids, Trans-nonachlor, Trichlorfon/TCF, Trifloxystrobin, etc.

Adverse impacts span the cellular, biomarker, performance, and disease levels. These chemicals impact the larger population through the food supply, and have devastating effects on the agricultural workforce. Given the ubiquitous nature of agricultural chemicals and industrial/household chemicals in daily life, eliminating them will be challenging.

IV-A3. Materials

The materials/particulates that constitute this category are broadly-based, and in many cases have become part of the average lifestyle. Some examples include:

-heavy metals (e.g., aluminum, arsenic, cadmium, calcium/Ca2/CaCl, calcium ionophore/A-23187/calcimycin , cobalt, copper, iron, lead, manganese, mercury , methylmercury, selenium, tin, zinc, etc)

-particulates (e.g., air pollution, surgical smoke, dust, etc)

-nanoparticles (e.g., iron nanoparticles, titanium dioxide nanoparticles, CdSe quantum dots, diesel exhaust nanoparticles, alumina nanoparticles, manganese oxide nanoparticles, copper nanoparticles, silicon dioxide nanoparticles, zinc oxide nanoparticles, silver nanoparticles, nickel nanoparticles, etc)

Impacts of these materials through diverse ingestion pathways cover the full spectrum of levels. Both metals and small sized particles have adverse effects. When the two are combined, the synergy becomes problematical. Metallic particles within the nanoparticle range (<100 nm) are able to cross many internal protective barriers, including the blood-brain-barrier (BBB), and cause myriad problems. While penetration of the BBB by nanoparticles is sometimes used for drug delivery, unwanted penetration (as reflected in the present study's references) can be quite harmful.

IV-B. Physical/Mechanical

This sub-category includes ionizing radiation, non-ionizing non-visible radiation, non-ionizing visible radiation, sound radiation, temperature fields, and force fields.

The ionizing radiation component includes, e.g., gamma radiation (dental X-rays, gamma rays, etc), particle radiation (56Fe-particle radiation, cosmic radiation, HZE particle radiation), radionuclide pollutants (uranium, cesium, cobalt, radon). The main impacts focus on the biomarker and performance levels, with some at the cellular levels and much less at the disease level.

The non-ionizing non-visible radiation component includes, e.g., electromagnetic fields at myriad frequencies, such as extremely low frequency/ELF-EMF, 900 MHz radiofrequency (RF), electromagnetic pulse/EMP, electroconvulsive shock/ECS, UV irradiation, etc. The references selected emphasize biomarker level impact, then performance level impacts, and some links to AD.

The non-ionizing visible radiation component includes e.g., UV irradiation, photolysis of 1-(2-nitrophenyl)ethyl sulfate, with impacts emphasizing Abeta production.

The sound radiation component includes, e.g., short-lasting impulse noise, chronic noise exposure, night-time aircraft noise, ultrasound sonication, etc. While impacts are identified at the cellular, biomarker, and disease levels, Abeta generation and exacerbation are emphasized.

The thermal component includes, e.g., cold water hypothermia, cold water stress, heat shock, heat stress, heating, hyperthermia, etc, and impacts the cellular, biomarker, and performance levels.

The physical force component includes, e.g., blasts, blast traumatic brain injury, hippocampal injury, accumulated mechanical stress, spinal cord injury, frequent strong Valsalva maneuvers, long hours of repetitive heavy lifting, sequences of blows during the playing of a wind instrument, forceful and repetitive cough, bearing-down efforts during parturition, history of head trauma, etc. The impacts cover all four levels, with perhaps added emphasis on AD.

The main components of this sub-category, the different types of physical fields with which we interact (electromagnetic, sound, temperature, pressure, force) are ubiquitous. Avoiding exposure to these

emissions/interactions would require a major change in lifestyle (and probably location) for most people. The 'Other' category is small, and contains adverse effects from over- and under-exposure to oxygen.

V. Psychosocial/Socioeconomic

Psychosocial/Socioeconomic are those foundational causes that reflect personal problems, social interactions, larger societal interactions, and economic relationships. Psychological and sociological stress were major causative factors; economic types of stress seemed to play less of a direct role.

V-A. Psychological

This sub-category includes, e.g., chronic stress (repeated stress, chronic mild stress, chronic psychological stress, multiple chronic stresses, behavioral stress, childhood trauma, bereavement, chronic restraint stress, high job stress), low mental activity (low cognitively engaging activity, low purposeful activities, low leisure activities/low hobbies, low music/drawing/meditation/reading/arts/crafts), etc. Impacts seemed to spread out over all four levels.

V-B. Sociological

This sub-category includes, e.g., social isolation (isolation, loneliness, living alone, unmarried, maternal separation, low social activity index, low social support at work, constricted life space), low education (illiteracy), etc. Impacts cover all four levels, with emphasis on the biomarker, performance, and disease levels.

V-C. Economic

This sub-category includes, e.g., economic stress (childhood socioeconomic circumstance), etc. In this small sub-category, impact focused on cognitive deficits.

8D. References - Chapter 8

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Chapter 9

CLASSIC AD PAPERS

9A. Overview

This chapter presents the 500 most cited papers in the AD/dementia literature [1-500], and addresses the role of foundational causes research in the context of this highly-cited literature.

AD research spans a wide gamut involving mechanisms of pathology, genetics, diagnostics, treatments, therapy and maintenance, etc. What is the role of risk factor identification and prioritization in this research spectrum? In particular, are there objective measures by which importance of "causes" research can be estimated, especially foundational "causes"?

Citation analysis may offer some useful insights here. In a citation analysis of three leading neuropsychology journals (*Cortex, Neuropsychologia, and Brain*) [501], it was shown that as citations increased in absolute amounts, the study type transitioned from the clinically oriented behavioral focus ("soft" technology) to the correlates with more objective measurements ("hard" technology, such as non-invasive diagnostics). Similarly, in a study of highly and lowly cited Lancet articles [502], it was shown that clinical drug trials, especially large-scale, and high-technology analytic techniques dominated the highly-cited group.

For the present chapter, a Medline query was generated to identify the most highly cited AD papers. The query focused on papers with AD or dementia in the Title and MeSH terms. About 150,000 papers were retrieved, arranged in descending order of times cited, and the 500 most cited papers were downloaded [1-500].

A taxonomy of types of papers was generated manually, and the 50 most cited papers were assigned to the different categories in the taxonomy. Some interesting patterns were identified from these category distributions.

9B. Results of Taxonomy Analysis

Three main categories covered ~95% of the papers. Diagnosis/Assessment/ Testing and Mechanisms/Pathology were the two largest categories, followed by Genetics. As article publication dates became more recent, higher technology was employed more frequentlyin diagnosis, chemical and physical analysis, and treatments. This was true not only in the fifty most cited papers, but throughout the list of most highly cited.

In the 250 most highly cited papers, only two had determination of non-genetic risk factors as their central theme. Reference [58] focused on correlation of plasma homocysteine levels with dementia, which would not be considered a foundational cause by our definition. Reference [146] concluded that statins were associated with lower risk of dementia, which would place them more into the treatment category rather than foundational cause category.

Further down the list, reference [302] concluded that high blood pressure and serum cholesterol were associated with increased AD risk, but these are not foundational factors. Reference [437] showed the seed of the neurotoxic plant Cycas circinalis L played an important role in the etiology in the high incidence of amyotrophic lateral sclerosis, parkinsonism, and Alzheimer-type dementia among the Chamorro population of the western Pacific islands of Guam and Rota. This reference is the first among the highly-cited papers whose main theme was identification of a foundational cause of AD, and, even so, addressed a rare (and low technology) contributing factor globally.

There were a few references among the 500 most highly cited papers whose main themes allowed foundational causes to be "backed out" of the findings. Reference [448] showed higher education levels were associated with lower dementia/AD risk, reference [452] showed similar results for leisure activities, reference [468] showed similar results for a socially integrated lifestyle, and reference [495] showed similar findings for physical activity.

What's wrong with this picture? Of the five papers (in the 500 cited most highly) that could in any way be construed as having their main theme focused on identifying foundational causes of AD/dementia, one focused on a rare neurotoxic plant and four focused on "soft" behavioral technologies. Yet, the central findings of the present monograph are that the introduction of modern technology ("hard" technology) and its lack of regulation constitute a large share of the foundational causes of AD/dementia, especially in the Occupational/Environmental, Iatrogenic, and portions of the Lifestyle categories. What is the reason for this disconnect?

There are myriad reasons for why papers are highly cited. Two obvious reasons are the numbers of researchers in allied fields who are available to cite related research in their own published papers, and the papers that pass the review process and end up in the literature available to be cited. In the latter case, the papers that are published in the journals with higher circulation would be seen by more readers, and would thus be more available for citation.

As was concluded in [503], research areas that receive strong funding from government and industry would attract more researchers. And, it was concluded in [503] that journals would be more prone to accept papers (all else being equal) that had the prospect of garnering more citations, and thereby increasing the journal Impact Factor. Thus, to some degree, there is a mutually re-inforcing sponsor-journal-performer system at work that amplifies the importance of those research areas that receive strong government and industry sponsorship, and, at the same time, reduces the importance of research areas that receive weak support.

As was also concluded in [503], industry, and to some degree government as well, have little motivation to advertise potential adverse effects of modern technologies. Thus, there is little motivation for government and industry to sponsor research in these areas. There are few incentives for research performers to focus on adverse effects from (mainly) modern technologies, and strong incentives to focus either on the adverse effects from "soft" technologies or on the positive effects enabled by modern technologies.

One can examine the medical approach to AD through two pathways: research and clinical. The research pathway should have the following structure: cause--->research on pathology/mechanisms--->research on treatments to exploit mechanisms. The clinical pathway should have the following structure: diagnosis--->cause--->elimination of cause and/or treatment--->therapy--->maintenance. Unfortunately, from the perspective of what the research community views as most important, as evidenced by high citations, the research community downplays foundational causes relative to 1) research on mechanisms/pathology and 2) research on treatments. Again, based on citations, this implies the clinical community places less emphasis on identification and elimination of causes, especially foundational causes, relative to emphasis on diagnosis, treatments, and therapy/maintenance. Both the sponsor and performer communities need to re-orient research and clinical priorities, and place much larger emphasis on identifying and eliminating foundational causes, especially those related to adverse effects from modern technologies, as part as an overall AD prevention and reversal strategy.

9C. References - Chapter 9

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