Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Modifiable contributing factors to COVID-19: A comprehensive review

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ABSTRACT

The devastating complications of coronavirus disease 2019 (COVID-19) result from an individual's dysfunctional immune response following the initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Multiple toxic stressors and behaviors contribute to underlying immune system dysfunction. SARS-CoV-2 exploits the dysfunctional immune system to trigger a chain of events ultimately leading to COVID-19.

The current study identifies eighty immune system dysfunction-enabling toxic stressors and behaviors (hereafter called modifiable contributing factors (CFs)) that also link directly to COVID-19. Each CF is assigned to one of the five categories in the CF taxonomy shown in Section 3.3.: Lifestyle (e.g., diet, substance abuse); Iatrogenic (e.g., drugs, surgery); Biotoxins (e.g., micro-organisms, mycotoxins); Occupational/Environmental (e.g., heavy metals, pesticides); Psychosocial/Socioeconomic (e.g., chronic stress, lower education).

The current study shows how each modifiable factor contributes to decreased immune system capability, increased inflammation and coagulation, and increased neural damage and neurodegeneration. It is unclear how real progress can be made in combatting COVID-19 and other similar diseases caused by viral variants without addressing and eliminating these modifiable CFs.

1. Introduction

The virus associated most closely with COVID-19 (SARS-CoV-2) is transmissible. Whether serious consequences occur from this transmission depends on the health of the host's immune system (Kostoff et al., 2020a, 2020b; Gorji and Khaleghi Ghadiri, 2020; https://smartech.gatech.edu/handle/1853/62907). The serious consequences from COVID-19 result from the effective exploitation of a dysfunctional immune system by the SARS-CoV-2 virus in our model. In this exploitive process, genetic disposition, real-life exposures to multiple toxic stressors, and toxic behaviors lay the ground work for immune system dysfunction (Tsatsakis et al., 2020). Following SARS-CoV-2 exposure, the dysfunctional immune system is unable to neutralize the SARS-CoV-2 virus, thereby allowing the virus to enter and replicate in the cell, and trigger a chain of events ultimately leading to COVID-19 (Kostoff et al., 2020a, b).

If immune system dysfunction is a/the major factor in the severity of infectious diseases, then a necessary, but not necessarily sufficient, condition for prevention and successful longstanding treatment is elimination of those factors that contribute to the dysfunction of the immune system. The dominant virology-centric approach used currently for COVID-19 reflects damage control for a dysfunctional immune system (e.g., quarantine, face masks, vaccines, anti-viral treatments, *etc.*). An expanded virology/toxicology-centric approach would be aimed at identifying and removing the modifiable CFs to immune system dysfunctionality. It would require going beyond current single-stressor laboratory experiments to more comprehensive stressor combination experiments (Kostoff et al., 2018, 2020a).

This study identifies eighty of these CFs that impact COVID-19 directly, mainly by exacerbating immune system dysfunction. In

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particular, the study shows how each CF contributes to decreased immune system capability, increased inflammation and coagulation, and increased neural damage and neurodegeneration.

2. Background

2.1. Overview

Our group has been developing protocols to prevent and reverse chronic diseases (Kostoff, 2021; https://smartech.gatech.edu/handle/1853/59311). The central component of our approach is identification and elimination of CFs to these myriad chronic diseases, although complementary treatments can be used for the disease reversal process when necessary. Our group also published two papers (Kostoff et al., 2021, 2022) showing the commonality of CFs that impact infectious and chronic diseases (COVID-19 and Inflammatory Bowel Disease (IBD) in the first study (Kostoff et al., 2021), and COVID-19 and Gastrointestinal Cancer (GIC) in the second study (Kostoff et al., 2022)). The results of these two studies imply that our toxicology-based approach for preventing and reversing chronic diseases can be integrated successfully with the present virology-based approach to preventing and reversing communicable diseases (that exploit immune system dysfunction), such as COVID-19.

Because of the nascent nature of the COVID-19 core literature when we did the IBD and GIC studies (the core COVID-19 literature was not much older than one year), the number of CFs that impacted COVID-19 directly (as obtained from the COVID-19 core literature) was modest. Consequently, our Literature-Related and Discovery (LRDI) methodology (Kostoff et al., 2020c) was used to supplement the number of CFs identified from the COVID-19 core literature. At the time the final data were gathered for the present study, the nascent COVID-19 database was almost two years old, and more direct impact CFs for COVID-19 (where the CF and COVID-19 co-occurred in the same article) could be identified from the core COVID-19 literature.

Our purpose in the present paper is twofold: 1) show the increasing breadth of CFs that adversely impact COVID-19 directly, and 2) show some of the mechanisms through which this impact is enabled. For the key components of COVID-19 and toxicology, the COVID-19 background can be found in the IBD paper (Kostoff et al., 2021), and the toxicology background can be found in the GIC paper (Kostoff et al., 2022). Both will be summarized briefly here.

2.2. COVID-19

Three major coronavirus-based infectious disease outbreaks/epidemics/pandemics have occurred since 2001: Severe Acute Respiratory Syndrome (SARS), 2002–2003; Middle East Respiratory Syndrome (MERS), starting in 2012; and COVID-19, starting in December 2019, since 2000. Underlying these three diseases are three single-stranded RNA beta coronaviruses (Rabaan et al., 2021). The resultant diseases have a number of similarities, including 1) the most affected demographic (elderly with multiple comorbidities), 2) frequent mutations, 3) clinical symptoms such as fever, cough, fatigue, sore throat, headache, diarrhea, septic shock, multi-organ failure, etc. (Rabaan et al., 2021; Fung and Liu, 2021; Zhu et al., 2020), 4) abnormal values of selected biomarkers such as thrombocytopenia, lymphocytopenia, leukopenia, elevated serum levels of alanine aminotransferase, lactate dehydrogenase, aspartate aminotransferase, C-reactive protein, D-dimer level, prothrombin time, neutrophils, lymphocytes, albumin, CRP, TNF-alpha, and pulmonary inflammation/damage (Rabaan et al., 2021; Fung and Liu, 2021; Zhu et al., 2020).

COVID-19 has lasted much longer (as a major pandemic) than SARS or MERS, and its impact has been much larger. So far, it has been characterized temporally (in the USA) by five waves of deaths (defined by, and reported to, the CDC), as shown on Fig. 1 (https://covid.cdc.gov/COVID-data-tracker/#trends_dailydeaths; accessed 28 May 2022).

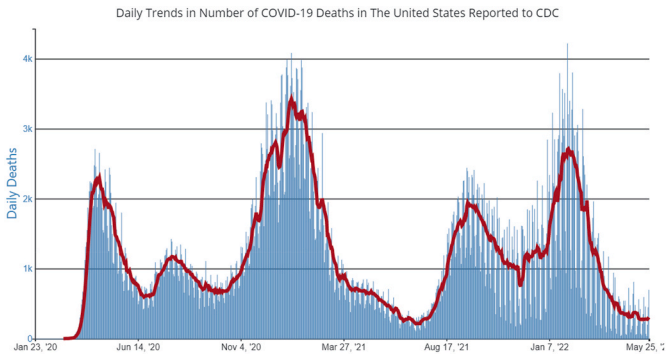

Fig. 1. Time trend of COVID-19 deaths in the USA reported to CDC.

Despite all the efforts taken to control this pandemic, there remains the possibility of further waves characterized by different mutated coronavirus strains. The goal of the present study is to provide a supplementary approach for potentially eliminating, or reducing substantially, the persistence of the present pandemic and the emergence of new pandemics.

2.3. Toxicology

Toxicology is the study of the impact that toxic stimuli and toxic behaviors, as well as their combinations, can have on all members of the animal kingdom and their environment. Its two most important components are epidemiological-type studies to identify potential adverse effects of candidate toxic stimuli and behaviors, and laboratory studies to identify mechanisms that link the stimuli to their adverse effects. Toxic stimuli exposures or toxic behaviors can range from acute to chronic, and the doses can span a wide spectrum.

The adverse impacts of toxic substances and behaviors on humans are grossly underestimated for two main reasons. First, exposure regulations are typically set much higher than warranted by laboratory studies. For example, a 2018 study of the USA OSHA (Occupational Safety and Health Administration) Permissible Exposure Limits (PELs) (https://smartech.gatech.edu/handle/1853/60067) showed that, for the sample of toxic substances examined, the PELs were orders of magnitude higher than the exposure levels shown in laboratory tests to cause damage.

Second, the exposure regulations are typically set based on single stressor experiments (Kostoff et al., 2020d). Under real-life conditions (Tsatsakis et al., 2017), humans are exposed to myriad toxic substances and engage in myriad toxic behaviors. Impacts of these toxic combinations, especially from strong synergies, could be far different from the sum of the impacts of each toxic substance and behavior measured in isolation (Kostoff et al., 2018). Some attempts have been made to develop regulation modifications to account for these combination effects (Kostoff et al., 2020d), but they are still in the nascent stage. Much more work is required to both improve these regulatory modifications and gather the laboratory data necessary to provide evidentiary confirmation of their effectiveness.

3. Methodology

3.1. Identification of CFs that impact COVID-19 directly

3.1.1. Overview

The methodologies used in the present paper to identify CFs that directly impact COVID-19 are similar to those used in the IBD and GIC papers mentioned earlier. The present paper draws extensively from those methodologies to identify the CFs that impact COVID-19 directly.

The rapid expansion of the COVID-19 core literature has resulted in the availability of sufficient numbers of direct impact COVID-19 CFs to

generate credible analyses based on direct impact CFs alone. The present study identified eighty CFs that impacted COVID-19 directly, although many more were possible with an adequately resourced study. We wanted to use these eighty direct impact CFs to identify how they increased vulnerability to COVID-19 specifically and how they exacerbated the course of the disease. In particular, the mechanistic targets focused on how these eighty CFs impacted 1) COVID-19 directly, 2) immune system weakening, 3) inflammation and coagulation, and 4) neural damage.

3.1.2. Dot-product approach

We used a dot-product approach (intersecting lists of known toxic substances with phrases from the COVID-19 core literature abstracts) to identify modifiable CFs related directly to COVID-19 (see Fig. 2.). The present approach is similar to the dot-product approach used in the IBD and GIC studies (Kostoff et al., 2021, 2022). A core literature query was defined for COVID-19, applied to PubMed, and the resultant retrieval (~146,000 records with abstracts, covering 1/2020-11/2021) was imported into VantagePoint (VP) software (www.theVantagePoint.com). The title and abstract phrases of the retrieved records were parsed, resulting in lists of many phrases. For example, the list of abstract phrases (the main list used for the study) contained ~12,700,000 phrases.

Essentially, we then intersected the ~12,700,000 abstract-derived phrases from the total COVID-19 Medline/Pubmed retrieval with a large list (~13,000) of known toxic substances 1) derived from myriad (mainly) government agencies and 2) combined with lists of CFs identified in our previous disease studies. These toxic substances covered a wide range of toxic materials, chemicals, drugs, radiations, microbes, behaviors, situations, etc. We visually inspected the ~3200 phrases that resulted from the intersection of the abstract phrases and toxic substance list phrases, identified those that had the potential for being classified as CFs, and then proceeded to validate the latter.

Limitations to the dot-product approach include: 1) only CFs that occurred within the COVID-19 core literatures were used for the dot-product; 2) all the matching and dot-product operations required *exact phrase matching*, where the slightest difference between any two phrases meant neither phrase survived the dot-product process; 3) substances that exhibit toxicity only in combination with other substances tend to be vastly underreported; 4) only Medline was used as a data source, excluding books, reports, etc. A more detailed description of these dot-product approach limitations can be found in the IBD paper (Kostoff et al., 2021).

3.1.3. Selection of candidate CFs for validation

The phrases identified as impacting COVID-19 directly should be viewed as candidate CFs, which must be validated as actual CFs by detailed analysis. Two criteria were used for selection of candidate CFs for validation: number of records in which the phrase/CF appeared and perceived importance of the phrase/CF in contributing to COVID-19. A tradeoff between numbers of CFs validated and marginal benefits for the reader resulted in eighty candidate CFs being validated.

These eighty included those deemed most significant and spanning the five-category taxonomy we have developed for classifying modifiable CFs to disease: Lifestyle, Iatrogenic, Biotoxins, Occupational/Environmental, Psychosocial/SocioEconomic (https://smartech.gatech.edu/handle/1853/59311). We did not include Genetics, since the CFs in our definition are viewed as modifiable, meaning they are somewhat under our control.

3.1.4. Evaluation of adverse mechanistic effects of eighty selected CFs

Queries were developed to identify the desired adverse mechanistic effects selected, and the queries were intersected with the eighty selected CFs. To ascertain whether the candidate CF carbon monoxide impacts the immune system adversely, a query (simplified) of the form (suppress* NEAR/10 "immune function* AND "carbon monoxide") was used. The full queries were entered into Pubmed and/or the Web of Knowledge version of Medline, and the retrieved records were analyzed.

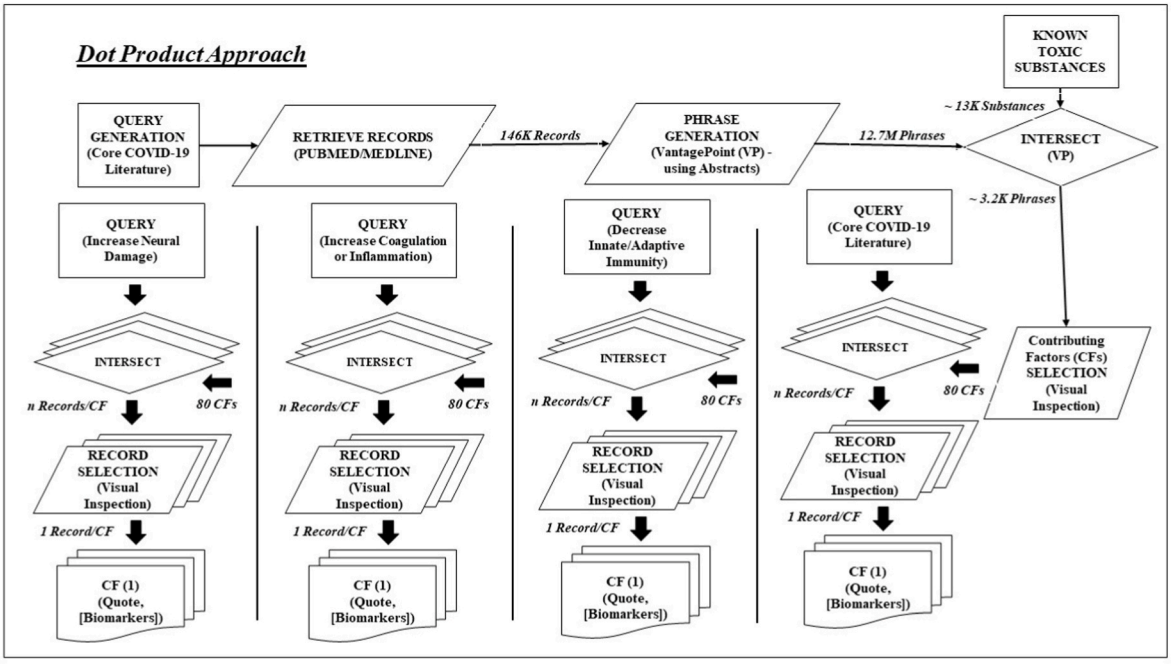

Fig. 2. Dot-Product approach for identifying CFs. Start from upper left. Generate query to retrieve core COVID-19 literature, and retrieve ~146,000 records from Pubmed. Import records into Vantage Point (VP) software, and parse abstract into ~12,700,000 phrases. Intersect 12,700,000 phrases with ~13,000 phrases of known toxic substances to generate ~3200 potential CF phrases. Select eighty phrases by visual inspection for CF validation. Intersect each potential CF with terms that reflect characteristics of each of the four target areas (impact COVID-19, weaken immunity, increase inflammation/coagulation, increase neural damage) to form query. Use this query to retrieve records showing adverse impact of potential CF for each of the four target areas. Select one record for each target area for each CF, and enter these four records for each CF in Table 1 for a total of 320 records.

The final queries used for the analysis are shown in Appendix 1.

3.2. Generate factor matrix

Fig. 3 shows the process used for generating the factor matrix.

3.3. Generate hierarchical text clustering taxonomy

The 3533 records used for the factor matrix were also used to generate the hierarchical text clustering taxonomy. The records were imported into the text clustering software (http://glaros.dtc.umn.edu/gkhome/cluto/cluto/overview), and the desired number of clusters were selected. The retrieved clusters were examined, and organized into a hierarchical taxonomy.

4. Results and discussion

4.1. Results

4.1.1. Eighty CFs and impacts on targets

The eighty CFs identified and validated are presented in Appendix 2, Table 1, along with their impacts on 1) COVID-19 directly, 2) weakening immune system, 3) increasing inflammation/coagulation, and 4) increasing neural damage. Each CF is assigned to one of the five categories in the CF taxonomy shown in Section 3.3.: lifestyle; iatrogenic; biotoxin; occupational/environmental; psychosocial/socioeconomic.

The Lifestyle category includes: advanced glycation end products; alcoholism; cholesterol; circadian disruption; fructose; high-fat-diet; iron deficiency; magnesium deficiency; malnutrition; maternal smoking; opioids; red meat; sedentary/physical inactivity; selenium deficiency; Smoking; sodium intake; substance abuse; Vitamin A deficiency; Vitamin B12 deficiency; Vitamin C deficiency; Vitamin D deficiency; Vitamin K deficiency; Western Diet; zinc deficiency. The main focus is on diet, but other issues include substance abuse, poor sleep, lack of proper exercise, and vitamin and mineral deficiencies that may or may not be related to diet.

The Iatrogenic category includes: analgesics; antidepressants; antipsychotic drugs; Bone marrow transplantation; chemotherapy; clozapine; cyclophosphamide; glucocorticoids; hemodialysis; immunotherapy; kidney transplantation; liver transplantation; methylprednisolone; monoclonal antibodies; nitrofurantoin; Omeprazole/proton pump inhibitors; ovariectomy; Pneumococcal vaccine; pregabalin; radiotherapy; rituximab; steroid use. The focus is mainly drugs, but includes some surgical procedures and non-drug therapies as well.

The Biotoxins category includes: cytomegalovirus; herpes simplex virus; mycotoxins. Many more micro-organisms could have been listed, as well as specific mycotoxins.

The Occupational/Environmental category includes: arsenic; benzene; benzidine; BPA; cadmium/Cd; carbon monoxide; chlorination of drinking water; chloroform; chromium/Cr; ionizing radiation; lead; mercury; methyl bromide; nanoparticles; Nitrate; nitric oxide; Nitrite; nitrogen dioxide/NO2/NO(2); organophosphates; ozone; perfluorinated alkylates; PM(10)/PM10; PM(2.5)/PM2.5; polycyclic aromatic hydrocarbons; silica; sulfur dioxide; TCDD [2,3,7,8-tetrachlorodibenzodioxin (TCDD)]. This was the largest category, and included heavy metals, atmospheric pollutants, pesticides, and many chemicals.

The Psychosocial/Socioeconomic category includes: chronic stress; less individual income; lower education; unmarried. Chronic stress in its myriad forms appears to exacerbate almost all the chronic diseases we have studied, and tends to be under-rated relative to the more tangible toxic exposures and toxic behaviors.

Table 1 contains eighty sub-tables, one sub-table for each CF. The heading for each sub-table is the CF that was validated followed by the category (CAT) to which the CF is assigned (1 = lifestyle; 2 = iatrogenic; 3 = biotoxin; 4 = occupational/environmental; 5 = psychosocial/socioeconomic). The sub-tables are listed in alphabetical order of the CFs. Thus, the first sub-table listed has the overall heading Advanced glycation end products [1], where Advanced glycation end products was the CF validated, and [1] was the category to which the CF was assigned.

Each sub-table of Table 1 contains three columns. The first column (TARG) is one of the four CF targets being addressed (ICOV-Impact COVID-19; WIS-Weaken Immune System; IIC-Increase Inflammation/Coagulation; DNS-Damage Neural System). The second column (QUOTES/REFERENCES) contains the narrative describing the link between the CF and the target of interest (QUOTES), followed by the reference from which the narrative was extracted. The third column (BIOMARKERS) contains the general and specific biomarkers from the cited reference's abstract.

It should be noted that many references were identified that linked each CF to 1) weakening the immune system, 2) increasing inflammation and coagulation, and 3) increasing neural damage, but only one reference was selected for each cell in the interest of brevity. Thus, for the eighty CFs identified and validated, with one reference shown for each of the four targets, there were 320 references presented, with some being redundant. As will be shown later, many of the above references that were identified but not included in Table 1 were used for the factor analysis and clustering taxonomy.

Table 1 includes the biomarkers that were altered by the CFs to establish their link to the relevant targets of interest. For those examples where the excerpts were extracted from the titles or abstracts,

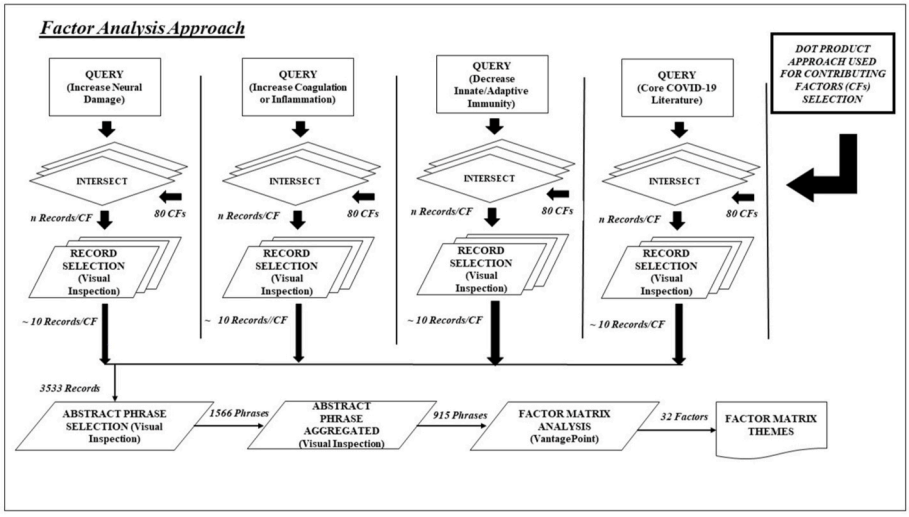

Fig. 3. Process for generating factor matrix. Start from upper right. Use dot-product approach from Fig. 2 to generate 80 CFs. Intersect each CF with each group of terms for characterizing the four targets (impact on COVID-19, weaken immune system, increase inflammation or coagulation, increase neurodegeneration) shown in Appendix 1. This will result in 320 queries, and 320 separate retrievals of records. Select (by visual inspection) an average of ~ten records from each retrieval that show clearly and unambiguously the adverse impact of the CF on the target. This results in a total selected retrieval of 3533 records. Parse the abstracts of these retrieved records into phrases, and select 1566 phrases for high information content initially by visual inspection. Aggregate these 1566 phrases into 915 phrases to eliminate redundancies. Input 915 phrases to VP to generate the factor matrix.

biomarkers shown are those listed in the titles and abstracts of the references listed. For those few examples where excerpts were extracted from the full-text, the relevant biomarkers from the full-text excerpts were also included.

Specific biomarkers (e.g., IL-1, CRP, etc.) were included wherever possible. More general biomarkers (e.g., inflammation, oxidative stress, mitochondrial dysfunction, etc.) were included, especially if specific biomarkers were lacking or minimal. Symptoms (e.g., fever, coughing, etc.) were included when specific or general biomarkers were minimal or absent. Diseases (AD, PD, etc.) were mentioned if biomarkers or symptoms were unavailable or minimal.

Thousands of general and specific biomarkers were identified in Table 1 from the 320 record abstracts, and ~400 of these occurred in three or more records. For the main categories used in the study (direct COVID-19 impact, immune system weakening, increased inflammation and coagulation, increased neural damage), the ~400 important biomarkers identified were not restricted to one category each; some of the biomarkers spanned multiple categories. Sample biomarkers restricted to each of these main categories are shown in Appendix 2, Table 2. As will be shown in the next section, an order-of-magnitude larger database (3533 records) was used for the factor analysis and document clustering analysis. A more adequately-resourced study would have used the larger database, including full text, for a more complete identification of relevant biomarkers.

4.1.2. Factor analysis

To understand better the latent themes of the impacts of the eighty CFs, a factor analysis of key abstract phrases was performed. A more comprehensive sampling than allowed by the 320 records in Table 1 was desired for the factor analysis. The queries shown in Appendix 1 were used to identify about forty + records (on average) for each of the eighty CFs, covering the four target areas of interest. A total of 3533 records were retrieved, and were used as the basis for the factor analysis. Originally, 1566 abstract phrases (from the 3533 records) were selected for the factor analysis by visual inspection, and were aggregated to 915 phrases to eliminate redundancies.

Then, a factor matrix consisting of 32 factors was generated using the VP software. For two of the factors, both "tails" of the factor had high absolute values of factor loadings (these high absolute values of factor loadings determine the factor theme), and were incorporated in the final results. The resulting factor matrix is presented as Table 3 in Appendix 3.

The factor themes/headings are listed below:

FACTOR 1 - MITOCHONDRIAL DYSFUNCTION
FACTOR 2 - INSULIN RESISTANCE
FACTOR 3 - COGNITIVE DECLINE
FACTOR 4 - PROINFLAMMATORY CYTOKINES
FACTOR 5 - COAGULATION
FACTOR 6 - AIR POLLUTION, EMPHASIZING PARTICULATE MATTER
FACTOR 7 - GUT DYSBIOSIS
FACTOR 8 - PULMONARY DAMAGE
FACTOR 9 - KIDNEY DYSFUNCTION
FACTOR 10 - OXIDATIVE STRESS
FACTOR 11 - CARDIAC DYSFUNCTION
FACTOR 12 - LIVER DISEASE
FACTOR 13 - CHRONIC ARYL HYDROCARBON RECEPTOR ACTIVATION
FACTOR 14 - BONE MARROW TRANSPLANTATION
FACTOR 15 - COLORECTAL CANCER
FACTOR 16 - BONE LOSS
FACTOR 17 - THYROID DYSFUNCTION
FACTOR 18 - ABNORMAL CHOLESTEROL LEVELS
FACTOR 19 - ANTIDEPRESSANTS
FACTOR 20 - ENDOTHELIAL DYSFUNCTION
FACTOR 21 - INFLAMMATORY BOWEL DISEASE
FACTOR 22 - SELENIUM DEFICIENCY
FACTOR 23 - VIRAL INFECTIONS
FACTOR 24 - NEUROLOGICAL DYSFUNCTION
FACTOR 25 - PERFLUORINATED ALKYLATES
FACTOR 26A - RESPIRATORY ALLERGIC REACTIONS
FACTOR 26B - BRAIN DAMAGE FROM NANOPARTICLES
FACTOR 27A – ADIPOSITY, ESPECIALLY OVARIECTOMY-INDUCED
FACTOR 27B – NEURO-DEGENERATIVE DISEASES
FACTOR 28 - LIVER DAMAGE BIOMARKERS
FACTOR 29 - SUBSTANCE ABUSE, EMPHASIZING SMOKING
FACTOR 30 - DNA DAMAGE
FACTOR 31 - IMMUNE RESPONSE
FACTOR 32 - NITRITE TOXICITY, ESPECIALLY PROTEIN OXIDATION

4.1.3. Hierarchical clustering taxonomy

While the factor analysis/factor matrix provide valuable insights to the underlying mechanisms by which the CFs cause damage, they are but one of many possible taxonomies. Another approach for providing structure and insights to the overall approach is text clustering analysis. As stated in Section 3.3, we used the same 3533 records that were used for the factor analysis, and used the CLUTO software (http://glaros.dtc.umn.edu/gkhome/cluto/cluto/overview) to create a hierarchical taxonomy that included 32 leaf (lowest level) clusters.

The resultant three-level taxonomy is presented as Table 4 in Appendix 3.

4.1.4. Biomarker data for each of the four targets

Appendix 4 contains tables of biomarker data (Tables (5–8)) for each of the four targets (COVID-19, weakened immune system, increased inflammation and coagulation, increased neural damage) and its purpose is to document this more detailed data for the interested reader.

4.2. Discussion

4.2.1. General

Eighty CFs that impact the vulnerability to COVID-19 infection and exacerbate the central COVID-19 characteristics of dysfunctional immune responses, increased coagulopathy and inflammation, and increased neurodegeneration (to name a few) were identified and validated. The impact of these CFs on critical biomarkers, organs, tissues, symptoms, and diseases was enumerated as part of the CF identification and validation process. Correlation of these impacts was shown in part by the factor analyses and text clustering of the retrieved CF adverse impact records.

The main CF data for the present study came from single stressor results, although some of the atmospheric pollutant results involved measuring groups of potential CFs in parallel. There are a large number of potential combinations of CFs that are possible from the present findings. Thus, the effects of eliminating any one CF or any combination of CFs on COVID-19 vulnerability or exacerbation for any individual or even groups of individuals will not be known with any degree of certainty because of the unrealistic number of experiments that would have to be performed to provide an evidentiary basis.

For example, in our population of eighty CFs, there are 3160 possible combinations of two CFs, 82160 combinations of three CFs, and 1,581,580 combinations of four CFs, as shown by the binomial coefficient (n!/(k! (n-k)!), where n = 80, and k = 2,3,4). If it were desired to identify the specific combination of e.g. four CFs to eliminate that would yield the largest impact on improving the dysfunctional immune system, over 1,000,000 experiments would have to be performed. The implication of the results is that reducing the vulnerability to COVID-19 and reducing the seriousness of the disease once infected require the discipline to 1) remove exposure to as many toxic substances as possible and 2) eliminate as many toxic behaviors as possible.

Finally, the most serious consequences from COVID-19, especially

death, tend to occur in individuals with comorbidities ("For over 5% of these deaths, COVID-19 was the only cause mentioned on the death certificate. For deaths with conditions or causes in addition to COVID-19, on average, there were 4.0 additional conditions or causes per death.")(https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm?fbclid=IwAR3-wrg3tTKK5-9tOHPGAHWFVO3DfslkJ0KsDEPQpWmPbKtp6EsoVV2Qs1Q). While many comorbidities have been observed, the most frequent tend to be diabetes, hypertension, obesity, and respiratory and renal illnesses (Almeida et al., 2022; Peterfi et al., 2022.), with diabetes and hypertension ranking near or at the top in most comorbidity studies (Shah et al., 2021; Shadnoush et al., 2022).

Many, if not all, of the CFs identified in the present study also have adverse impacts on the COVID-19 comorbidities. Consider the following three example CFs identified in this study: high-fat-diet, organophosphate pesticides, and heavy metals. High-fat-diet has been shown to impact diabetes (da Cruz et al., 2022), hypertension (Logvinov et al., 2021), obesity (Kang et al., 2022), and respiratory diseases (Li et al., 2021a). Organophosphate pesticides (and pesticides in general) have been shown to impact diabetes (Miranda et al., 2022), hypertension (Ledda et al., 2015), obesity (Miranda et al., 2022), and respiratory diseases (Bugay et al., 2022), and heavy metals have been shown to impact diabetes (Wang et al., 2022), hypertension (Tang et al., 2022a), obesity (Duc et al., 2022), and respiratory diseases (Yao et al., 2021). More data are required to state with confidence that there are strong overlaps between the CFs to COVID-19 and its comorbidities. An expanded and updated study evaluating the CFs that impact both COVID-19 and its major comorbidities directly would be able to generate this information, and, if such strong overlaps do exist, would further support our unified theory of infectious and chronic diseases.

4.2.2. Specific

4.2.2.1. CF distributions among categories. In Table 1, Categories 1 (Lifestyle), 2 (Iatrogenic), and 4 (Occupational/Environmental) are the most heavily represented, with each having twenty + entries. Categories 3 (Biotoxins) and 5 (Psychosocial/Socioeconomic) are the least represented, each having low single digit entries. The Lifestyle category tends to be the most modifiable on an individual basis; people can typically choose what they eat, how much activity they have, what vitamin/mineral supplements they take, etc. Conversely, the Occupational/Environmental category has limited modifiability on an individual basis. While some of the exposures shown may be known and avoidable, many others may be beyond an individual's control. They are either unknown to the individual, or they are known but unmodifiable from an individual's perspective. Toxic substances in the workplace or environment may require stricter regulation to control, and that is in the province of government responsibility (typically).

The items in the Iatrogenic category are modifiable in theory. However, for those undergoing medical treatment, the options are narrowed. Members of classes of drugs and radiation treatments tend to have similar benefits and adverse effects. As long as treatment is required, CF modifiability is limited. Some surgeries may be elective, but others may be imperative for all practical purposes, with minimal modifiability.

Members of the Biotoxins category tend to have very limited modifiability; there is little that can be done to avoid viruses, bacteria, etc. Mycotoxins tend to be related to CFs for a number of diseases, and their exposure could be limited by proper food storage, cleanliness, etc. The Psychosocial/Socioeconomic category members tend to be situational, where (in many cases) the individual has little control of the situation. Perhaps the largest and most pervasive contributor from this category is psychological stress in all its dimensions. Stress tends to exacerbate the adverse impacts of many of the other CFs. It is a reaction to myriad stimuli, and this reaction can be controlled to some extent.

The numbers of CFs shown could have been adjusted up or down by altering the breadth of any CF. For example, the number of opioids, mycotoxins, AGEs, etc. could have been increased substantially by listing each member of those respective classes, and the number could be decreased by aggregating members of a class under their class category. Our past studies on chronic diseases have shown hundreds of CFs for any chronic disease, and we would expect a similar result (given the present findings) for COVID-19, once its core literature becomes sufficiently matured to have included all the necessary experiments.

4.2.2.2. Factor matrix results

4.2.2.2.1. Overview of results. From the factor matrix (Appendix 3 - Table 3), the main organs impacted adversely by the eighty CFs are the lung, heart, gut, liver, brain, kidney, and thyroid. The main general biomarkers that reflect the level of damage include inflammation, immune response, oxidative stress, insulin resistance, and coagulation. At the cellular level, DNA, mitochondrial and endothelial damage predominate in the present data. Abnormal values of the specific biomarkers (shown in Table 3) categorized under the general biomarkers shown above reflect 1) the damage done by inflammation, oxidative stress, insulin resistance, and coagulation, and 2) the damage to the mitochondria, DNA, and epithelium in Table 3.

4.2.2.2.2. Linkages among factors. The factor matrix also shows some of the links among the factors. There appear to be six main groupings, but these groups are not fully independent of each other. In the list of main groupings below, each factor title/theme is followed by the factor number, in parentheses.

Group 1 consists of three factors: Proinflammatory Cytokines (F4), Immune Response (F31), and Viral Infections (F23). This group can be viewed as dysfunctional immune system response, mainly focused on the abnormal presence of proinflammatory cytokines. It links to other groupings and themes through its component factors including 1) mechanisms such as oxidative stress, DNA damage, endothelial dysfunction, chronic AhR activation, and respiratory allergic reactions; 2) diseases such as lung damage, liver damage, encephalitis, and colorectal cancer; and 3) CFs such as selenium deficiency, perfluorinated alkylates, and bone marrow transplantation.

Group 2 consists of four factors: Mitochondrial Dysfunction (F1), Oxidative Stress (F10), DNA Damage (F30), and Chronic Aryl Hydrocarbon Receptor Activation (F13). This group can be viewed as damage to the mitochondria and DNA associated with oxidative stress. It links to other groupings and themes through its component factors including 1) mechanisms such as dysfunctional immune response, endothelial dysfunction, and insulin resistance; 2) diseases such as kidney damage, liver damage, and colorectal cancer; and 3) CFs such as selenium deficiency and sodium nitrite.

Group 3 consists of three factors: Cardiac Dysfunction (F11), Endothelial Dysfunction (F20), and Coagulation (F5). This group can be viewed as cardiac dysfunction associated with endothelial dysfunction and coagulopathy. It links to other groupings and themes through its component factors including 1) mechanisms such as insulin resistance, proinflammatory cytokines/inflammation, and oxidative stress; and 2) diseases such as viral infections, liver disease, and pulmonary damage.

Group 4 consists of four factors: Insulin Resistance (F2), Abnormal Cholesterol Levels (F18), Ovariectomy-Induced Adiposity (F27A), Liver Disease (F12). This group can be viewed as metabolic dysfunction due mainly to dietary factors. It links to other groupings and themes through its component factors including 1) mechanisms such as oxidative stress and chronic AhR activation; 2) diseases such as cardiac dysfunction, gut dysbiosis, coagulopathies, thyroid dysfunction, endothelial dysfunction, inflammatory bowel disease, and kidney dysfunction; and 3) CFs such as selenium deficiency and sodium nitrite.

Group 5 consists of three factors: Inflammatory Bowel Disease (F21), Gut Dysbiosis (F7), and Colorectal Cancer (F15). This group can be viewed as diseases of the gut due to microbiome imbalances. It links to other groupings and themes through its component factors including 1) mechanisms such as insulin resistance, inflammation/proinflammatory

cytokines, chronic AhR activation, and DNA damage; 2) diseases such as osteoporosis, adiposity, and thyroid dysfunction; and 3) CFs such as selenium deficiency and sodium nitrite.

Group 6 consists of four factors: Cognitive Decline (F3), Neurological Dysfunction (F24), Brain Damage from Nanoparticles (26B), and Neurodegenerative Diseases (F27B). This group can be viewed as neurodegenerative diseases. It links to other groupings and themes through its component factors including 1) mechanisms such as neuroinflammation; 2) diseases such as Alzheimer's Disease, Parkinson's Disease, and Multiple Sclerosis; and 3) CFs such as methyl bromide and silica nanoparticles.

In the aggregate, based on the factor analysis results, the CFs are impacting the immune, circulatory, endocrine, and neural systems through fundamental mechanisms of inflammation, oxidative stress, coagulation, insulin resistance, and chronic AhR activation. In turn, these mechanisms stimulate endothelial dysfunction, DNA damage, gut dysbiosis, pulmonary damage, cardiac dysfunction, thyroid dysfunction, and kidney dysfunction, eventually leading to diseases that damage the major organs of heart, lung, brain, kidney, liver, thyroid, bone, and gut.

4.2.2.2.3. Factor matrix limitations. It should be emphasized that, while the factor analysis provides an overview of the skeletal structure of the findings, it reflects mainly the groupings defined. There were 915 "cleaned" terms that provided the basis for the factor analysis computations. A very small fraction of the 915 terms was used to determine the theme of each factor (those with high factor loadings). We estimate that the number of unique terms used for theme determination was, at most, about 300, or about 1/3 of the total terms. This means that about 2/3 of the total terms (over 600 terms) were not used for theme determination. The fact that these terms were not determinant in theme selection does not diminish their importance. Their exclusion from theme determination only reflects the narrow extent of their focus, not the importance of this focus.

4.2.2.3. Hierarchical clustering taxonomy. Table 4 (Appendix 3) shows three levels of the multi-level clustering taxonomy, Levels 2, 4, and 6. The format for each cluster in each of the levels includes the cluster number, followed by the number of records in each cluster (in parentheses), followed by the theme of the cluster. The theme of each cluster is obtained by visual inspection of numerous records in each cluster, along with phrase metrics for each cluster.

Level 6 contains all the leaf (lowest level) clusters. In the hierarchy, each cluster divides into two sub-clusters, until the leaf cluster is reached. If there were perfect symmetry, all the leaf clusters would be contained in Level 6. Some branch pathways contain more link clusters than others, where some leaf clusters could end up in Level 4 and others could end up in Level 8, reflecting an asymmetry. All the 32 leaf clusters were placed in Level 6 for clarity of display.

Level 2 reflects the first subdivision of the full 3533 records (Level 1) into Clusters 60 and 61. Cluster 60 reflects clinical aspects of the toxicological effects of the CFs and Cluster 61 reflects laboratory research aspects of these CF toxicological effects. This initial subdivision into clinical and research laboratory themes is not unique to the present study, but has occurred in most of our previous applications of CLUTO to biomedical issues.

Level 3 (not shown) contains four clusters, and Level 4 contains eight clusters. The following narrative will briefly address each Level 4 cluster and the Level 6 leaf clusters under its purview.

Starting from the top of Level 4, Cluster 8 reflects the adverse impacts of air pollutants on health. As an example of the asymmetry discussed previously, it is also a leaf cluster (it is repeated in Level 6). It did not divide further.

Next in line is Cluster 53, which reflects a combination of the impacts of toxic personal habits and exposure to toxic substances on development of disease. The toxic personal habits component is shown in Level 6 by Cluster 25 (impacts of maternal smoking and smoke exposure on children), Cluster 30 (adverse health impacts of malnutrition and sedentary lifestyle), and Cluster 3 (risks of red meat consumption, especially for cancer). The exposure to toxic substances component is shown by Cluster 20 (risks of polycyclic aromatic hydrocarbons for cancer), and Cluster 22 (DNA damage, especially from ionizing radiation and polycyclic aromatic hydrocarbons).

Next in Level 4 is Cluster 18, which is also a leaf cluster. Cluster 18's very specific focus is T-cell responses to viral infections.

Cluster 56 (next in Level 4) is rather broad in scope, addressing mainly adverse effects of medical treatments and substance abuse on development and exacerbation of chronic and infectious disease in humans. The substance abuse component is reflected by Cluster 12 (role of substance abuse (especially alcohol) in developing chronic and infectious diseases), and Cluster 14 (opioid-induced chronic and infectious diseases). The medical treatments component is reflected by Cluster 24 (adverse effects of drugs (especially nitrofurantoin, methyl prednisolone, rituximab), with emphasis on inducing liver disease in autoimmune patients), Cluster 26 (toxicity of cancer treatments, especially radiotherapy, immunotherapy, chemotherapy), Cluster 15 (role of antipsychotics (especially clozapine) and antidepressants in developing chronic and infectious diseases), Cluster 6 (adverse events after pneumococcal vaccination), and Cluster 4 (increased risk of infectious and chronic diseases from proton pump inhibitors). There is also a stand-alone toxic exposure component reflected by Cluster 0 (toxicity of PFOS and PFOA).

Cluster 48 (next in Level 4), covers the association of vitamin and mineral deficiencies with development and exacerbation of chronic and infectious diseases. This relatively focused theme is reflected by Cluster 1 (adverse effects of Vitamin B12 deficiency on chronic diseases), Cluster 2 (adverse effects of Vitamin D deficiency on chronic and infectious diseases), and Cluster 7 (primary emphasis on adverse effects of Vitamin K deficiency in chronic and infectious diseases, and secondary emphasis on adverse effects of Iron deficiency on chronic diseases).

Next in line is Cluster 49, which addresses adverse impacts of vitamin (mainly C) and mineral (mainly Se, Zn,Fe, Mg) deficiencies on biomarkers (mainly inflammation and oxidative stress) of organ and tissue damage. It complements Cluster 48, which has more of a disease focus of these deficiencies. Cluster 49's relatively focused theme is reflected by Cluster 5 (adverse effects of selenium deficiency on organs and tissues, especially inflammation and oxidative stress), Cluster 9 (adverse effects of Vitamin C deficiency primarily, and Zinc deficiency secondarily, on chronic and infectious diseases), and Cluster 16 (primarily adverse effects of Zinc deficiency on chronic and infectious diseases, and secondarily adverse effects of Iron deficiency on chronic diseases).

Next in line in Level 4 is another leaf cluster (Cluster 28), which covers the adverse effects of high-fat/Western diet on chronic diseases.

The final cluster in Level 4 is Cluster 55, a rather comprehensive cluster covering adverse impacts of toxic substance exposures (especially heavy metals, BPA, mycotoxins, dioxins, benzene, chlorinated drinking water, air pollutants, and nanoparticles) on tissue and organ biomarkers (emphasizing oxidative stress and inflammation). Its component leaf clusters include Cluster 31 (contributing factors to increases in oxidative stress), Cluster 23 (adverse effects of heavy metals on tissue and organ biomarkers), Cluster 13 (adverse effects of BPA primarily and Mercury secondarily on tissue and organ biomarkers), Cluster 29 (toxic effects of lead primarily and mycotoxins secondarily on tissues and organs), Cluster 10 (mechanisms of TCDD toxicity effects on organs, tissues, and cells primarily and benzene toxicity effects on organs, tissues, and cells secondarily), Cluster 21 (toxicity of chloroform in drinking water and exposure to nitrites and nitrates), Cluster 7 (damage to lungs from air pollutants), Cluster 11 (association of circadian disruption with diseases), and Cluster 19 (health risks of Methyl Bromide primarily and nanoparticle exposure secondarily).

4.2.2.4. Comparison of factor matrix results with clustering results. The structure of the individual clusters, as reflected in the themes, is much

more uniform than the structure of the individual factors. Typically, the cluster themes address the impact of one or more CFs on development of diseases or symptoms, or the adverse impacts on organs/tissues and/or biomarkers. The factor themes are typically much narrower. They focus on CFs (Factor 6, 14, 19, 22, 25, 26B, 27A, 29, 32), diseases/symptoms (Factor 1, 3, 7, 8, 9, 11, 12, 15, 16, 17, 20, 21, 23, 24, 26A, 27B, 30), or biomarkers (Factor 2, 4, 5, 10, 13, 18, 28, 31). The linkages among these individual factors are shown by the groupings of factors we identified, although 26B and 27A do address the linkage between the CF and the disease/symptom.

4.2.2.5. Diseases mentioned most frequently with CFs. We visually inspected the abstract phrases from the 3533 records using the VP software, and identified diseases that occurred in ten records or more. These diseases included cancer (lymphoma, colorectal cancer, lung cancer, leukemia, breast cancer), Diabetes Mellitus, cardiovascular disease (heart disease, atherosclerosis, stroke, thrombosis), metabolic syndrome (hypertension, obesity, hyperglycemia, dyslipidemia), infectious disease (COVID-19, pneumonia, Herpes, hepatitis), neurodegenerative disease (Alzheimer's disease, Multiple Sclerosis, Parkinson's Disease), lung disease (asthma, Chronic Obstructive Pulmonary Disease), anemia, chronic kidney disease, liver disease, Osteoporosis, arthritis, Inflammatory Bowel Disease, colitis, schizophrenia, and Autism.

Our past studies involving abstract phrases have shown that the bulk of terms in any category tend to occur at the lowest record frequencies. Thus, we would expect many diseases to be present in the lower phrase frequency region that was not examined. The diseases shown above are limited to those that were mentioned in many records.

5. Conclusions

Myriad toxic stimuli and toxic behaviors contribute to the development and exacerbation of COVID-19. In the current study, eighty toxic stimuli and behaviors were identified and validated from a relatively nascent (two years old) core COVID-19 literature, but many more could have been identified from a more adequately resourced study. Further, as the COVID-19 literature matures and more time is available for experiments linking specific toxic substances to COVID-19 to come to fruition, it is expected that the number of CFs to COVID-19 will increase substantially.

The CFs that contribute to COVID-19 also contribute to the development and exacerbation of many chronic diseases, as the results from this study and from our recent COVID-19-chronic disease commonality studies have shown (Kostoff et al., 2021, 2022). From the perspective of causality, COVID-19 and associated comorbidities have very similar origins. Any long-term strategy for addressing either COVID-19 or the associated comorbidities must involve reducing/eliminating exposure to toxic stimuli and modifying/eliminating toxic behaviors.

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CRediT authors contribution statement

Kostoff RN contributed to this paper with conception, query development, data analysis, and writing the manuscript; Briggs MB participated in data analysis, results validation, and table development; Kanduc D participated in data analysis and writing the manuscript; Dewanjee S contributed to query development and data analysis; Kandimalla R contributed to query development and data analysis; Shoenfeld Y contributed to data analysis and editing; Porter AL contributed to query development and editing; Tsatsakis A contributed to writing and editing; all the authors approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

APPENDIX 1. QUERIES USED FOR PRESENT STUDY

1. CORE COVID-19 LITERATURE RETRIEVAL– PUBMED FORMAT

(2019-nCoV OR 2019nCoV OR COVID-19 OR COVID* OR SARSCOV* OR SARS-COV* OR SARS-CoV-2 OR ((wuhan AND coronavirus).
CONSTRAINTS.

- RECORDS WITH ABSTRACTS ONLY
- DATE RANGE: 12/1/2019-11/30/2021

2. CF RECORDS IN CORE LITERATURE

INTERSECT CF OF INTEREST WITH QUERY 1.

3. DECREASE INNATE/ADAPTIVE IMMUNITY - TOPIC

(((DECREAS* OR REDUC* OR LOWER* OR SUPPRESS*) NEAR/10 (IMMUNITY OR "IMMUNE SYSTEM" OR "IMMUNE FUNCTION" OR "NK CELL*" OR "NATURAL KILLER" OR MACROPHAG* OR INTERFERON* OR "B-CELL*" OR "B-LYMPHOCYTE*" OR "T-CELL*" OR "T-LYMPHOCYTE*")) OR ((INCREASE* OR RAISE* OR ENHANCE* OR PROMOTE*) NEAR/10 ("IMMUNE DYSFUNCTION" OR "IMMUNE DYSREGULATION")))
AND.
[DIRECT IMPACT CF]

4. INCREASE COAGULATION OR INFLAMMATION - TOPIC

(("*COAGULA*" OR "*thrombo*" OR "*THROMBI*" OR "emboli*" OR "*FIBRIN*" OR "FIBROS*" OR "ENDOTHELI*" CLOT OR CLOTS OR

CLOTTING OR ((“INCREAS*” OR “ELEVAT*” OR “HIGH*”) NEAR/5 (“AGGREGAT*” OR “VWF” OR “von Willebrand Factor” OR “PAI-1” OR “troponin” OR “TnI” OR “hs-TnI” OR “AST” OR “ALT” OR “alanine aminotransferase” OR “aspartate aminotransferase” OR “tissue factor” OR “fractalkine” OR “vascular cell adhesion molecule-1” OR “VCAM-1” OR “intercellular adhesion molecule 1” OR “ICAM-1” OR “vascular adhesion protein-1” OR “VAP-1” OR “Lactate Dehydrogenase” OR “LDH” OR “D-dimer”)))

OR.

(“*INFLAMM*” OR “cytokine storm*” OR “macrophage activation” OR “oxidative stress” OR “oxidative damage” OR “Hypercytokinemia” OR “lymphopenia” OR “lymphocytopenia” OR ((“INCREAS*” OR “ELEVAT*” OR “HIGH*”) NEAR/5 (“ROS” OR “reactive oxygen species” OR “C-reactive protein” OR “CRP” OR “PROCALCITONIN” OR “PCT” OR “FERRITIN” OR “tumor necrosis factor alpha” OR “tumor necrosis factor-alpha” OR “TNFα” OR “TNF-α” OR “tumor necrosis factor-α” OR “neutrophil to lymphocyte ratio” OR “NLR” OR “neutrophil lymphocyte ratio” OR “neutrophil/lymphocyte ratio” OR “neutrophil-to-lymphocyte ratio” OR “IL-6” OR “interleukin-6” OR “interleukin (IL)-6” OR “interleukin 6 (IL-6)” OR “interleukin-1” OR “interleukin (IL)-1β” OR “IL-1β” OR “IL-2R″ OR “interleukin-2” OR “interleukin-10” OR “IL-10” OR “interleukin-8” OR “IL-8” OR “IL-17” OR “INTERLEUKIN-17” OR “IL-18” OR “INTERLEUKIN-18” OR “creatinine” OR “neutrophil*” OR “WBC” OR “white blood cell*” OR “ESR” OR “erythrocyte sedimentation rate” OR “Leukocyte*” OR “leukocyte*” OR “TBIL” OR “calprotectin” OR “BNP” OR “B-type natriuretic peptide” OR “CEA” OR “carcinoembryonic antigen” OR “monocyte distribution width” OR “MDW” OR “sTIM-3” OR “myeloperoxidase”)) OR ((“DECREAS*” OR “REDUC*” OR “LOW*) NEAR/5 (lymphocyte*” OR “ALBUMIN” OR “CD4” OR “CD4+” OR “CD4(+)” OR “CD8+” OR “CD8” OR “CD8(+)” OR “CD3+” OR “CD3”))))

AND.

[DIRECT IMPACT CF]

5. INCREASE NEURAL DAMAGE - TOPIC

((neurodegenerat* OR neuropathol* OR neuro*) NEAR/5 dysfunction*) OR neuroinflamm* OR (astrocyte* NEAR/5 infect*) OR (pericyte* NEAR/5 infect*) OR (neuron* NEAR/5 damage*) OR Alzheimer* OR Parkinson* OR (increase* NEAR/5 tremor*) OR (neurologic* NEAR/5 manifestation*) OR anosmia OR dysgeusia OR “mild cognitive impairment” OR (neuro* NEAR/5 damage) OR stroke* OR ((increase* OR elevat* OR high* OR raise*) NEAR/5 (p-tau217 OR sLRP1 OR S100B OR GFAP OR UCH-L1 OR NfL OR D-dimer OR C-Reactive Protein OR ferritin)) OR (cognitive NEAR/5 deficit*) OR dementia OR encephalopathy OR (blood-brain-barrier NEAR/5 permeab*) OR “central nervous system” OR “peripheral nervous system” OR “multiple sclerosis” OR epilepsy OR delirium OR aphasia OR dysarthria OR “myasthenia gravis” OR (neuro* NEAR/5 complication*) OR neurotoxic* OR (neuro* NEAR/5 toxic*) OR encephalitis OR meningitis OR myelitis OR “Guillain-Barré syndrome” OR seizure* OR ataxia OR “sensory impairment*” OR “nerve pain” OR (α-synuclein NEAR/5 accumulat*) OR (microglia* NEAR/5 activat*) OR (death NEAR/5 “dopaminergic neuron*”) OR dysarthria OR “gait instability” OR ophthalmoplegia OR “movement disorder*” OR ((decreas* OR reduce* OR low*) NEAR/5 (mir-21 OR mir-124 OR mir-146a OR PPARS OR SOCS1 OR CEBPA)) OR ((increase* OR elevat* OR high* OR raise*) NEAR/5 (IL-12p53 OR Stat3 OR TRAF6 OR mir-326 OR mir-155 OR mir-27b)))

AND.

[DIRECT IMPACT CF]

APPENDIX 2CF Linkage Mechanisms and Biomarkers

Table 1
Links of Eighty CFs to Targets of Interest

Advanced glycation end products [1].		
TARG	QUOTES/REFERENCES	BIOMARKERS
ICOV	“There are many features of diabetes and obesity that may accentuate the clinical response to SARS-CoV-2 infection: including an impaired immune response, an atherothrombotic state, accumulation of advanced glycation end products and a chronic inflammatory state." Holly et al. (2020)	infectious disease; obesity; diabetes; excess calorie consumption; limited physical activity; impaired immune response; atherothrombotic state; advanced glycation end products; chronic inflammatory state; exaggerated cytokine response; viral infection; cytokine storm; septic shock; acute respiratory distress syndrome; multi-organ failure; tissue damage; increased metabolic activity
WIS	“Advanced glycation end products reduce macrophage-mediated killing of *Staphylococcus aureus* by ARL8 upregulation and inhibition of autolysosome formation ….AGEs accelerate *S. aureus* immune evasion in macrophages by ARL8-dependent suppression of autophagosome-lysosome fusion and bactericidal capability" Xie et al. (2020)	*Staphylococcus aureus*; Autophagy; phagocytes; macrophages; infections; *S. aureus*; diabetes; advanced glycation end products; AGEs; human monocytic cell line THP-1; autophagosome; lysosome; ARL8
IIC	“Modifiable environmental factors including high levels of refined and simple carbohydrate diets, hypercaloric diets and sedentary lifestyles drive endogenous formation of advanced glycation end-products via accumulation of highly reactive glycolysis intermediates and activation of the polyol/aldose reductase pathway producing high intracellular fructose. High advanced glycation end-products overwhelm innate defenses of enzymes and receptor-mediated endocytosis and promote cell damage via the pro-inflammatory and pro-oxidant receptor for advanced glycation end-products. Oxidative stress disturbs cell signal transduction, especially insulin-mediated metabolic responses." (Ottum and Mistry, 2015)	oxidative damage; proteins; lipids; nucleotides; advanced glycation end-products; glucose uptake; glycolysis intermediates; polyol/aldose reductase pathway; intracellular fructose; enzymes; receptor-mediated endocytosis; cell damage; receptor for advanced glycation end-products; cell signal transduction; insulin-mediated metabolic responses; diabetes; polycystic ovary syndrome; dementia

(*continued on next page*)

Table 1 (*continued*)

DNS	"glycation and AGEs play a role in neurological disorders by several mechanisms that include the toxic effects of dicarbonyls on neurons, glia and vessels, the enhancing of oxidative stress, the modification of key proteins for neuronal function, the interference with catabolism of protein aggregates and the activation of the RAGE pathway" Munch et al. (2012)	RAGE; AGE deposits; macrophagesmicroglia activation; cerebral amyloid angiopathy; TPI deficiency; HMGB1; ROS; methylglyoxal; triose phosphate isomerase; GSH; GSSG; neuroinflammation; IL-1; IL-6; TNF-α; NF-κB; iNOS; DHAP; PARP; GAPDH; PKC; NADPH
Alcoholism [1].		
ICOV	"Indeed, the negative impact of alcohol on susceptibility to infection and on lung barrier function is now well documented. Thus, the alcohol lung represents a very likely comorbidity for the negative consequences of both COVID-19 susceptibility and severity." Bailey et al. (2021)	pathophysiology of the lung; alcohol-mediated tissue injury; infection; lung barrier function
WIS	"these results demonstrate that chronic alcohol consumption negatively affects the resting memory CD8 T cell response and reduces the ability of memory T cells to be recruited to the site of infection upon subsequent exposures, therein contributing to an enhanced susceptibility to IAV infections." (Zacharias and Legge, 2019)	pulmonary infections; influenza A virus; IAV; CD8 T cell; CXCL10; CXCL11; chemokines; T cell; resting memory CD8 T cell response; memory T cells
IIC	"The demographics of the patients including age, sex, body mass index (BMI), smoking and alcohol addict were compared among the groups. … The concentration of plasma s-CD62P is elevated as a early biomarker in patients with sepsis, and it serves as one of the pathogenic factors responsible for endothelial cell damage. Coagulation and mediators of inflammation promote each other, aggravating the severity of sepsis. Plasma s-CD62P may be an important factor for the development of coagulation and inflammatory reaction." Ding et al. (2013)	CD62P; cardiovascular diseases; sepsis; endothelial cell injury; inflammation; coagulation; soluble CD62P; s-CD62P; systemic inflammatory response syndrome; SIRS; high blood pressure; diabetes; age; sex; body mass index; BMI; TNF-α; hs-CRP; platelet; prothrombin; activated partial thromboplastin time; APTT; D-dimer; antithrombin-III; AT-III; sequential organ failure assessment; SOFA; ANOVA; Kruskal-Wallis test; inflammatory cytokines; endothelial cell damage
DNS	"Chronic alcohol consumption can produce numerous neurological manifestations. The most common are polyneuropathy, cerebellar degeneration and dementia, and the most serious are WE, Korsakoff syndrome and Marchiafava–Bignami disease." Planas-Ballve et al. (2017)	NMDA receptor; glutamate NMDA receptor; withdrawal syndrome; cytotoxic edema; glutamate neurotoxicity; transglutaminase 2 antibodies; CK; hepatic encephalopathy
Analgesics [2].		
ICOV	"Analgesics, particularly pregabalin (RR = 1.55; CI95%0.86–2.79), gabapentin (RR = 1.39; CI95%0.75–2.58) and opioids (RR = 1.25; CI95%0.85–1.83) showed an increased RR for COVID-19." Blanch-Rubio et al. (2020)	osteoporosis; non-inflammatory rheumatic conditions; osteoarthritis; fibromyalgia
WIS	"These results indicate that APAP suppresses the humoral and cell-mediated immune responses at a dose that causes liver injury." Ueno et al. (2000)	immune system; serum glutamic-pyruvic transaminase; T cell-independent antibody-producing responses; TNP-Ficoll; thymocytes; hypersensitivity; lymphocyte; cell-mediated immunity; humoral and cell-mediated immune responses
IIC	"The use of non-steroidal anti-inflammatory drugs (NSAID) is widespread but NSAIDs have the highest risk of adverse drug reactions and drug interactions. In particular, the gastrointestinal, cardiovascular, renal and coagulation systems are affected." Gosch (2015)	multimorbid geriatric patients; age-related pharmacokinetic and pharmacodynamic changes; gastrointestinal system; cardiovascular system; renal system; coagulation system; toxic effect on the liver; serotonin syndrome; pain management
DNS	"Our findings argue strongly that interactions between opiates and HIV-1 Tat that reduce neuron survival are driven primarily by glial cells expressing μ-opioid receptors, either astrocytes or microglia, or perhaps both acting in concert." Zou et al. (2011)	μ-Opioid receptor; glutamate, ROS, ionized calcium-binding adaptor molecule 1; 3-nitrotyrosine; GFAP; Iba-1
Antidepressants [2].		
ICOV	"In the case of antidepressants, SSRIs presented an RR of 1.54 (CI95%1.00–2.36). The tricyclic antidepressant amitriptyline presented an RR of 1.38 (CI95% 0.7, 2.71) and the RR of all dual-action antidepressants together was 1.22 (CI95% 0.72, 2.08)." Blanch-Rubio et al. (2020)	osteoporosis; non-inflammatory rheumatic conditions; osteoarthritis; fibromyalgia
WIS	"Norepinephrine-enhancing antidepressant exposure associated with reduced antiviral effect of interferon alpha on hepatitis C″ Fialho et al. (2016)	depressive disorder; interferon alpha; hepatitis C; DSM-IV major depression; inflammatory; norepinephrine
IIC	"Our novel findings suggest that a) monocyte activation and altered coagulation may represent two pathways through which depression increases HIV-CVD risk and that b) tricyclic antidepressants may elevate and selective serotonin reuptake inhibitors may attenuate HIV-CVD risk by influencing monocyte and inflammatory activation." Stewart et al. (2020)	soluble CD14; sCD14; inflammatory; interleukin-6; IL-6; coagulation marker levels; D-dimer; depression-related factors; CVD-relevant biomarkers; monocyte activation; inflammatory activation
DNS	"We found that treatment with 10 μM sertraline and 20 μM paroxetine significantly reduced cell viability. We further explored the underlying mechanisms and found induction of the [Ca2+]i level in astrocytes. We also revealed that sertraline and paroxetine induced mitochondrial damage, ROS generation, and astrocyte apoptosis with elevation of cleaved-caspase 3 and cleaved-PARP levels. Ultimately, we validated these mechanisms in primary cultured astrocytes and neuron cells and obtained consistent results. These results suggest that sertraline and paroxetine cause astrocyte dysfunction, and this impairment may be involved in the pathogenesis of neurodegenerative diseases." Then et al. (2017)	ATP; ROS; astrocyte apoptosis; mitochondrial hyperpolarization; mitochondrial damage; caspase 3; PARP; calcium influx; [Ca2+]i
Antipsychotic drugs [2].		
ICOV	"we tested a pre-specified list of drugs postulated at the start of the epidemic to increase risk of severe COVID-19 ….the strongest associations are with antipsychotic drugs" (McKeigue et al., 2021)	number of non-cardiovascular drug classes dispensed; sedation; respiratory depression; dyskinesia; anticholinergic effects; gastrointestinal system

(*continued on next page*)

Table 1 (*continued*)

Antipsychotic drugs [2].		
WIS	"The antipsychotic medication, risperidone, causes global immunosuppression in healthy mice" (May et al., 2019)	schizophrenia; bipolar disorder; depression; infections; however; bone marrow; hematopoietic system; inflammatory; immune function;
IIC	"The syndrome of systemic inflammatory response, which is observed alongside antipsychotic poisoning, occurs simultaneously with the initiation of fibrinolysis and hypercoagulation processes. In this regard, the most pronounced correlation is between the SIRS score, plasma D-dimer level, and the plasma level of D-dimer derivatives, oligopeptides." Zhang et al. (2020a)	systemic inflammatory response syndrome; SIRS; fibrinolysis; endotoxemia; coagulation; C-reactive protein; fibrinogen; IL-6; SIRS score; plasma D-dimer level; plasma level oligopeptides
DNS	"Most antipsychotics and antidepressants lower the seizure threshold and can cause seizures; the risk is greater with clozapine than with other atypical antipsychotics and greater with tricyclic antidepressants (TCAs) than with SSRIs. In randomised controlled trials in elderly patients with dementia atypical antipsychotics are associated with a higher risk of stroke and death than placebo." (Haddad and Dursun, 2008)	Creatinine phosphate kinase; WBC; serotonin, dopamine; neuromuscular hyperactivity; autonomic hyperactivity
Arsenic [4].		
ICOV	"The existing data demonstrate that As, Cd, Hg, and Pb exposure is associated with respiratory dysfunction and respiratory diseases (COPD, bronchitis) ….reduction of toxic metal exposure may be considered as a potential tool for reducing susceptibility and severity of viral diseases affecting the respiratory system, including COVID-19." Skalny et al. (2020)	respiratory dysfunction; immunotoxicity; viral diseases; COVID-19; COPD; bronchitis; impaired mucociliary clearance; reduced barrier function; airway inflammation; oxidative stress; apoptosis; influenza; respiratory syncytial virus; adaptive immunity; smoking; particulate pollution; PM2.5; tobacco smoke; respiratory dysfunction; immunotoxicity; viral diseases; respiratory diseases; COPD; bronchitis; airway inflammation; oxidative stress; apoptosis; respiratory system; COVID-19
WIS	"the results from the study demonstrated that environmentally-relevant concentrations of As+3 induced cytotoxicity and suppressed the major cellular functions in THP-1 derived macrophages. The macrophages were showed to be relatively sensitive to As+3, and could be the essential target of the toxicity induced by environmental arsenic exposures" Xu et al. (2018)	immunotoxicity; Macrophages; phagocytes; immune system; THP-1 human monocyte cell line; Apoptosis; pro-inflammatory cytokines; IL-1β; TNF-α; nitric oxide; superoxide; cytotoxicity
IIC	"arsenic induces endothelial dysfunction, including inflammatory and coagulating activity as well as impairs nitric oxide (NO) balance." (Simeonova and Luster, 2004)	vascular diseases; atherosclerosis; endothelial dysfunction; inflammatory; coagulating; nitric oxide; NO
DNS	"several toxicity mechanisms of iAs parallel those mechanisms associated with neurodegeneration, including oxidative stress and inflammation, impaired protein degradation, autophagy, and intracellular accumulation, endoplasmic reticulum stress, and mitochondrial dysfunction. Additionally, different reports have shown that specifically in brain tissue, iAs and its metabolites induce hyper-phosphorylation of the tau protein and over-regulation of the amyloid precursor protein, impaired neurotransmitters synthesis and synaptic transmission, increased glutamate receptors activation, and decreased glutamate transporters expression. Interestingly, increased and sustained pro-inflammatory responses mediated by cytokines and related factors, seems to be the triggering factor for all of such cellular pathological effects." Escudero-Lourdes (2016)	Oxidative stress; mitochondrial dysfunction; reticulum endoplasmic stress; ROS; NADPH oxidases; cytochrome *c*; cytochrome *c* oxidase; Prdx2; iSOD; GSH; AP-1/c-Jun; ERK1/2; hsp; neuroinflammation; NF-κB; IL-6; IL8; IL-1; MIF; TNF-α; DA; NE; EPN; 5-HT; DOPAC; HVA; β-secretase; PPARγ; autophagy impairment
Benzene [4].		
ICOV	"The airborne benzene concentration was the leading risk factor in 24% of the counties" Luo et al. (2021)	going to work by walking; airborne benzene concentration; householder with a mortgage; unemployment; PM2.5 concentration; per cent of the black or African American
WIS	"In conclusion, the recent thymic output function and the T-cell immune function were apparently impaired in workers after benzene exposure." Li et al. (2009)	blood disorders; toxicity; lymphopoiesis; aplastic anaemia; leukemia; T-cell receptor excision DNA circles; TRECs; peripheral blood mononuclear cells; PBMCs; thymic output; naive T-cells; T-cell immune function; DNA
IIC	"trinitro-benzene-sulfonic acid (TNBS)-induced colitis mice were used. … IBD patients and mice had increased expression of FGL2 compared with controls. Furthermore, FGL2 expression was correlated with intestinal and plasmatic TNF-α expression, mean platelet volume (MPV), platelet count (PLT), platelet-crit (PCT), and fibrinogen. Our data indicate that FGL2 may mediate immune coagulation in IBD patients." Dong et al. (2018)	fibrinogen-like protein 2 prothrombinase; FGL2; IBD; TNF-α; macrophages; fibrin; inflammatory infiltrating cells; microvascular vessels; TNF-α; mean platelet volume; MPV; platelet count; PLT; platelet-crit; PCT; fibrinogen
DNS	"Long-term exposure to benzene vapor can damage the hematopoietic system (3,4), immune system (5), and nervous system (6), which leads to leukopenia, decreased platelets, infection, hemorrhage, cognitive dysfunction, et cetera (7,8)." Hu et al. (2021b)	P-Tau; T-Tau; β-amyloid peptide
Benzidine [4].		
ICOV	"COVID-19 mortality and individual factors were examined using mixed-effect negative binomial regression models, with multiple comparisons addressed, and (2) in Phase 2, a multivariable regression model including all variables that are significant … All the 4 variables that were significant in both sets in Phase 1 remained statistically significant in Phase 2, including two air toxicants (i.e., nitrogen dioxide or NO2, and benzidine) … It confirmed some of the previously reported environmental factors associated with COVID-19 mortality" Hu et al. (2021a)	external exposome; nitrogen dioxide; NO2; benzidine; vacant land measure; food environment measure

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Benzidine [4].		
WIS	"Benzidine (4,4′-diaminobiphenyl), a known human bladder carcinogen used in the synthesis of dyes, was immunosuppressive in mice after subchronic exposure …. These data suggest that the development of neoplastic disease may be facilitated by the ability of benzidine to alter the immune response ….The addition of benzidine in vitro to mitogen-activated lymphocytes mimicked the suppression of lymphocyte responsiveness in vivo. In vitro studies suggested that alterations in metabolites of the arachidonic acid/lipoxygenase pathway were responsible for the immune alterations." Luster et al. (1985)	immunosuppressive; cell-mediated immunity; lymphoproliferative; hypersensitivity; host resistance; immune response; mitogen-activated lymphocytes; lymphocyte; arachidonic acid/lipoxygenase pathway; immune alterations; arachidonic acid; hydroperoxidases
IIC	"The administration of benzidine dihydrochloride in water to mice for up to 39 weeks resulted in hemosiderosis of the spleen, focal vacuolization of the transitional epithelium of the urinary bladder, and chronic inflammation and cytologic and neoplastic changes in the liver." (Frith and Dooley, 1976)	hemosiderosis; spleen; transitional epithelium; urinary bladder; chronic inflammation; neoplastic; liver; liver tumors
DNS	"Spongiform leukoencephalopathy (central nervous system damage resulting in vacuolization of white matter) was observed in mice after lifetime exposure to 20 ppm of benzidine dihydrochloride in drinking water" Choudhary (1996)	White matter vacuolization; CNS damage
Bone marrow transplantation [2].		
ICOV	"a 51-year-old allogeneic bone marrow transplant recipient. Both patients were on immunosuppressant therapy and had stable graft function before COVID-19 infection. After the diagnosis of COVID-19, immunosuppressive agents were discontinued and methylprednisolone with prophylactic antibiotics were initiated, however, the lung injury progressed. The T cells were extremely low in both patients after infection. Both patients died despite the maximal mechanical ventilatory support. Therefore, the prognosis of COVID-19 pneumonia following transplantation is not optimistic and remains guarded. Lower T cell count may be a surrogate for poor outcome." Huang et al. (2020)	renal transplant recipient; allogeneic bone marrow transplant recipient; immunosuppressant therapy; lung injury; T cells; infection; COVID-19 pneumonia; transplantation; Lower T cell count
WIS	"Impaired CD8(+) T cell immunity after allogeneic bone marrow transplantation leads to persistent and severe respiratory viral infection ….these results indicate that allogeneic BMT results in more severe RVI based on the failure to develop an appropriate pulmonary CD8(+) T cell response" Gowdy et al. (2015)	respiratory viral infections; antiviral T cell immunity; immunosuppression; Bone marrow; splenocytes; parainfluenza virus type 1; mPIV-1; airway inflammation; epithelial injury; enhanced mortality; viral clearance; viral transcripts; CD8(+) T cells; inhibitory receptor programmed death-1; PD-1;
IIC	"We report a 47-year-old man with acute leukemia … On day 5 after stem cell transplantation, progressive local tissue necrosis led to septicemia and disseminated intravascular coagulation. … A recombinant thrombomodulin might have not only resolved the coagulation problem but also prevented multiple organ failure associated with the systemic inflammatory response." Ito et al. (2011)	necrotizing fasciitis; *Clostridium perfringens*; local tissue necrosis; septicemia; intravascular coagulation; multiple organ failure; systemic inflammatory response
DNS	"Neurological complications are an important contribution to the morbidity and mortality after BMT. Stroke has been noted anecdotally following BMT and several of the above-referenced series reported relatively small numbers of cerebrovascular complications." Coplin et al. (2001)	GOS scores; thrombocytopenia; intracranial hemorrhage; brain infection
BPA [4].		
ICOV	"this paper focuses on the potential role of BPA in promoting comorbidities associated with severe COVID-19, as well as on potential BPA-induced effects on key SARS-CoV-2 infection mediators, such as angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) ….BPA exposure may impact on the local expression of these SARS-CoV-2 infection mediators. Overall, the potential role of BPA on the risk and severity of COVID-19 merits further investigation." Zahra et al. (2020)	Infection; asthma; cancer; cardiovascular disease; hypertension; diabetes; obesity; cardio-metabolic diseases; endocrine-related cancers; immune system dysregulation; COVID-19; nuclear oestrogen receptors; ERα; ERβ; membrane-bound oestrogen receptor; G protein-coupled receptor 30; GPR30; human nuclear receptor oestrogen-related receptor gamma; angiotensin-converting enzyme 2; ACE2; transmembrane serine protease 2; TMPRSS2
WIS	"we discuss the current literature on the effects of BPA on the function of immune system that potentially increases the susceptibility to infections by the virtue of acting as a pro-inflammatory molecule. Thus, it appears that BPA ….can worsen the prognosis of diseases that are adversely affected by inflammation." Del Rio Araiza et al. (2021)	endocrine-disruptor; estrogenic activity; endocrine modulating; immune system; immune response; immune cell populations; infections; pro-inflammatory; inflammation.
IIC	"An extended time was observed in BPA-treated but not BPS-treated animals in bleeding time; … Taken together, these data show BPA and BPS as capable of interfering with the coagulation process via FVIIa." Chagas et al. (2021)	cancer; blood coagulation; human factor VII sequence; bleeding time; APTT in bisphenols; platelet aggregation; Protein alignment; FVIIa
DNS	"BPA also causes aberrant cognitive function, behavioral disturbances, and neurodegenerative diseases, including Parkinson's disease, amyotrophic lateral sclerosis (ALS), and multiple sclerosis. It has recently been proposed that exposure to BPA may be associated with the development of certain neurodegenerative diseases and neurodevelopmental disorders" (Rebolledo-Solleiro et al., 2021)	NMDA; subunit NR2; AMPA GluR1 subunit; NMDAR subunits NR1, NR2A, and 2B; ERα; DNMT; BDNF; Grin2b/GRIN2B gene; ROS; amyloid β peptide; BACE-1; inflammation; TNF-α; IL-1β; IL-6; NF-κB; MAPKs; oxidative stress; mitochondrial damage; Drp-1; Ca2+ homeostasis; myelin loss
Cadmium/Cd [4].		
ICOV	"Urinary concentrations of chromium, manganese, copper, selenium, cadmium, mercury and lead after creatinine adjustment were found to be higher in severe patients than the non-severe cases with COVID-19. … These results suggest abnormities in urinary levels of the trace metals were tightly associated with the	urinary trace elements; inflammatory; serum cytokines; IL-1B; IL2R; IL6; IL8; IL10; TNFα; ferritin; neutrophil count; white blood cell count; urinary creatinine-adjusted copper

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Cadmium/Cd [4].		
	severe illness and fatal outcome of COVID-19." Zeng et al. (2021)	
WIS	"Cd accumulates in immune cells, modulates the function of the immune system, triggers immunological responses, and leads to diverse health problems. Cd acts as an immunotoxic agent by regulating the activity and apoptosis of immune cells, altering the secretion of immune cytokines, inducing reactive oxygen species (ROS) production and oxidative stress, changing the frequency of T lymphocyte subsets, and altering the production of selective antibodies in immune cells." Wang et al. (2021)	immunotoxicity; immune cells; immune system; immunological responses; immunotoxic agent; apoptosis; immune cytokines; reactive oxygen species; ROS; oxidative stress; T lymphocyte; antibodies; Cd toxicity; innate immunity; adaptive immunity
IIC	"We found consistent positive associations between the following biomarkers and PM(2.5) chemical constituents across different models: TNF-α with secondary organic carbon, chloride, zinc, molybdenum and stannum; fibrinogen with magnesium, iron, titanium, cobalt and cadmium; PAI-1 with titanium, cobalt and manganese; t-PA with cadmium and selenium;" Wu et al. (2012)	systemic inflammation; hypercoagulability; plasma homocysteine; PM(2.5); hs-CRP; TNF-α; fibrinogen; plasminogen activator inhibitor type 1; PAI-1; tissue-type plasminogen activator; t-PA; von Willebrand factor; vWF; soluble platelet selectin; sP-selectin; total homocysteine; tHcy; TNF-α; organic carbon; chloride; zinc; molybdenum; stannum; fibrinogen; magnesium; iron; titanium; cobalt; cadmium; nitrate; sodium; manganese
DNS	"Cadmium (Cd) is an environmental contaminant, which is a potential risk factor in the progression of aging-associated neurodegenerative diseases." Ali et al. (2021a)	Synap; PSD-95; oxidative stress; ROS; MDA; GSH; synaptic dysfunction; Nrf2; HO-1; p-JNK; BACE-1; amyloid β peptide; apolipoprotein E
Carbon monoxide [4].		
ICOV	"Air pollutants such as PM10, PM2.5, SO2, NO2, and CO showed a significant correlation with the COVID-19 epidemic." (Ali and Islam, 2020)	air pollution; PM2.5; nitrogen dioxide; NO2; PM10; SO2; CO; O3; age; pre-existing medical conditions
WIS	"Noise and/or low-concentration CO exposure may suppress innate and adaptive immune functions and induce inflammatory responses. Noise exposure mainly affected the innate immune function of rats, whereas low-concentration CO exposure mainly affected adaptive immune functions. Combined exposure presented higher immunotoxicity than noise or CO alone, suggesting that exposure to noise and low-concentration CO in the living and working environments can affect the immune system." She et al. (2021)	immunotoxicity; immune organs; immune functions; thymus; spleen; leukocyte counts; inflammatory factors; immunoglobulin; Ig concentrations: red-pulp; white-pulp; splenic nodules; neutrophil infiltration; lymphocyte counts; serum IgM; serum IgG levels; tumor necrosis factor-α; interferon-γ levels; Eosinophils; IgA; interleukin-1; Monocytes; innate immunity; adaptive immunity; inflammatory responses
IIC	"We found effects of particle number, black carbon, nitrogen dioxide (NO(2)), and carbon monoxide (CO) on fibrinogen. Ozone was a predictor of C-reactive protein and ICAM-1. Particle number, black carbon, NO(2), CO, PM(2.5), and sulfates were associated with ICAM-1 and VCAM-1." Bind et al. (2012)	thrombosis; inflammation; endothelial dysfunction; fibrinogen; C-reactive protein; intercellular adhesion molecule-1 (ICAM-1); vascular cell adhesion molecule-1 (VCAM-1); Alu; LINE-1; tissue factor (F3); Toll-like receptor 2 (TLR-2)
DNS	"Survivors of CO poisoning suffer from long-term neurocognitive sequelae related to brain injury (12, 15). Symptoms include impaired memory, cognitive dysfunction, depression, anxiety, and/or vestibular and motor deficits" Rose et al. (2017)	Neurologic deficits; neurocognitive deficits; COHb; mitochondrial cytochrome *c* oxidase; glutamate; neuroinflammation; NMDA; oxidative stress; ROS; RNS; HO-1; myeloperoxidase; white matter hyperintensities; hippocampal atrophy
Chemotherapy [2].		
ICOV	" Meta-analysis of multivariate adjusted OR of death for active chemotherapy was consistently associated with higher risk of death compared to no active chemotherapy ….Active chemotherapy appears to be associated with higher risk of death in cancer patients with COVID-19." Park et al. (2021b)	COVID-19; risk factor; clinical diagnosis of COVID-19; death; cancer
WIS	"This case controlled study measured the measles antibody titer in children who survived cancer after chemotherapy to determine the patient's immune status against the measles vaccine ….The cancer survivors had significantly lower measles antibody titers than the healthy control participants, and 78.9% of cancer survivors were unprotected (seronegative) compared to 7.9% in healthy controls ….These results underline the need for post-chemotherapy measles antibody testing and revaccination of seronegative survivors." Abdelaziz et al. (2021)	measles antibody titer; immune status; humoral immunity
IIC	"We report the case of a 72-year-old woman with endometrial cancer who was undergoing treatment for hypertension, obesity and diabetes mellitus. … On day 5 of chemotherapy, she developed the systemic inflammatory response syndrome including febrile neutropenia and sepsis. She then developed disseminated intravascular coagulation (DIC) and septic shock." (Ishikawa et al., 2021)	Neutropenic enterocolitis; lung cancer; breast cancer; gastric cancer; ovarian cancer; death; endometrial cancer; hypertension; obesity; diabetes mellitus; paralytic ileus; systemic inflammatory response syndrome; febrile neutropenia; sepsis; disseminated intravascular coagulation; DIC; septic shock; gut distention; bowel damage; bacterial translocation
DNS	"There is increasing clinical evidence that chemotherapeutic agents induce neurological side effects, including memory deficits and mood disorders" (Yang, Moon, 2013)	Spatial working memory impairment; BDNF; loss of hippocampal neurogenesis; DCX; hippocampal cell proliferation; dendritic swelling; ROS; RNS, GSH; ATP; NF-κB; PI3K; Akt; MAPK; CYP; neuronal cell death
Chlorination of drinking water [4].		
ICOV	"There is a striking correlation between the level of environmental pollutants including pesticides, dioxins, and air pollution such as NO(2) known to affect immune function and healthy metabolism with the rate of mortality in COVID-19 pandemic in these European countries. There is also a correlation with the use of chlorination of drinking water in these regions." Bornstein et al. (2020)	SARS-CoV-2; environmental pollutants; pesticides; dioxins; air pollution; NO2; immune function; healthy metabolism; chlorination of drinking water; metabolic inflammation; altered vascular perfusion; neurodegeneration
WIS	"Male Sprague-Dawley rats were exposed to chlorine-based disinfectants in the drinking water from weaning to 12 weeks of age, at which time they were terminated and assessed for immune competence ….These results extend the earlier observations of others that macrophage function of laboratory rodents may be	immune competence; immunity; spleen weight; thymus weight; antibody production; delayed-type hypersensitivity reactions; natural killer cell cytotoxicity; oxidative metabolism response; chemiluminescence; phagocytosis by macrophages;

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Chlorination of drinking water [4].		
	impaired by exposure to high concentrations of chlorinated drinking water. Furthermore, the function of other major populations of immunocytes and types of immune responses may also be altered following subchronic exposure to high concentrations of chlorinated drinking water. These types of effects on the immune system are a previously unrecognized potential side-effect of the ubiquitous practice of disinfection of water with chlorine compounds." Exon et al. (1987)	immunoregulatory cytokines; interleukin 2; IL2; prostaglandin E2; PGE2; immune system
IIC	"Upregulation of autophagy decreases chlorine-induced mitochondrial injury and lung inflammation" Jurkuvenaite et al. (2015)	lung epithelial cell mitochondria; activation of autophagy; NCI–H441; human lung adenocarcinoma epithelial cells; bioenergetics; cellular bioenergetic function; mitochondrial membrane potential; MitoSOX signal; bioenergetic dysfunction; white blood cells; bronchoalveolar lavage fluid; alveolar permeability; cell infiltration; lung inflammation
DNS	"Chlorination of water results in the formation of a variety of DBP such as trihalomethanes, haloacetonitriles (HAN) and haloacetic acids (HAA; Meier et al., 1985). Epidemiological studies indicate an association between DBP exposure and fetal abnormalities including neural tube defects and fetal death" Ahmed et al. (2005)	Apoptotic neurodegeneration; oxidative stress; GSH; GSSG; MDA; 4-HNE; DNA oxidation; 8-OHdG
Chloroform [4].		
ICOV	"All the 4 variables that were significant in both sets in Phase 1 remained statistically significant in Phase 2, including two air toxicants (i.e., nitrogen dioxide or NO2, and benzidine) …. This external ExWAS of county-level COVID-19 mortality in the contiguous US provides new insights into the role of long-term exposures to the external exposome in COVID-19 mortality. We confirmed a previously reported association (i.e. NO2), and identified novel environmental factors associated with COVID-19 mortality, including air toxicants (i.e., methyl bromide, benzidine, and chloroform)" Hu et al. (2021a)	external exposome; nitrogen dioxide; NO2; benzidine; vacant land measure; food environment measure
WIS	"exposure to chloroform can cause illnesses such as cancer, especially in the liver and kidneys. The aim of the study was to analyze the effects of chloroform on redox imbalance and pulmonary inflammatory response in adult C57BL/6 mice ….This study highlights the risks of occupational chloroform exposure at low concentrations and the intensity of oxidative damage related to gender. de Oliveira et al. (2015)	cancer; redox imbalance; pulmonary inflammatory response; Total cell counts; differential cell counts; protein carbonyl; antioxidant enzyme catalase activity; CAT; alveolar area; volume density of alveolar septa; inflammatory cell influx; oxidative damage
IIC	"Two cases with an uncommon complication due to chloroform intoxication are presented. … Possibly, chloroform and/or its derivates may interact with pattern recognition receptors and activate the same pro-inflammatory mediators (cytokines, interleukins, prostaglandins, leukotrienes) that cause SIRS in bacterial sepsis." Dettling et al. (2016)	drowsiness; nausea; liver damage; dyspnea; toxic pulmonary edema; systemic inflammatory response syndrome; SIRS; white blood cell counts; C-reactive protein; procalcitonin levels; skin areas; blood sample; unconscious; SIRS without growth of bacteria; died; multi-organ failure; mimicking bacterial-induced sepsis; pattern recognition receptors; pro-inflammatory mediators; cytokines; interleukins; prostaglandins; leukotrienes; SIRS in bacterial sepsis.
DNS	"Target organs for chloroform toxicity are CNS, the liver, and kidneys. Chloroform is a respiratory and CNS depressant, inducing narcosis and anesthesia at high concentrations." Lionte (2010)	Cerebral edema; cerebral hemorrhage; Cerebellar damage; encephalopathy; vagal stimulation
Cholesterol [1].		
ICOV	"The addition of exogenous cholesterol to M beta CD-treated cells or virions moderately restored PDCoV infectivity ….Taken together, the current data indicate that the cholesterol present in the cell membrane and viral envelope contributes to PDCoV replication by acting as a key component in viral entry" (Jeon and Lee, 2018)	cellular cholesterol levels; viral cholesterol levels; porcine deltacoronavirus replication; PDCoV replication; virus attachment; virus internalization; cell membrane; viral envelope; viral entry
WIS	"The main objective of this study was to evaluate the effects of a high cholesterol (HC) dietary challenge on cholesterol tissue accumulation, inflammation, adipocyte differentiation, and macrophage infiltration in guinea pigs ….Higher concentrations of total ($P < 0.005$) and free ($P < 0.05$) cholesterol were observed in both adipose tissue and aortas of guinea pigs fed the HC compared to those in the LC group. In addition, higher concentrations of pro-inflammatory cytokines in the adipose tissue ($P < 0.005$) and lower concentrations of anti-inflammatory interleukin (IL)-10 were observed in the HC group ($P < 0.05$) compared to the LC group ….The results of this study strongly suggest that HC induces metabolic dysregulation associated with inflammation in adipose tissue and that L-CHO is more effective than H–CHO in attenuating these detrimental effects." Aguilar et al. (2014)	cholesterol tissue accumulation; inflammation; adipocyte differentiation; macrophage infiltration; cholesterol; pro-inflammatory cytokines; interleukin (IL)-10; adipocytes; concentrations of cholesterol; adipose cells; metabolic dysregulation
IIC	"Modified lipoproteins induce local inflammation possibly due to activation of nuclear factor (NF-)kappaB and subsequent expression of adhesion molecules, release of pro-inflammatory cytokines, growth factors and mitogens, which are mediators for cell growth, proliferation and lipid deposition. Furthermore, activation of collagenases and proteases in combination with prothrombotic processes attenuate clot formation, plaque rupture and occlusion of vessels." Fraunberger et al. (2005)	pro-inflammatory; procoagulatory factors; lipoprotein profile and composition; local inflammation; nuclear factor (NF-)kappaB; adhesion molecules; pro-inflammatory cytokines; growth factors; mitogens; cell growth; cell proliferation; lipid deposition

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Cholesterol [1].		
DNS	"Dysregulation of cholesterol homeostasis in the brain is increasingly being linked to chronic neurodegenerative disorders, including Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), Niemann-Pick type C (NPC) disease and Smith-Lemli Opitz syndrome (SLOS)." Vance (2012)	Amyloid β peptide; APP; hyperphosphorylated Tau; cognitive decline; α/β/γ-secretases; plasma cholesterol; cholesterol metabolism; apolipoprotein E; ABCA1; α-synuclein; 27-hydroxycholesterol; ACAT-1; dopamine
Chromium/Cr [4].		
ICOV	"Urinary concentrations of chromium, manganese, copper, selenium, cadmium, mercury and lead after creatinine adjustment were found to be higher in severe patients than the non-severe cases with COVID-19. … These results suggest abnormities in urinary levels of the trace metals were tightly associated with the severe illness and fatal outcome of COVID-19." Zeng et al. (2021)	urinary trace elements; inflammatory; serum cytokines; IL-1B; IL2R; IL6; IL8; IL10; TNFα; ferritin; neutrophil count; white blood cell count; urinary creatinine-adjusted copper
WIS	"Long-term (135 days) oral exposure of Wistar rats to chromium in the form of K2Cr2O7 (exposed group~20 mg/kg/day) led to a decrease in thymus mass and thymocytes' number and caused structural and functional changes in the lymph nodes and spleen, namely lymphoreticular hyperplasia and plasmocytic macrophage transformation. Programmed cell death was increased in both thymocytes and splenocytes and decreased in lymphocytes in the T-zones of spleen and lymph nodes. Moreover, Cr (VI) administration decreased myeloid cells' and neutrophils' number, while it increased lymphoid and erythroid cells' number in bone marrow. Cr (VI) immune system effects seem to be related to oxidative stress induction, as depicted by the increased levels of diene conjugates and malondialdehyde in the spleen and liver and by the decreased activity of catalase and superoxide dismutase in rats' erythrocytes." Karaulov et al. (2019)	thymus mass; thymocytes' number; lymph nodes; spleen; lymphoreticular hyperplasia; plasmocytic macrophage transformation; Programmed cell death; lymphocytes; myeloid cells; neutrophils; lymphoid cells; erythroid cells: oxidative stress; diene conjugates; malondialdehyde; catalase; superoxide dismutase; erythrocytes
IIC	"Cobalt-chrome (CoCr), a metal alloy, used as a biomaterial for vascular stents, has been shown to be potentially pro-thrombotic and pro-inflammatory." Gossart et al. (2019)	Monocytes; cytokines; tissue factor; TF; pro-thrombotic; pro-inflammatory; fibrin formation; fibrinogen; fibronectin; complement; C3; C4; C8; monocytes; macrophages
DNS	"chromium and nickel could contribute to the pathophysiology of tauopathies such as PSP by promoting tau accumulation and neuronal cell death." Alquezar et al. (2020)	Neuronal death; Tau; LIN28A; NANOG; PODXL; POU5F1; SOX2; apoptosis; Bax; Bcl2; caspase 3; caspase 9
Chronic stress [5].		
ICOV	"we evaluate preclinical and clinical literature suggesting that chronic stress-induced hyperinflammation interacts synergistically with COVID-19-related inflammation, contributing to a potentially fatal cytokine storm syndrome. In particular, we hypothesize that both chronic stress and COVID-19-related hyperinflammation are a product of glucocorticoid insufficiency. We discuss the devastating effects of SARS-CoV-2 on structural and functional aspects of the biological stress response and how these induce exaggerated inflammatory responses, particularly interleukin (IL)-6 hypersecretion. We postulate that chronic stress should be considered a significant risk factor for adverse COVID-19-related health outcomes, given overlapping peripheral and central immune dysregulation in both conditions." Lamontagne et al. (2021)	respiratory system; hyperinflammatory responses; hypertension; obesity; diabetes; inflammation; chronic stress-induced hyperinflammation; cytokine storm syndrome; glucocorticoid insufficiency; biological stress response; interleukin (IL)-6 hypersecretion; immune dysregulation
WIS	"Stress is known to suppress immune function and increase susceptibility to infections and cancer ….stress may suppress immune function under some conditions while enhancing it under others ….Chronic or long-term stress can suppress immunity by decreasing immune cell numbers and function and/or increasing active immunosuppressive mechanisms (e.g. regulatory T cells). Chronic stress can also dysregulate immune function by promoting proinflammatory and type-2 cytokine-driven responses ….Effects of stress on leukocyte distribution: Compartments that are ….depleted of leukocytes, show immunosuppression …. Endogenous hormones at pharmacologic concentrations, and synthetic hormones, are immunosuppressive ….immunosuppression may be observed at late stages of the immune response." Dhabhar (2009)	immune function; infections; cancer; asthma; allergic diseases; autoimmune diseases; inflammatory diseases; immunosuppression; immune activation; innate immune responses; adaptive immune responses; immune cell numbers; regulatory T cells; type-2 cytokine-driven responses; leukocyte distribution; immune cells; immunoenhancement; immunosuppression; glucocorticoids; Endogenous hormones
IIC	"Psychological stress induces different alterations in the organism in order to maintain homeostasis, including changes in hematopoiesis and hemostasis. In particular, stress-induced hyper activation of the autonomic nervous system and hypothalamic-pituitary-adrenal axis can trigger cellular and molecular alterations in platelets, coagulation factors, endothelial function, redox balance, and sterile inflammatory response." Sandrini et al. (2020)	cellular alterations; molecular alterations; platelets; coagulation factors; endothelial function; redox balance; inflammatory response; thrombosis
DNS	"There is now ample evidence for cause-effect relationships between prolonged stress, elevated GC levels, and cognitive and mood disorders while the evidence for a link between chronic stress/GC and neurodegenerative disorders such as Alzheimer's (AD) and Parkinson's (PD) diseases is growing" Vyas et al. (2016)	Cell death/arrest; ROS; Bax; Bcl2; caspase 3; p53; neuronal atrophy; synaptic dysfunction/loss; Tau missorting; hyperphosphorylated Tau; Tau; glutamate; GR; BDNF; CRF; α-synuclein; amyloid β peptide; amyloid β peptide receptors; SRA; CD36; RAGE; BACE-1; APP; GSK3β; CDK5; Hsp90; Hsp70; neuroinflammation; TNF-α;, IL-1β; IL-6; MMP9; neprilysin; cognitive impairments; TREM2; apolipoprotein E
Circadian disruption [1].		
ICOV	"Shiftworkers show increased risk for developing viral infections due to possible compromise of both innate and acquired immunity responses. Short sleep and sleep loss, common consequences of shiftwork, are associated with altered integrity of the immune system." da Silva et al. (2020)	sleep deprivation; circadian time structure; Immune system; circadian rhythms; immune function; viral infections; innate immunity responses; acquired immunity responses; Short sleep; sleep loss; sleep imbalance

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WIS	"chronic circadian disruption impairs natural killer (NK) cell immunosurveillance ….mRNA and protein levels of period 1 (per1) and per2 were suppressed, while circadian locomotor output cycle kaput (CLOCK) was increased in the shifted mice ….Chronic shift-lag promoted NK cell ageing, which is likely due to the reduction in Ly49 family receptor expression in shifted NK ….Chronic shift-lag inhibited NK cell secretion of granular CD107a and interferon gamma. Moreover, chronic shift-lag attenuated the clearance of MHC-I-deficient tumour cells by NK cells in vivo and promoted lung metastasis of B16F10 melanomas. Furthermore, chronic shift-lag reduced NK cell killing function, which may be due to the suppression of Eomes transcription factor expression, which inhibiting the transcription of CD122. In conclusion, our findings suggest that chronic circadian disruption attenuates NK cell cytolytic activity by decreasing the expression of CD122." Zeng et al. (2020)	chronic circadian disruption; natural killer cell; NK cell; immunosurveillance;. NK cell development; mRNA; protein levels; NK cell ageing; Ly49 family receptor expression; granular CD107a; MHC-I-deficient tumour cells; B16F10 melanomas; Eomes transcription factor expression; CD122
IIC	"Circadian misalignment significantly increased plasma tumor necrosis factor-alpha (TNF-α), interleukin 10 (IL-10) and C-reactive protein (CRP) ($p < 0.05$). Little change was observed for the TNF-α/IL-10 ratio during circadian misalignment, whereas the TNF-α/IL-10 ratio and CRP levels decreased in the synchronized control group across weeks of circadian entrainment." Wright et al. (2015)	Cortisol; inflammatory proteins; blood cortisol; melatonin; tumor necrosis factor-alpha; TNF-α; interleukin 10; IL-10; C-reactive protein' CRP; pro- inflammatory proteins; anti-inflammatory proteins.
DNS	"Evidence from preliminary studies suggest that circadian rhythm disruptions, in addition to being a symptom of neurodegeneration, might also be a potential risk factor for developing Alzheimer's disease and related dementias, and Parkinson's disease" Leng et al. (2019)	Rest-activity rhythm; melatonin rhythm; cortisol rhythm; peripheral clock gene expression; mild cognitive impairment; oxidative stress; neuroinflammation; phosphorylated Tau; amyloid β peptide; CLOCK; Bmal1; CBT
Clozapine [2].		
ICOV	"These findings provide support for the hypothesis that clozapine treatment is associated with an increased risk of COVID-19 infection." Govind et al. (2021)	treatment-resistant psychosis; infection; pneumonia; COVID-19
WIS	"Lozano et al. [4] were the first to find a statistical association between clozapine use and selective immunoglobulin (Ig) M immunodeficiency ….Ponsford et al. [5] found significantly reduced Ig serum levels in clozapine-treated patients compared with clozapine-naive patients. Interestingly, a significant association was found between clozapine treatment duration and the degree of reduction in IgG serum levels, with an annual 0.15 g/L decline of serum IgG, thus suggesting a cumulative effect of clozapine on antibody production …. clozapine use was associated with an increased proportion of patients using more than five antibiotic courses in a year ….Ponsford et al. [6] found significant pan-hypogammaglobulinemia, impaired vaccine responses and reduction of class-switched memory B cells (CSMB). Recurrent infections were documented in 10/17 subjects (59%), predominately reflecting sinopulmonary infections. These abnormalities are consistent with those observed in patients with common variable immunodeficiency [9] ….Many studies and reviews of the literature evoke an increased risk of pneumonia in patients treated with antipsychotics and, compared to other antipsychotics, clozapine carries higher risks of pneumonia and lethality during pneumonia [7]." Aubignat (2021)	immunoglobulin M; IgM; immunodeficiency; IgG serum levels; pan-hypogammaglobulinemia; vaccine responses; class-switched memory B cells; CSMB; Recurrent infections; sinopulmonary infections; pneumonia; immunoglobulin levels; interleukin-1 receptor antagonist; swallowing; salivation; sedation; muscarinic receptors; hypersalivation; histamine-1 receptors; cytochrome P450 enzymes; 1A2; 2C19; 3A4; 2D6; cytokines
IIC	"clozapine, by itself, can cause inflammation, particularly during titration that is too rapid for that patient;" (Aulakh and Singh, 2008)	systemic inflammation; clozapine level; inflammation; risk of infection; risk of pneumonia; high mortality; impairing immunological mechanisms; fever; pneumonia
DNS	"Our study also suggests that patients with long-term clozapine monotherapy displayed more severe and extensive GM loss in the bilateral prefrontal and left cuneus cortex" Liu et al. (2020a)	Gray matter deficits; neuroinflammation; microglial activation; extracellular volume; PANSS score
Cyclophosphamide [2].		
ICOV	"High levels of immunosuppression with methylprednisolone or cyclophosphamide pulse therapy and chronic oral GC were associated with unfavourable outcomes of the SARS-CoV-2 infection" Marques et al. (2021)	methylprednisolone; cyclophosphamide; glucocorticoids; inflammatory process
WIS	"The aim of this study was to verify the effect of immunosuppression by cyclophosphamide (Cy) on susceptibility of BALB/c mice subjected to challenge with recombinant strains of Toxoplasma gondii ….In conclusion, BALB/c mice susceptibility to reinfection by T. gondii is related to genetic differences among the strains used for primary and challenge infections. Alteration of the host's immune integrity by Cy probably compromises the protection previously established by primary infection." Silva et al. (2012)	immunosuppression; leukopenia; reinfection; IgA; immune integrity
IIC	"We report a case of VAC-induced hepatopathy with coagulopathy and severe inflammation. A 15-year-old male with rhabdomyosarcoma receiving adjuvant chemotherapy presented with refractory thrombocytopenia, followed by abdominal tenderness and non-neutropenic fever. Hepatic dysfunction and coagulopathy subsequently emerged with persistent fever. This condition indicated disseminated intravascular coagulation." Kobayashi et al. (2019)	vincristine; hepatopathy; coagulopathy; inflammation; refractory thrombocytopenia; abdominal tenderness; non-neutropenic fever; hepatic dysfunction; persistent fever; disseminated intravascular coagulation; pro-inflammatory cytokines

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Cyclophosphamide [2].		
DNS	"The introduction of cyclophosphamide caused motor incoordination, learning and memory shortfalls, and expanded AChE and oxidative worry in the hippocampus." (Singh and Kumar, 2019)	Learning impairment; memory impairment; AChE; oxidative imbalance; MDA; CAT; SOD; GPx; GSH; neurodegeneration
Cytomegalovirus [3].		
ICOV	"Cytomegalovirus (CMV), a persistent herpesvirus infection whose prevalence increases with age, is a major modulator of immune function and several observations suggest that infection might act to influence clinical outcome following SARS-CoV-2 infection." Moss (2020)	Cytomegalovirus; CMV; herpesvirus infection; immune function; immune senescence; cardiovascular disorders; metabolic disorders
WIS	"Cytomegalovirus (CMV), a persistent herpesvirus infection whose prevalence increases with age, is a major modulator of immune function and several observations suggest that infection might act to influence clinical outcome following SARS-CoV-2 infection."Cytomegalovirus (CMV) serologic prevalence increases with age, and associates with inflammatory-mediated diseases in the elderly ….Chronic CMV infection in healthy, older adults is associated with indicators of immune dysregulation, both of which correlate to differences in EpiAge."Cytomegalovirus (CMV), a persistent herpesvirus infection whose prevalence increases with age, is a major modulator of immune function and several observations suggest that infection might act to influence clinical outcome following SARS-CoV-2 infection." Poloni et al. (2022)	infectious diseases; inflammatory-mediated diseases; immune dysregulation; CMV seropositive; lymphocytes; CD8 T cells; CD28 negative T cells; CD4/CD8 cell ratios; EpiAge; CD4; numbers of CD4 T cells
IIC	"The infection … brings about a procoagulant response, which is relatively rapid compared to the tissue factor mediated response induced by inflammatory mediators. The time course and the coagulation factor dependency suggest a facilitated interaction of coagulation factors on the surface of infected cells. … Merocyanine 540 staining suggests that CMV infection leads to membrane perturbations." van Dam-Mieras et al. (1992)	cellular procoagulant activity; plasminogen activator inhibitor; PAI-1; urokinase-type plasminogen activator; u-PA; factor X; Merocyanine 540 staining; procoagulant response; tissue factor mediated response; coagulation factor dependency; coagulation factors; infected cells; chromogenic activity; internalization of factor X; internalization of factor Xa; endothelial cell surface; membrane perturbations
DNS	"In the prolonged phase of infection, CMV preferentially infects neuronal cells. Infection of neurons may tend to become persistent by evasion of immune reactions, anti-apoptotic effects and neuron-specific activation of the e1-promoter, presumably causing functional neuronal disorders. It has also been shown that CMV infection in developing brains may become latent in neural immature cells." Tsutsui et al. (2005)	Microcephaly; brain malformation; brain malfunction; Cmv-1; β-galactosidase; IFN-γ, NOS2; NO; e1 gene; NMDAR1; NSE; GFAP; NMDA receptor
Fructose [1].		
ICOV	"High fructose consumption result in SREBPs activation, altered cholesterol and lipid synthesis and may establish an innate immune memory in the cells, leading to severe COVID-19 in patients with obesity." Sohrabi et al. (2021)	inflammation; lipid synthesis; lipid metabolism; cholesterol synthesis; sterol regulatory element binding protein-2; SREBP-2; cytokine storm; SREBPs activation; innate immune memory
WIS	"Our objective was to test this sweetener under and at average concentrations of consumption, evaluating parameters of cytotoxicity, genotoxicity, and immunotoxicity ….Our data showed a reduction in all lymphocyte subfractions evaluated, resulting in a reduction in total lymphocytes, as well as an increase in the DNA damage of cells exposed to fructose ….Although fructose is used globally as a sweetener, its use should be cautious, as our study points out that it has cytotoxic and genotoxic effects ….Fructose is one of the most sold and used sweeteners in the world. We show here that its use must be restricted and used carefully because it can alter the gene expression and also interfere with cellular and genetic metabolism and may even interfere with the immune response." Pasqualli et al. (2020)	cytotoxicity; genotoxicity; immunotoxicity; lymphocyte; $CD4^{+}$; CD8+DNA; gene expression; MAPK8; APTX; TUBGCP3; LST1; genes; genetic metabolism; immune response.
IIC	"These results suggest that the HFD as well as the HCD causes a pre-hypercoagulative state due to the increase in plasma fibrinogen level and activities in other coagulative and fibrinolytic factors." Okazaki et al. (1994)	hyperlipidemia; serum lipids; plasma fibrinogen level; factor XIII activity; antithrombin III; alpha 2-plasmin inhibitor; total cholesterol; free cholesterol; phospholipid; coagulant XIII activity; alpha 2-plasmin inhibitor activity; pre-hypercoagulative state; coagulative; fibrinolytic factors
DNS	"a high fructose intake in the diet evokes biomolecular and metabolic alterations in the hippocampus that are mediated by CML accumulation, involving impairment of Glo-1 activity. Since these alterations can be related to cognitive impairment, dietary fructose can thus represent a feasible risk factor for neurodegeneration onset" Mastrocola et al. (2016)	AGEs; RAGE; glyoxalase; carboxy methyllysine; NF-κB; KHK; CML; Glut-5; Glo-1; GFAP; oxidative metabolism; oxidative stress; ROS; GSH; GSSG; MnSOD; Nrf-2; Keap1; respiratory complexes; NADH; ubiquinone oxidoreductase; succinate dehydrogenase; decyl ubiquinol cytochrome *c* oxidoreductase; cytochrome *c* oxidase; neurodegeneration; gliosis
Glucocorticoids [2].		
ICOV	"Age >50 years and immunosuppression with GC and cyclophosphamide were associated with unfavourable outcomes of COVID-19" Marques et al. (2021)	methylprednisolone; cyclophosphamide; glucocorticoids; inflammatory process
WIS	"Glucocorticoids inhibit the innate immune system of human corneal fibroblast through their suppression of toll-like receptors" Jin et al. (2009)	Toll-like receptors; TLRs; TLR2; TLR4; pIkappaB-alpha proteins; IL-6; IL-8
IIC	"The mechanisms of glucocorticoid-induced hypertension include increased systemic vascular resistance, increased extracellular volume, and increased cardiac contractility." (Aulakh and Singh, 2008)	inflammatory; autoimmune diseases

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Glucocorticoids [2].		
DNS	"chronic GCs exposure increases neuroinflammation via NLRP-1 inflammasome and promotes neuronal degeneration" Hu et al. (2016)	NLRP inflammosomes; MAP2; GR; neuroinflammation; NF-κB; TNF-α; IL-1β; IL-6; IL-18; ASC; MAP2; neurodegeneration; apoptosis; caspase 1; caspase 5; motor deficit
Hemodialysis [2].		
ICOV	"Chronic renal replacement therapy by either a kidney transplant (KTX) or hemodialysis (HD) predisposes patients to an increased risk for adverse outcomes of COVID-19″ Villa et al. (2021)	COVID-1; severe acute respiratory distress syndrome coronavirus 2; SARS-CoV-2
WIS	"Decreased Peripheral Naive T Cell Number and Its Role in Predicting Cardiovascular and Infection Events in Hemodialysis Patients ….HD patients exhibited accelerated T-cell senescence, which was positively related to inflammation. A reduction of naïve T cell could be a strong predictor of CVEs [cardiovascular events] and infection episodes in HD patients." Xiang et al. (2021)	disturbed immune response; T-cell senescence; cardiovascular events; CVEs; systemic inflammation; C-reactive protein; naïve T cell levels; tumor necrosis factor-α; interleukin 6; central memory T cell; T effector memory CD45RA cell; $CD4^+$; $CD8^+$; inflammation; infection
IIC	"results showed an association between fibrinolytic/endothelial cell function and increased inflammatory markers in CKD patients. The increased levels of Ddimer, tPA and inflammatory markers in CKD patients using a CVC, led us to propose a relationship between the type of VA chosen for HD, and the risk of thrombogenesis." Costa et al. (2008)	fibrinolytic/endothelial cell function; inflammatory markers; plasminogen activator inhibitor type-1; PAI-1; tissue plasminogen activator; tPA; D-dimers; C-reactive protein; CRP; soluble interleukin (IL)-2 receptor; s-IL2R; IL-6; serum albumin levels; tPA/PAI-1 ratio; thrombogenesis
DNS	"Recent studies describe the strong graded relation between estimated glomerular filtration rate (eGFR) and cognitive function in CKD patients. The process of conventional hemodialysis may induce recurrent episodes of acute cerebral ischemia, which in turn may contribute to acute decline in cognitive function during dialysis." Murray (2008)	Tau; amyloid β peptide; cystatin C; CSF/plasma albumin ratio; IL-6; homocysteine; APOD-4; β2-microglobulin; microalbumin; cognitive impairment; delirium; stroke; cerebrovascular disease; encephalopathy; neurodegeneration
Herpes simplex virus [3].		
ICOV	"Individuals with more severe COVID-19 exhibited stronger and broader SARS-CoV-2 responses, weaker antibody responses to prior infections, and higher incidence of cytomegalovirus and herpes simplex virus 1, possibly influenced by demographic covariates." Shrock et al. (2020)	humoral responses; severe acute respiratory syndrome coronavirus 2; SARS-CoV-2; epitopes; SARS-CoV-2 proteome; neutralizing antibodies; spike protein; nucleoprotein; peptides; infections; cytomegalovirus; herpes simplex virus 1; antibody responses
WIS	"GADD45gamma Activated Early in the Course of Herpes Simplex Virus 1 Infection Suppresses the Activation of a Network of Innate Immunity Genes ….innate immunity to HSV-1 is normally repressed in unstressed cells and repression appears to be determined by two mechanisms. The first, illustrated here, is through activation by HSV-1 infection of the gene encoding GADD45γ. The second mechanism requires constitutively active expression of LGP2 and HDAC4." She et al. (2019)	stress response gene; GADD45γ; GADD45β; innate immunity; IFI16; IFIT1; MDA5; RIG-I; LGP2; HDAC4
IIC	"The HSV1 (herpes simplex virus type 1) surface has been shown recently to initiate blood coagulation by FVIIa (activated Factor VII)-dependent proteolytic activation of FX (Factor X)." Livingston et al. (2006)	FVIIa; activated Factor VII; proteolytic activation of FX; Factor X; host cell-encoded tissue factor; virus-encoded gC; glycoprotein C; free 125I-ligand; Ca2+; FX; dissociation constant; K(d); gC; soluble recombinant form of gC; sgC; number of binding sites; gC/FX stoichiometry
DNS	"HSV-1 can reach the brain by several mechanisms and modulate numerous key cellular processes, such as apoptosis, autophagy and cellular oxidation suggest that neuron infection with this virus can lead to brain damage because of direct damage to its cells. Furthermore, CNS damage is likely favored by the inflammation of the brain and the secretion of numerous immune-modulatory cytokines in this tissue. Importantly, some studies provide compelling data that suggest close ties between HSV-1 infection of the brain and neurodegenerative diseases" Duarte et al. (2019)	Oct1; HCF-1; LAG-3; TIM-3; PD1; CD160; KLRG-1; ICP22; ICP27; US3; gD; gJ; UL41; UL46; apoptosis; p53; Bax; Bcl-2; BCL-xL; MCL-1; caspase 8; caspase 9; TNFR; c-FLIP; MAPKs; CREB; Akt; amyloid β peptide; autophagy; Beclin-1, Atg5/7; PKR; eIF2α; AMBRA 1; BECN1; TBK1; mitochondrial dysfunction; cytochrome *c* oxidase subunit 1; oxidative Stress; TLRs; 8-OH-dG; HO-1; F4-NP; F2-IP; F-neuroprostanes; F-isoprostanes; 4-HNE; DNA damage; CNS inflammation; TRAF3; IRF3; TYK2; MAVS; TRIF; STAT; TNF-α; IFN-γ; TNF-α; IL-1β; IL-6; IL-8; $CD8^+$ and $CD4^+$ T infiltration; MIP-1α, chemokines; CCL5; CXCL10
High-fat diet [1].		
ICOV	"high-fat diet ….enhance intestinal permeability ….it is very likely that gut microbiome dysbiosis and endotoxemia represent the additional pathophysiological explanation for increased COVID-19 severity in obesity." Belancic (2020)	intestinal lipopolysaccharide (LPS) composition; obesity; immunosilent; immunoinhibitory Bacteroidetes LPS subtypes; proinflammatory LPS; gut microbiome dysbiosis; intestinal permeability; paracellular absorption; chylomicrons; endogenous endotoxin; circulatory system; endotoxemia; lipid A; signaling cascade; proinflammatory pathways; oxidative stress; toll-like receptor 4; TLR4
WIS	"Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection ….type 2 diabetes was induced by administering a high-fat diet ….increased disease severity observed in individuals with MERS and comorbid type 2 diabetes is likely due to a dysregulated immune response, which results in more severe and prolonged lung pathology." Kulcsar et al. (2019)	diabetes; human DPP4; inflammation; inflammatory monocyte/macrophages; $CD4^+$ T cells; Ccl2; Cxcl10; Tnfa; Il6; Il12b; Arg1; Il17a; immune response
IIC	"Short-term high-fat diet intake leads to exacerbation of concanavalin A-induced liver injury through the induction of procoagulation state" Nanizawa et al. (2020)	proinflammatory states; procoagulation states; thromboembolic diseases; non-alcoholic fatty liver disease; NAFLD; nonalcoholic steatohepatitis; NASH; inflammation; coagulation; metabolism; cellular stresses; IFN-γ; TNF-α; IL-10; monocyte chemotactic protein-1; MCP-1; tissue factor; TF; plasminogen activator inhibitor-1; PAI-1 mRNAs; fibrin/fibrinogen; metabolic alterations; endoplasmic reticulum (ER) stresses; liver injury
DNS	"Our data provided evidence regarding the link between HFD and low-grade systemic inflammation, but also inflammation and oxidative stress in the brain cortex. The effect is even more pronounced in the synaptic regions indicating the strong impact of the diet on neuronal plasticity. The oxidative stress depends on the	Triglycerides; cholesterol; leptin; adiponectin; glucose; insulin; oxidative stress; MDA; SOD; GSH; GSSG; succinate; pyruvate; neuroinflammation; TNF-α; IL-1β; mitochondrial impairment; oxidative phosphorylation; synaptic plasticity; BDNF; pCREB/CREB; TrkB

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High-fat diet [1].		
	overproduction of free radicals that is partially due to the impaired mitochondrial functions. Indeed, HFD induces in brain mitochondria a decrease in mild uncoupling, that has the role to maintain mitochondrial membrane potential below the critical threshold for ROS production." Cavaliere et al. (2019)	
Immunotherapy [2].		
ICOV	"Among patients with cancer, current treatment with chemotherapy or immunotherapy was associated with a 2.2-fold increased risk of a positive test" Lee et al. (2021)	cancer; coronavirus disease 2019; chemotherapy; immunotherapy
WIS	"Patients with multiple sclerosis (MS) have a particular vulnerability to infections through their use of immunosuppressive disease-modifying therapies (DMTs). Specific DMTs pose particular risk based on their mechanisms of action (MOA). As a result, patients require individualized approaches to starting new treatments and continuation of therapy. Additionally, vaccinations must be considered carefully, and individuals on long-term B cell–depleting therapies may have diminished immune responses to vaccination, based on preserved T cells and diminished but present antibody titers to influenza vaccines ….Most concerning are immunosuppressive drugs that deplete T cells, B cells, or both such as alemtuzumab, ocrelizumab, ofatumumab, and cladribine. These agents may weaken cellular and humoral immune responses to the virus by eliminating cytotoxic T cells and antibody-producing plasma cells. Therapy that sequesters lymphocytes in lymphoid tissue such as the sphingosine-1 phosphate receptor (S1PR) modulator family of drugs (fingolimod and siponimod among others) causes significant leukopenia and may increase the risk for worse outcomes. Therapy-induced lymphopenia can be compounded by the fact that SARS-CoV-2 infects leukocytes triggering apoptosis, which correlates with a worsened disease course." (Bhise and Dhib-Jalbut, 2021)	infections; B cell; immune responses; T cells; antibody titers; cellular immune response; humoral immune response; antibody-producing plasma cells; lymphocytes; lymphoid tissue; sphingosine-1 phosphate receptor (S1PR) leukopenia; lymphopenia; apoptosis
IIC	"Acquired Coagulopathy With Immune Checkpoint Inhibitors: An Underrecognized Association Between Inflammation and Coagulation" Joseph et al. (2020)	autoimmune cytopenias; hemolysis; coagulation factors; cytokine release; fever; fatigue; disorientation; fever; myalgias; skin rash; abnormal coagulation profile; low fibrinogen levels; D-dimer; ferritin; triglycerides
DNS	"Neurological adverse events are infrequent but highly relevant complications of ICI-therapy as they can lead to long-term disability or death. Compared with central nervous system disorders, symptoms of the peripheral nervous system have been described more often and in more detail. Exhibiting unique characteristics and especially overlapping symptoms, immune-related neuromuscular adverse events seem to define a new disease entity." Mohn et al. (2019)	Immune-related adverse events; PD-1; PD-L1; LAG-3; TIM-3; CTLA-4; CSF protein concentration; CSF cell count; AChR; neuromuscular adverse events; myositis; myopathy
Ionizing radiation [4].		
ICOV	"We discuss how long-term exposure to thousand chemicals in mixtures, mostly fossil fuel derivatives, exposure to particle matters, metals, ultraviolet (UV)–B radiation, ionizing radiation and lifestyle contribute to immunodeficiency observed in the contemporary pandemic, such as COVID-19," Tsatsakis et al. (2020)	chronic diseases; immunotoxicity; allergies; autoimmune diseases; immune deficiency; immunopathological; immunodeficiency
WIS	"Sublethal total body γ irradiation (TBI) of mammals causes generalized immunosuppression, in part by induction of lymphocyte apoptosis. Here, we provide evidence that a part of this immune suppression may be attributable to dysfunction of immune regulation. We investigated the effects of sublethal TBI on T cell memory responses to gain insight into the potential for loss of vaccine immunity following such exposure ….These findings have potential importance as regards the immunologic status of T memory responses in victims of ionizing radiation exposure and apoptosis-inducing therapies." McFarland et al. (2012)	immunosuppression; lymphocyte apoptosis; immune regulation; T cell; MHC class I alloantigen; anti-CD4; anti-CD25; regulatory T cell; T reg; Foxp3+; $CD8^+$; T effector cells; apoptosis
IIC	"RT-upregulated proteins were associated with acute phase, inflammatory response, and complement activation. RT-downregulated proteins were associated with transport and metabolism of lipids (plasma apolipoproteins) and blood coagulation. RT-induced changes were much weaker in prostate cancer patients, which corresponded to differences in acute radiation toxicity observed in both groups. Nevertheless, general patterns of RT-induced sera proteome changes were similar in both of the groups of cancer patients." Widlak et al. (2015)	upregulated proteins; downregulated proteins; RT-upregulated proteins; inflammatory response; complement activation; RT-downregulated proteins; lipid transport; lipid metabolism; plasma apolipoproteins; blood coagulation
DNS	"In the brain, the effect of IR is widely seen in the Hippocampus, a radio-sensitive region of the brain which hosts proliferating progenitor cells (Harada et al., 2014; Pospisil et al., 2015). It has been shown that differentiating cells amalgamated into the hippocampal network leads to apoptosis or dysfunction due to exposure to high doses of irradiation and lead to changes in synaptic protein levels, dendritic complexity, morphology and spine density alterations." Sharma et al. (2018)	Oxidative stress; ROS; H2AX; hypoxia; DNA damage; mitochondrial impairment; protein degradation/aggregation; ECM damage; neuroinflammation; immune activation; IFN-γ; IL-6; IL-2; IL-17; IL-10; TNF-α; ICAM-1; chemokines; CCL2; CCR2; TLRs; HMGB1; E-selectin; amyloid β peptide; cyclin D1; FUS; α-synuclein; neurodegeneration
Iron deficiency [1].		
ICOV	"Anemia was also considered as a risk factor for severity and negative outcomes in patients with SARS-CoV-2 infection." Uta et al. (2022)	Anemia; pregnancy; infection; Low birth weight; prematurity; APGAR scores; iron; folate; blood count; Puerperal infection; emergency c-section; small for gestational age

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Iron deficiency [1].		
WIS	"Iron is necessary for appropriate immunological functions; hence, iron deficiency may hinder cancer immunosurveillance and potentially modify the tumor immune microenvironment, both of which may assist cancer development. This is supported by studies showing that patients with colorectal cancer with iron deficiency have inferior outcomes and reduced response to therapy." Phipps et al. (2021)	Gut luminal iron; colorectal cancer; cancer immunosurveillance; tumor immune microenvironment
IIC	"Controlling the inflammation and managing iron deficiency could lead to reversal of thrombocytosis in IBD patients" Voudoukis et al. (2013)	Thrombocytosis; inflammatory bowel disease; IBD; platelets; mean platelet volume; platelet distribution width; plateletcrit; hematocrit levels; hemoglobulin levels; mean corpuscular volume; red cell distribution width; ferritin levels; soluble transferrin receptor levels; the sTfR-F index; vitamin B12; folate; Thrombocytosis; Crohn's Disease Activity Index; Simple Clinical Colitis Activity Index; C-reactive protein
DNS	"Abnormalities indicating altered liver function, lipid dysregulation, and increased acute phase reactants were present in ID. In CSF, we measured 210 metabolites and 1,560 proteins with changes in ID infants indicative of metabolomic and proteomic differences indexing disrupted synaptogenesis." Sandri et al. (2022)	Brain health; metabolic dysfunction; metabolites; proteins; altered liver function; lipid dysregulation; acute phase reactants; synaptogenesis; hepatic dysfunction; acute phase response
Kidney transplantation [2].		
ICOV	"Liver and kidney transplant recipients have an increased risk of mortality compared with the general population due to COVID-19. More specifically, pediatric patients and those with low albumin levels are at higher risks of death due COVID-19." Ali Malekhosseini et al. (2021)	organ transplantations; fever; cough; myalgia; Dyspnea; oxygen saturation; kidney transplantations; liver transplantations; leukopenia; low albumin levels
WIS	"B lymphocytes are known to play a role in kidney transplantation (KT) outcomes. Here, we evaluated the proportion of B cell subsets before and after KT ….the proportion of immature B cells (CD24(+)CD38(+)/CD19(+) B cells) decreased significantly after transplantation ($P < 0.01$). The levels of IL-10, and IL-21, and expression of the B cell marker BLNK also decreased significantly after transplantation ….Taken together, these results show that while the total B lymphocyte count and the proportion of memory/mature B cell subsets do not change after KT, the proportion of immature B cells and the associated cytokines that they secrete decrease significantly." Chung et al. (2014)	B lymphocytes; peripheral blood mononuclear cells; PBMCs; CD19(+) B cells; leukocyte; CD24(+) lymphocytes; mature B cells; CD24(Int); CD38(Inter); memory B cells; immature B cells; IL-10; IL-21; BLNK; cytokines
IIC	"Ischemia-reperfusion- (IR-) induced kidney injury is difficult to avoid during renal transplantation and robot-assisted partial nephrectomy. Renal IR injury is characterized by tubular damage, microcirculation failure, and inflammation …. Protease-activated receptor-1 (PAR-1) and its ligand, thrombin, are involved in coagulation and were shown to be associated with epithelial cell injury …. Inhibition of PAR-1 ameliorated injury possibly by improving renal microcirculation and tubular cell survival/proliferation." Guan et al. (2021)	renal transplantation; Renal IR injury; tubular damage; microcirculation failure; inflammation; Protease-activated receptor-1; PAR-1; thrombin; coagulation; epithelial cell injury; histopathology; blood cell flow; cell proliferation; apoptosis in the tubules
DNS	"Neurological symptoms are a significant contributor to morbidity and mortality after kidney transplant. Serious neurological complications result in hospitalization, and therefore physicians must be aware of the conditions unique to this population." (Shoskes, Wilson, 2019)	CNS infection; immunosuppression; TNF-α; IL-1; IL-6; IL-8; IFN-γ; calcineurin; calcineurin inhibitor; pain syndrome; electrolyte disturbances; glucose; neuropathy; posterior reversible encephalopathy syndrome
Lead [4].		
ICOV	"The existing data demonstrate that As, Cd, Hg, and Pb exposure is associated with respiratory dysfunction and respiratory diseases (COPD, bronchitis) ….reduction of toxic metal exposure may be considered as a potential tool for reducing susceptibility and severity of viral diseases affecting the respiratory system, including COVID-19." Skalny et al. (2020)	respiratory dysfunction; immunotoxicity; viral diseases; COVID-19; COPD; bronchitis; impaired mucociliary clearance; reduced barrier function; airway inflammation; oxidative stress; apoptosis; influenza; respiratory syncytial virus; adaptive immunity; smoking; particulate pollution; PM2.5; tobacco smoke; respiratory dysfunction; immunotoxicity; viral diseases; respiratory diseases; COPD; bronchitis; reduced barrier function; respiratory system; COVID-20
WIS	"The present study aimed to measure Pb exposure and its immunologic effects in boatyard workers ….The median blood Pb concentration was 8.7-fold higher in workers than controls ….Workers had 8.4% lower phagocytic active cells than controls ….chronic high Pb exposure may cause a shift towards humoral immune response, together with a suppression of cellular immunity, thereby suggesting an elevation in cancer risk in Pb-exposed workers." Pukanha et al. (2020)	immunologic; age; body mass index; blood Pb concentration; phagocytic active cells; peripheral blood mononuclear cells; PBMCs; interleukin-4; IL-4; interferon-γ; cytotoxic T cells; Tc; regulatory T cells; Treg; humoral immune response; cellular immunity; cancer
IIC	"Co-exposure to SiNPs and Pb could aggravate the cardiovascular toxicity via endothelial damage, hypercoagulation, and cardiac injury in vivo." Feng et al. (2018)	heart; aortic arch; abdominal aorta; blood components; fibrinolytic factors; plasmin factors; inflammation-related factors; myocardial-related enzyme in serum; leukocytosis; thrombocytopenia; aspartate aminotransferase; AST; cholesterol; CHO; triglyceride; TG; high-density lipoprotein-cholesterol; HDL-C; low-density lipoprotein-cholesterol; LDL-C; fibrinolytic and plasmin factors; thrombin time; TT; prothrombin time; PT; activated partial thromboplastin time; APTT; tissue-type plasminogen activator; t-PA; tissue factor pathway inhibitor; TFPI; antithrombin III; AT III; human fibrinogen; FIB; D-dimer; D2D; myocardial-related enzyme in serum; atrial natriuretic peptide; brain natriuretic peptide; C-reactive protein; CRP; IL-6; TNF-α; angiotensin II; ANG II; endothelin 1; ET-1; blood vessels

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Lead [4].		
DNS	"Exposure to Pb causes neurotoxicity that ranges from neurodevelopmental disorders to serious neurodegenerative lesions, leading to impairments in learning, memory, and cognitive function" Zhou et al. (2020)	RyR3; intracellular calcium disorder; [Ca2+]i; phospho-CaMKIIα; phospho-CREB; Bcl2; phospho-Erk1/2; NGF; amyloid β peptide; Tau; neurodegeneration; cognitive function; long-term potentiation
Less individual income [5].		
ICOV	"By means of individual-level survival analysis we demonstrate that being male, having less individual income, lower education, not being married all independently predict a higher risk of death from COVID-19 and from all other causes of death. Being an immigrant from a low- or middle-income country predicts higher risk of death from COVID-19 but not for all other causes of death." Drefahl et al. (2020)	male; less individual income; lower education; not being married; immigrant from a low- or middle-income country
WIS	"Small intestine bacterial overgrowth (SIBO) occurs when colonic quantities of commensal bacteria are present in the small bowel ….Recent data show that SIBO is also found in children living in unsanitary conditions who do not have access to clean water ….SIBO also disrupts mucosal immunity and has been implicated in oral vaccination underperformance and the development of celiac disease. SIBO in the setting of the impoverished human habitats may be an under-recognized cause of pediatric morbidity and mortality in the developing world." (Donowitz and Petri, 2015)	Small intestine bacterial overgrowth; SIBO; commensal bacteria; gastrointestinal motility; impaired micronutrient absorption; gastrointestinal permeability; mucosal immunity; celiac disease; pediatric morbidity
IIC	"In a large prospective study of HIV-infected adults, we found a high incidence of hypertension associated with HIV-related inflammation. Baseline hypertension conferred a more than two-fold increased risk of death. Among HIV-infected adults in low-income countries, hypertension should be considered a serious threat to long-term survival." Batavia et al. (2018)	blood pressure; hypertension; inflammation; mortality; low-income country; HIV-infected adults; coagulation; age; BMI; interleukin (IL)-6; Systolic pressure
DNS	"Even though dementia incidence and prevalence are on the rise globally, significant regional differences have been described, with a much stronger increase in low-income vs high-income countries." Perneczky (2019)	Apolipoprotein E; neurodegeneration; dementia; cognitive function
Liver transplantation [2].		
ICOV	"Liver and kidney transplant recipients have an increased risk of mortality compared with the general population due to COVID-19. More specifically, pediatric patients and those with low albumin levels are at higher risks of death due COVID-19." Ali Malekhosseini et al. (2021)	organ transplantations; fever; cough; myalgia; Dyspnea; oxygen saturation; kidney transplantations; liver transplantations; leukopenia; low albumin levels
WIS	"Liver transplantation (LT) is a life-saving strategy for patients with end-stage liver disease, hepatocellular carcinoma and acute liver failure. LT success can be hampered by several short-term and long-term complications. Among them, bacterial infections, especially due to multidrug-resistant germs, are particularly frequent with a prevalence between 19 and 33% in the first 100 days after transplantation ….there is growing evidence of the crucial role of GM in shaping the immune response, both locally and systemically, against pathogens ….we provide an overview of the current understanding on the interplay between gut microbiota and the immune system in liver transplant recipients and the role of the former in infections." Ancona et al. (2021)	end-stage liver disease; hepatocellular carcinoma; acute liver failure; bacterial infections; multidrug-resistant germs; gut microbiota; intestinal homeostasis; gut-liver axis; dysbiosis; chronic hepatitis; fatty liver disease; cirrhosis; hepatocellular carcinoma; immune response; infectious risk; gut microbiota; immune system; infections
IIC	"In the liver transplantation in addition to the operation shock deterioratingly comes the intensive blood contact with the often heavily damaged graft cells, the effectors of the immune system (rejection), the temporary disturbance of the clearance function of the liver RES and the basic disease of the recipient which in most cases disposes to the disseminated intravasal coagulation. The reduction of thrombocytes and coagulation factors extensively transgresses the changes which are to be expected by a weakness of the synthesis during and immediately after the anhepatic phase." Muller et al. (1981)	intoxications; vitamin-K; congenital dysproteinoses; coagulation factors; hepatocyte; shock; tumors; inflammations; sepsis; intoxications; portal hypertension; coagulation system; coagulopathy; operation shock; graft cells; effectors of the immune system; clearance function of the liver RES; intravasal coagulation; thrombocytes; coagulation-activating moments; minimum times of ischemia; anastomoses; disseminated intravasal coagulation
DNS	"Neurological and neurocognitive complications are particularly frequent after LT compared with cardiac or renal transplantation. Apart from certain classical neurological conditions that have to either be rapidly ruled out or adequately treated, some patients display neurocognitive impairment that is likely the result of decompensation of an unknown cerebral condition that was present but ignored prior to LT." (Weiss and Thabut, 2019)	Neurocognitive complication; osmotic demyelination syndrome; hepatic encephalopathy; encephalopathy; brain injury; stroke; CNS infections; delirium glutamate; glutamate + glulamine; choline; N-acetylaspartate; creatine; myoinositol; Glx/Cr ratio
Lower education [5].		
ICOV	"By means of individual-level survival analysis we demonstrate that being male, having less individual income, lower education, not being married all independently predict a higher risk of death from COVID-19 and from all other causes of death." Drefahl et al. (2020)	male; less individual income; lower education; not being married; immigrant from a low- or middle-income country
WIS	"The epidemiological picture of TB showed that ….More than 51% of the cases were in productive age group which affects the socioeconomic condition of family and society. More than 2/3 of patients were from lower socioeconomic group with low BMI. Therefore improving nutrition and immunity can play an important role." Jain et al. (2018)	MDR TB; BMI; undernourished; cough; fever; Dyspnea; Anorexia; chest pain; haemoptysis; anemia; moderate lesion; extensive lesion; immunity

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Lower education [5].		
IIC	"Educational status was linked to higher anger control among men (B = 0.14, p = .001). Significant inverse correlations emerged between education and IL-6, CRP, and fibrinogen (r values ≥ −0.09, p values < 0.004) and between anger control and IL-6 and CRP (r values = −0.07, p values < 0.03)." (Boylan and Ryff, 2013)	educational status; inflammation; coagulation markers; anger questionnaires; interleukin-6 (IL-6); C-reactive protein; CRP; fibrinogen
DNS	"The associations between neuropathological variables and clinical dementia differed according to the 'dose' of education such that more education reduced dementia risk largely independently of severity of pathology." (Bayne et al., 2010)	Dementia; neocortical neuritic plaques; hippocampal neuritic plaques; diffuse plaques; tangles; cerebral amyloid angiopathy; atrophy; lacunes; infarcts; white matter pallor; Braak stage; brain weight; neurodegeneration
Magnesium deficiency [1].		
ICOV	"Magnesium deficiency increases endothelial cell susceptibility to oxidative stress, promotes endothelial dysfunction, reduces fibrinolysis and increases coagulation. Furthermore, magnesium deficient animals and humans have depressed immune responses, which, when supplemented with magnesium, a partial or near full reversal of the immunodeficiency occurs. Moreover, intracellular free magnesium levels in natural killer cells and CD8 killer T cells regulates their cytotoxicity. Considering that magnesium and vitamin D are important for immune function and cellular resilience, a deficiency in either may contribute to cytokine storm in the novel coronavirus 2019 (COVID-19) infection." (DiNicolantonio and O'Keefe, 2021)	immune system; cytokine storm; coagulation cascade; COVID-19; infections; upper respiratory tract infections; pulmonary epithelial; oxidative stress; endothelial cell; endothelial dysfunction; fibrinolysis; coagulation; immune responses; immunodeficiency; intracellular free magnesium; natural killer cells; CD8 killer T cells; cytotoxicity; immune function; cellular resilience
WIS	"Chronic Mg deficiency may result in increased oxidative stress and low-grade inflammation, which may be linked to several age-related diseases, including higher predisposition to infectious diseases. Mg might play a role in the immune response being a cofactor for immunoglobulin synthesis and other processes strictly associated with the function of T and B cells. Mg is necessary for the biosynthesis, transport, and activation of vitamin D, another key factor in the pathogenesis of infectious diseases. The regulation of cytosolic free Mg in immune cells involves Mg transport systems, such as the melastatin-like transient receptor potential 7 channel, the solute carrier family, and the magnesium transporter 1 (MAGT1)." Dominguez et al. (2021)	oxidative stress; inflammation; immune response; immunoglobulin synthesis; T cells; B cells; immune cells; melastatin-like transient receptor potential 7 channel; magnesium transporter 1; MAGT1; primary immunodeficiency XMEN; X-linked immunodeficiency with Mg defect; Epstein-Barr virus infection; neoplasia; immune system; infectious diseases
IIC	"Some of the critical mechanisms that mediate chronic kidney disease (CKD) progression are associated with vascular calcifications, disbalance of mineral metabolism, increased oxidative and metabolic stress, inflammation, coagulation abnormalities, endothelial dysfunction, or accumulation of uremic toxins. Also, it is widely accepted that pathologies with a strong influence in CKD progression are diabetes, hypertension, and cardiovascular disease (CVD). A disbalance in magnesium (Mg) homeostasis, more specifically hypomagnesemia, is associated with the development and progression of the comorbidities mentioned above, and some mechanisms might explain why low serum Mg is associated with negative clinical outcomes such as major adverse cardiovascular and renal events. Furthermore, it is likely that hypomagnesemia causes the release of inflammatory cytokines and C-reactive protein and promotes insulin resistance …. Mg deficiency worsens kidney injury induced by an increased tubular load of phosphate. One important consequence of excessive tubular load of phosphate is the reduction of renal tubule expression of α-Klotho in moderate CKD. Low Mg levels worsen the reduction of Klotho induced by the tubular load of phosphate." Rodelo-Haad et al. (2020)	vascular calcifications; mineral metabolism; oxidative stress; metabolic stress; inflammation; coagulation; endothelial dysfunction; uremic toxins; diabetes; hypertension; cardiovascular disease; CVD; magnesium (Mg) homeostasis; hypomagnesemia; inflammatory cytokines; C-reactive protein; insulin resistance; coronary artery calcifications; peripheral vasodilation; Wnt/β-catenin signaling pathway; tubular load of phosphate; α-Klotho; CKD; Klotho; phosphate
DNS	"Acute Mg deficiency leads to metabolic encephalopathy and alteration of neuromuscular excitability, such as deprementia and nervousness. By contrast, chronic Mg deficiency is characterized by spasm. Although the potential role of Mg in neurological diseases has been established for decades, the clinical arena of translation is difficult to isolate (3). Mg deficiency leads to neurological disorders ranging from apathy to psychosis. Moreover, Mg has an effect on the regulation of synaptic plasticity" Xue et al. (2019)	Cerebral vasospasm; stroke; inflammation; NMDA receptor; oxidative stress; Tau; aspartate; α-synuclein; cognitive decline; amyloid β peptide; 5-HT; NO; substance P; calcitonin gene-related peptide
Malnutrition [1].		
ICOV	"Elderly individuals and patients with comorbidities such as obesity, diabetes, and hypertension show a higher risk of hospitalization, severe disease, and mortality by acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. These patients frequently show exacerbated secretion of proinflammatory cytokines associated with an overreaction of the immune system, the so-called cytokine storm. Host nutritional status plays a pivotal role in the outcome of a variety of different infectious diseases. It is known that the immune system is highly affected by malnutrition, leading to decreased immune responses with consequent augmented risk of infection and disease severity." Silverio et al. (2021)	COVID-19; obesity; diabetes; hypertension; proinflammatory cytokines; immune system; cytokine storm; infectious diseases; malnutrition; immune responses; Body composition; low lean mass; high adiposity; nutritional status; viral infection
WIS	"MN [malnutrition] is associated with hyperinflammation and immunosuppression in COVID-19 patients, and it may contribute to disease progression." Liu et al. (2021)	inflammatory response; immune response; Serum cytokines; T-cell subpopulations; interleukin 6; IL-6; IL-4; IL-10; $CD8^+$ T cells; hyperinflammation; immunosuppression
IIC	"Long-term sustained stress (starvation) leads to sustained chronic inflammatory state, and stimulated the release of related inflammatory factors and activation of the coagulation system after infection." Li et al. (2019)	weight of body; weight of thymus; weight of spleen; spleen; $CD3^+$T lymphocytes; $CD4^+$T lymphocytes; M1 macrophages; IL-6; Kaplan-Meier survival analysis; mRNA; TF; PAI-1; liver; IL-10

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Malnutrition [1].		
DNS	"Malnutrition is associated with cognitive impairment or functional loss, but it is also known that an inadequate nutritional status predisposes to cognitive frailty. Additionally, nutritional factors that may influence vascular risk factors will potentially have an effect on dementia decline among patients with cognitive frailty." (Gomez-Gomez and Zapico, 2019)	ROS; RNS; α-synuclein; amyloid β peptide; ADAM10; BACE-1; Erk; JNK; PI3K; Akt; N-SMase; ceramide; oxidative phosphorylation system; inflammation; COX-2; 5-LOX; NADPH oxidase; PP2A; cognitive frailty; dementia; α/β-secretase
Maternal smoking [1].		
ICOV	"Maternal smoking was positively associated with COVID-19 infection" Didikoglu et al. (2021)	maternal smoking; birth weight; birth month; breastfeeding; COVID-19 infection; lower birthweight
WIS	"these results provide evidence for association of inflammation with PPE and strong correlation of smoking with inflammatory signatures in PPE." Zhao et al. (2021)	hypertension; proteinuria; organ damage; soluble fms-like tyrosine kinase 1; sFlt1; soluble endoglin; sEng; maternal immune system; inflammation; IL-6; IL-35; TNF-α; IL-10; MMP-12; TLR4; HMGB-1; iNOS; Foxp3; CD56
IIC	"We discovered a statistically significant decrease in factor II and protein S levels and an elevation in t-PA and factor VIII concentrations in newborns of smoking mothers, without clinical manifestations of altered haemostasis. There were no significant differentiations in other coagulation or fibrinolytic parameters." Mitsiakos et al. (2009)	coagulation; fibrinolysis; inflammation; fibrinogen synthesis; clotting factors; neonatal haemostasis; Blood samples; PT; INR; aPTT; fibrinogen; coagulation factor II; coagulation factor V; coagulation factor VII; coagulation factor VIII; coagulation factor IX; coagulation factor X; coagulation factor XI; coagulation factor XII; vWillebrand factor; vWF; protein C; protein S; APCr; anti-thrombin; AT; t-PA; PAI-1; coagulation; fibrinolytic
DNS	"maternal smoking during pregnancy may disrupt pathways relevant in neurodevelopment, and potentially influence risk of neuropsychiatric disease in offspring—particularly autism spectrum disorder." Semick et al. (2020)	Neuroteratogenic effects; neuropsychiatric disorders; CNTN4; EPHA8; KCNN2; MARCO; GABRA4; NRCAM; TENM3; SDC1; CNTN4; CHSY3; ZNF608; CEP85; IL1RAPL2
Mercury [4].		
ICOV	"The existing data demonstrate that As, Cd, Hg, and Pb exposure is associated with respiratory dysfunction and respiratory diseases (COPD, bronchitis) ….reduction of toxic metal exposure may be considered as a potential tool for reducing susceptibility and severity of viral diseases affecting the respiratory system, including COVID-19." Skalny et al. (2020)	respiratory dysfunction; immunotoxicity; viral diseases; COVID-19; COPD; bronchitis; impaired mucociliary clearance; reduced barrier function; airway inflammation; oxidative stress; apoptosis; influenza; respiratory syncytial virus; adaptive immunity; smoking; particulate pollution; PM2.5; tobacco smoke; respiratory dysfunction; immunotoxicity; viral diseases; respiratory diseases; COPD; bronchitis; reduced barrier function; airway inflammation; respiratory system; COVID-19
WIS	"toxicity produced by Hg can lead to disruption of immune processes and related pathological conditions linked to this system. Many harmful outcomes of Hg have been reported above the specific range of the Hg that is toxic to human health. Previously performed animal modeling studies, such as on different strains of mouse, highlight immunotoxic effects of Hg at the gene expression level" Maqbool et al. (2017)	toxicity; immunotoxic; genotoxic; carcinogenic; teratogenic
IIC	"Frequent vaccinations with live virus and toxic mercurial content (thimerosal) are a plausible etiologic factor. … Immune system abnormalities encompass derangement of antibody production, skewing of T cell subsets, aberrant cytokine profiles, and other impairments consistent with chronic inflammation and autoimmunity. Coagulation abnormalities have been reported." Kidd (2002)	Autism; autistic spectrum disorders; ASD; neurodevelopmental disorder; metallothionein impairment; sulfur metabolism impairments; intestinal lining integrity; dysbiosis; food intolerances; exorphin (opioid) intoxication; casein; gluten; Immune system; antibody; T cell subsets; cytokine profiles; chronic inflammation; autoimmunity; Coagulation
DNS	"Mercury can alter neurobiological processes such as synaptic transmission, causing neuronal damage through overactivation of NMDA (N-methyl-D-aspartate) receptors … … Mercury was also largely investigated for toxic and neurotoxic characteristics of its organic methylmercury form and for its implication in intracellular abnormal protein accumulation and in inflammatory processes that occur in neurodegenerative disease such as AD, PD, ALS, and MS." Cariccio et al. (2019)	CNS damage; neurotoxicity; methylmercury; NMDA receptor; oxidative stress; ROS; SOD; GPx, GSH; TrXR; α-synuclein; amyloid β peptide; Tau; SOD1; ND1; Cytb; ATP6; D-Loop; glutamate; apoptosis; AIF; cytochrome C; APAF-1; caspase 3; caspase 9; Bax; Bcl-2; c-Fos; BDNF; CREB; MAPKs; PARKs; DJ-1; apoliprotein E; tubulin; Na/K ATPase dysfunction
Methyl bromide [4].		
ICOV	"All the 4 variables that were significant in both sets in Phase 1 remained statistically significant in Phase 2, including two air toxicants (i.e., nitrogen dioxide or NO2, and benzidine) …. This external ExWAS of county-level COVID-19 mortality in the contiguous US provides new insights into the role of long-term exposures to the external exposome in COVID-19 mortality. We confirmed a previously reported association (i.e. NO2), and identified novel environmental factors associated with COVID-19 mortality, including air toxicants (i.e., methyl bromide, benzidine, and chloroform)" Hu et al. (2021a)	external exposome; nitrogen dioxide; NO2; benzidine; vacant land measure; food environment measure
WIS	"Background: Some pesticides are immunotoxic and have been associated with an increased risk of immune-mediated diseases. The risk of shingles, the clinical reactivation of varicella-zoster virus, increases with aging and immunosuppression ….Incident shingles was reported by 590 participants. Associations were positive (HRs>1.2) for ….methyl bromide ….in older participants, shingles was associated with a history of a high pesticide exposure event" Parks et al. (2021)	immunotoxic; immune-mediated diseases; shingles; varicella-zoster virus; immunosuppression
IIC	"1-methyl-3-octylimidazolium bromide ([C8mim]Br) … the present study indicates that chronic exposure to [C8mim]Br induces inflammation in fish spleen and that oxidative stress-mediated p38MAPK/NF-κB signalling and miRNAs may play a key role in this process." Ma et al. (2019)	superoxide dismutase; SOD; catalase; CAT; glutathione peroxidase; GPx; glutathione; GSH; malondialdehyde; MDA; protein carbonyl; PC; spleen; oxidative stress; nuclear factor-κB; NF-κB; inducible nitric oxide synthase; iNOS; interleukin-1β; IL-1β; IL-6; tumour necrosis factor-α; TNF-α; interferon-γ; IFN-γ; transforming growth factor-β; TGF-β; mRNA; p38MAPK; c-fos; c-jun; c-myc; p38MAPK/NF-κB signalling; lysozyme activity; complement 3; C3; immunoglobulin M; IgM; immunotoxic; miR-125b; miR-143; miR-155; miR-21; inflammation; oxidative stress

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Methyl bromide [4].		
DNS	"Acute MB intoxication mainly involves the central nervous system (CNS) and is often related with poor outcome such as coma and seizures(6). Chronic intoxication includes syndrome in acute exposure plus visual and hearing disorders, axonal polyneuropathy, ataxia and psychological symptoms" (Suwanlaong and Phanthumchinda, 2008)	Serum methyl bromide; neuropsychiatric disturbances; ataxic gait; cerebellar sign impairment; hyperactive reflex impairment; abnormal hypersignal intensity; catecholamines; tyrosine hydroxylase
Methylprednisolone [2].		
ICOV	"High levels of immunosuppression with methylprednisolone or cyclophosphamide pulse therapy and chronic oral GC were associated with unfavourable outcomes of the SARS-CoV-2 infection" Marques et al. (2021)	methylprednisolone; cyclophosphamide; glucocorticoids; inflammatory process
WIS	"Drug-induced immune thrombocytopenia (DITP) is a rare but severe drug side effect caused by antibodies that bind platelets only in the presence of a drug. Drug-dependent antibodies (DDabs) usually target platelet-specific glycoproteins (Gp), such as GpIIb/IIIa or GpIb/IX.1, 2 About a 100 different drugs have been linked to DITP.3 Immune severe thrombocytopenia occurs quickly after the administration of the drug, following an extended period of well-tolerated drug administration, and resolves within 1–10 days after drug withdrawal. We describe six patients who experienced severe thrombocytopenia due to methylprednisolone (MP) DITP." Dubert et al. (2020)	immune thrombocytopenia; DITP; antibodies; platelets; Drug-dependent antibodies; DDabs; platelet-specific glycoproteins; GpIIb/IIIa; GpIb/IX; Immune severe thrombocytopenia
IIC	"Incidence of acute spinal cord injury and associated complications of methylprednisolone therapy: a national population-based study in South Korea" Choi et al. (2020)	acute spinal cord injury; SCI; high dose methylprednisolone; pneumonia; GI bleeding; UTI
DNS	"MP reduces the inhibitory effect of GABA while augmenting the excitatory effect of glutamate. By reducing the inhibitory effect of GABA, MP can reduce the inhibitory synaptic input to the postsynaptic cell, causing neuronal hyperexcitability (Figure 10B). By augmenting the excitatory effect of glutamate, MP can increase the excitatory synaptic input to the postsynaptic cell, also causing neuronal hyperexcitability (Figure 12B). This dual action of MP can induce excitotoxicity, which in turn, can explain MP's neurotoxic action." Foroutan et al. (1996)	Neurotoxicity; brain aging; neuronal hyperexcitability; synaptic activity; sEPSCs; sIPSCs; GABA; GABA A subtype; GABA channel; GABA-gated currents; glutamate; glutamate chennel; NMDA; AMPA; kainite; metabotropic receptor subtypes; Ca2+
Monoclonal antibodies [2].		
ICOV	"Patients receiving monoclonal antibody-based therapy had a significantly greater (HR 2.02) risk of death vs those not receiving active antineoplastic treatment, while those receiving active conventional chemotherapy were 50% more likely to die from COVID-19." Garcia-Suarez et al. (2020)	hematologic malignancies; immunosuppression; respiratory viral infections; solid tumors; all-cause mortality; acute myeloid leukemia; non-Hodgkin lymphoma; monoclonal antibodies; Ph-negative myeloproliferative neoplasms; hypomethylating agents; antiviral therapy; higher age
WIS	"activated immune responses, by monoclonal antibodies, can target nonspecific cancer cells, causing frequent immune-related adverse events that can lead to permanent disorders among cancer patients. The immune-related adverse events pose a risk of cardiac toxicity that includes hypertension, heart failure, arrhythmias, and left ventricular dysfunction during and after monoclonal antibody immunotherapy." Kumar et al. (2021)	cancer; chimeric antigenic receptor T-cells; inflammation; cardiac immune modulation; cardiac failure; cardiotoxicity; pluripotent stem cell-derived cardiomyocytes; cardiac-stromal progenitor cells; cardiac organoid cultures
IIC	" … 10 patients (12%) developed diseases associated with the disorder of coagulation-fibrinolysis system. … occurred in patients with high PD-L1 expression and in the early period of ICI initiation. … high tumor responses (72%) were observed, … demonstrate T-cell activation strongly induces production of a primary initiator of coagulation, tissue factor in peripheral PD-L1high monocytes, in vitro. This study suggests a previously unrecognized pivotal role for immune activation in triggering disorders of the coagulation-fibrinolysis system in cancer patients during treatment with ICI." Sato et al. (2019)	immune checkpoints; immune homeostasis; coagulation-fibrinolysis system; clotting; bleeding; tumor PD-L1 expression; PD-L1; ICI initiation; T-cell activation; tissue factor; peripheral PD-L1^{high} monocytes
DNS	"immune complexes formed by Aβ oligomers or other oligomeric/multimeric antigens and their specific antibodies can cause death and loss of neurons in primary neuronal-glial cultures via Fc-dependent microglial activation." Morkuniene et al. (2013)	Neurotoxicity; microglia activation; amyloid β peptide; Fcγ receptors; inflammation; TNF-α
Mycotoxins [3].		
ICOV	"Our findings suggest that mycotoxin could influence the prevalence of coronavirus and provide new ideas for the prevention and control of coronavirus." Liu et al. (2020b)	toxic metabolites; mycotoxinsIPEC-J2 cells; porcine epidemic diarrhea virus; PEDV; diarrhea rates; gut barrier injury; autophagosome-like vesicles; autophagy-related proteins; CRISPR-Cas9; LC3B; p38 signaling inhibitor
WIS	"People exposed to molds and mycotoxins present with symptoms affecting multiple organs, including the lungs, musculoskeletal system, as well as the central and peripheral nervous systems. Furthermore, evidence has recently implicated exposure to mycotoxins in the pathogenesis of autism spectrum disorder. The effects of mycotoxins can be mediated via different pathways that include the secretion of pro-inflammatory cytokines, especially from mast cells ….exposure to mold and mycotoxins can affect the nervous system, directly or through immune cell activation, thus contributing to neurodevelopmental disorders such as autism spectrum disorder." Ratnaseelan et al. (2018)	immunity; inflammation; Alzheimer's; autism; allergies; asthma; autism spectrum disorder; pro-inflammatory cytokines; mast cells; immune cell activation

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Mycotoxins [3].		
IIC	"Twenty-three male lambs were intoxicated with 2.5 ppm aflatoxins in their feed for a period of 3 weeks. … An increase ($P < 0.05$) in fibrinogen concentration was detected beginning on d 21, instead of the expected decrease. This was probably due to the inflammation found in the lungs of the intoxicated animals. … These results suggest that there was a significant change in some coagulation factors of the extrinsic pathway in the intoxicated lambs … " Fernandez et al. (1995)	coagulation; prothrombin time; fibrinogen concentration; inflammation
DNS	"Mycotoxins, including T-2 toxin and DON, cause neurotoxicity and cognitive impairment based on pathological changes in the nervous system. The neurotoxic mechanism(s) of T-2 toxin and DON are related to changes in neurotransmitters, abnormal lipid peroxidation, changes in gene expression, impaired signal transduction pathways, and neuronal apoptosis. These toxins affect nervous system function through many mechanisms and even lead to cognitive impairment and neurodegenerative diseases" Zhang et al. (2020b)	CaM; 5-HT; MMPs; oxidative stress; MDA; protein carbonyl; SOD; GPx; Nrf-2; HO-1; hypoxia-inducible factors; immune evasion; central neuroinflammation; NO; TNF-α; COX-2;; IL-1β; IL-6; PBCEC; IGF-BP3; Hsp70; mitochondrial dysfunction; apoptosis; p53; caspase 2; caspase 3; PARP; MAPKs; MAO; Ras; brain dopamine; astrocyte and microglia viability; neurodegeneration; amyloid β peptide; necrosis
Nanoparticles [4].		
ICOV	"MMC residents with pre-SARS-CoV-2 accumulation of misfolded proteins diagnostic of AD and PD and metal-rich, magnetic nanoparticles damaging key neural organelles are an ideal host for neurotropic SARS-CoV-2 RNA virus invading the body through the same portals damaged by nanoparticles: nasal olfactory epithelium, the gastrointestinal tract, and the alveolar-capillary portal." Calderon-Garciduenas et al. (2020)	Alzheimer's disease; Parkinson's disease; SARS-CoV-2 neurotropic RNA virus; neurological complications; neuroinflammatory; neurodegenerative; misfolded proteins; metal-rich, magnetic nanoparticles; nasal olfactory epithelium; gastrointestinal tract; alveolar-capillary portal; suicide; mental disease
WIS	"burning coal generates large quantities of otherwise rare Magnéli phase titanium suboxides from TiO2 minerals naturally present in coal. These nanoscale Magnéli phases are biologically active without photostimulation and toxic to airway epithelial cells in vitro and to zebrafish in vivo. Here, we sought to determine the clinical and physiological impact of pulmonary exposure to Magnéli phases using mice as mammalian model organisms ….macrophages are the cell type most impacted by exposure to these nanoscale particles. Following phagocytosis, macrophages fail to properly eliminate Magnéli phases, resulting in increased oxidative stress, mitochondrial dysfunction, and ultimately apoptosis. In the lungs, these nanoparticles become concentrated in macrophages, resulting in a feedback loop of reactive oxygen species production, cell death, and the initiation of gene expression profiles consistent with lung injury within 6 weeks of exposure. Chronic exposure and accumulation of Magnéli phases ultimately results in significantly reduced lung function impacting airway resistance, compliance, and elastance. Together, these studies demonstrate that Magnéli phases are toxic in the mammalian airway" McDaniel et al. (2019)	airway epithelial cells; titanium concentrations; lung pathology; bone marrow derived macrophages; phagocytosis; oxidative stress; mitochondrial dysfunction; apoptosis; reactive oxygen species production; cell death; gene expression profiles; lung injury; lung function; airway resistance; airway compliance; airway elastance
IIC	"our data demonstrated that SiNPs could induce inflammation-coagulation response and thrombotic effects via JAK1/TF signaling pathway." Duan et al. (2018)	vascular endothelial damage; inflammation-coagulation response; thrombotic; endothelial cells; zebrafish embryos; mitochondria; autophagosome; cytoskeleton organization; vascular endothelial cells; proinflammatory cytokines; procoagulant cytokines; IL-6; IL-8; MCP-1; PECAM-1; TF; vWF; neutrophil; inflammation; blood flow; blood velocity; hypercoagulable; erythrocyte aggregation; JAK1/TF signaling pathway; il6st; jak1; f3b; il6st knockdown groups
DNS	"Research indicated that these nanomaterials (NMs) not only reach the brain, but also can cause a certain degree of brain tissue damage, including cytotoxicity, genotoxicity, induction of oxidative stress, and inflammation, all potentially involved in the onset and progression of neurodegeneration. Surface chemistry of the NMs may play an important role in their localization and subsequent effects on the brain of rodents. In addition, NM shape differences may induce varying degrees of neurotoxicity." Migliore et al. (2015)	Neurotoxicity; AChE; amyloid β peptide; apoptosis; caspase 9; caspase 8; Bcl-2; GFAP; neuroinflammation; NF-κB; TNF-α; PGE-2; COX-2; IL-6; IL-1β; IL-10; iNOS; 5-HT; MMP-9; MIP-1α; MCP-1; AP-1; oxidative stress; HO-1; Nrf-2; GSH; GPx; SOD; MDA; LDH; JNK; Park2; Txnrd1; neurodegeneration
Nitrate [4].		
ICOV	"Oxidative stress and NO contribute to this cycle, establishing a cascade inflammatory state that can kill the patient. … Nitrite, nitrate (the metabolites of NO), … Nitrite, nitrate, methemoglobin, and oxidative stress were significantly increased in patients in comparison to healthy individuals. … In conclusion, NO, methemoglobin and oxidative stress may play a central role in the pathogenesis of critical COVID-19 disease." Alamdari et al. (2020)	severe acute respiratory syndrome; hypoxia; macrophages; inflammatory molecules; nitric oxide; NO; Oxidative stress; Nitrite; nitrate; methemoglobin; prooxidant-antioxidant-balance levels; cytokine cascade syndrome
WIS	"Positive associations existed (bivariate fit) between higher nitrate exposure and body mass index, lower recreational activity, perceived poorer health, and perceptions of susceptibility to illness. A directly proportionate relationship was seen between methemoglobin level in the blood and nitrate ingestion. High tumor necrosis factor-beta (TNF-beta) expression was also seen (bivariate fit, $f = 3.76$, $p = .05$). Complaints of stomach/intestinal difficulties (heartburn/reflux >50%; $f = 5.274$, $p = .0231$) and bone, muscle, and nerve complaints (osteoarthritis [rheumatoid excluded] = 47%; $f = 6.0533$, $p = .0150$) were found with increasing nitrate exposure." Zeman et al. (2011)	hemoglobin fractions; body mass index; lower recreational activity; methemoglobin level; tumor necrosis factor-beta; TNF-beta; heartburn; reflux; osteoarthritis; bone/joint disorders; Th2/Treg cytokine interleukin-10

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Nitrate [4].		
IIC	"Our results provided evidence that some constituents in PM2.5 (OC, EC, NO3-, SO42-, and NH4+) might play crucial roles in inducing systematic inflammation and coagulation, but their roles varied by the selected biomarkers." Liu et al. (2017)	inflammatory biomarkers; fibrinogen; C-reactive protein; monocyte chemoattractant protein-1; tumor necrosis factor-α; interleukin-1b; intercellular adhesion molecule-1; P-selectin; vascular cell adhesion molecule-1; coagulation; plasminogen activator inhibitor-1; soluble CD40 ligand
DNS	"a decrease of nitrate in CSF of PD, MSA and AD patients may reflect a diminished production of the neurotransmitter NO. This may be involved in the pathophysiology of these neurodegenerative diseases." Kuiper et al. (1994)	Neurotoxicty; CSF nitrate; CSF nitrite; NO; NOS; ROS; tetrahydrobiopterin; L-arginine; microglial activation; neurodegeneration
Nitric oxide [4].		
ICOV	"The markers of poor air quality, such as NO and SO2 were associated with an increased rate of COVID-19 related deaths across England" (Ali and Islam, 2020)	air pollution; PM2.5; nitrogen dioxide; NO2; PM10; SO2; CO; O3; age; pre-existing medical conditions
WIS	"Elevated nitric oxide (NO) has been associated with destructive periodontal disease …. exogenous NO may suppress a protective T helper 1-like murine immune response to A. actinomycetemcomitans LPS by an endogenous NO-independent but a cyclic GMP-dependent mechanism." Sosroseno et al. (2009)	immunized; immunoglobulin G; IgG; interferon-gamma; IFN-gamma; interleukin-4; IL-4; splenic inducible nitric oxide synthase; iNOS; skin lesions; T helper 1; immune response
IIC	"Correlation analysis suggests that the serum NO level is positively correlated with IL-17 ($p < 0.05$). Conclusions: The increased levels of NO and IL-17 may be related to dysregulated lymphocytes' immune response in children with influenza A viral pneumonia. These abnormalities may be the main cause of inflammatory lung damage," Zhao et al. (2015)	peripheral blood lymphocytes; nitric oxide; NO; cytokines; NO level; nitrite; NO2; IFN-γ; IL-17; $CD3^+$, $CD3^+CD4^+$ T lymphocytes; $CD56+CD16^+$; natural killer cells; $CD3^+CD8^+$ T lymphocytes; $CD4^-CD8^-$ T lymphocytes
DNS	"a major role for lipid peroxidation alterations in cerebral cortex of AD patients and showed not only a decrease in nitrite/nitrate levels in frontal cortex of AD cases in relation to young and old individuals, but also a reduction in these nitric oxide metabolites in the other cortical areas as related to young controls." Miranda et al. (2000)	Brain nitrate; brain nitrite; NO; NMDA; NMDA receptor; MDA; TBARS; polyunsaturated acid; ROS; SOD; GPx; DNA damage
Nitrite [4].		
ICOV	Oxidative stress and NO contribute to this cycle, establishing a cascade inflammatory state that can kill the patient. … Nitrite, nitrate (the metabolites of NO), … Nitrite, nitrate, methemoglobin, and oxidative stress were significantly increased in patients in comparison to healthy individuals. … In conclusion, NO, methemoglobin and oxidative stress may play a central role in the pathogenesis of critical COVID-19 disease. Alamdari et al. (2020)	severe acute respiratory syndrome; hypoxia; macrophages; inflammatory molecules; nitric oxide; NO; Oxidative stress; Nitrite; nitrate; methemoglobin; prooxidant-antioxidant-balance levels; cytokine cascade syndrome
WIS	"Nitrite is a major environmental pollutant in aquatic environments that negatively affects aquatic species ….These results indicated that nitrite exposure altered the blood physiological status and immune system response, resulting in dysfunction and immunotoxicity in *T. rubripes*." Gao et al. (2020)	immune responses; total protein; albumin; glutamic-oxaloacetic transaminase; glutamic-pyruvic transaminase; complement C3; complement C4; immunoglobulin; lysozyme activity; mRNA; heat shock protein 70; heat shock protein 90; tumor necrosis factor α; B-cell activating factor; interleukin-6; interleukin-12; immunotoxicity
IIC	"Glycyrrhizic acid ameliorates sodium nitrite-induced lung and salivary gland toxicity: Impact on oxidative stress, inflammation and fibrosis" Elsherbini et al. (2021)	body organs; lung; submandibular salivary gland; SMG; oxidative stress; histopathological changes; fibrosis; MTC; TGF-β; α-SMA; inflammation; TNF-α; IL-1β; CD-68; MDA levels; collagen deposition; macrophages; pulmonary and salivary morphological changes
DNS	"This study investigated the neurotoxicity of three representative alkyl nitrites (isobutyl nitrite, isoamyl nitrite, and butyl nitrite), and whether it affected learning/memory function and motor coordination in rodents ….All tested alkyl nitrites lowered the rodents' capacity for learning and memory, as assessed by both the acquisition and retention tests ….Collectively, our findings suggest that alkyl nitrites may induce neurotoxicity, especially on the aspect of learning and memory function." Cha et al. (2016)	recreational drugs; central nervous system; neurotoxicity; alkyl nitrites; learning/memory function; motor coordination; memory acquisition; memory retention;
Nitrofurantoin [2].		
ICOV	"the effect of commonly used medications on the expression of SARS-CoV-2 receptor, angiotensin-converting enzyme (ACE)2, and TMPRSS2 protein in kidney tissues was evaluated. This was done by in silico analyses of publicly available transcriptomic databases of kidney tissues of rats treated with multiple doses of commonly used medications. Of 59 tested medications, 56% modified ACE2 expression, whereas 24% modified TMPRSS2 expression. ACE2 was increased with only a few of the tested medication groups, namely the renin-angiotensin inhibitors, such as enalapril, antibacterial agents, such as nitrofurantoin, and the proton pump inhibitor, omeprazole" Sharif-Askari et al. (2020)	respiratory system; severe acute respiratory syndrome-coronavirus 2; kidneys; kidney cells; SARS-CoV-2 receptor; angiotensin-converting enzyme (ACE)2; TMPRSS2 protein; kidney tissues; renin-angiotensin inhibitors
WIS	"Nitrofurantoin-induced immune-mediated liver injury is a particularly serious complication, resulting in both acute hepatic failure and cirrhosis" Hydes et al. (2014)	urinary tract infections; immune-mediated liver injury; acute hepatic failure; cirrhosis
IIC	"Systemic Inflammatory Response Syndrome Secondary to Nitrofurantoin" McGarry et al. (2021)	gastrointestinal complaints; systemic inflammatory response syndrome-like reaction; urinary tract infections

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Nitrofurantoin [2].		
DNS	"nitrofurantoin was associated with a sensorimotor peripheral neuropathy, first as paresthesias and dysesthesias beginning in the distal extremities and ascending bilaterally in a 'stockingglove' distribution. Only one report of an associated retrobulbar neuritis implicated the drug in cranial nerve disturbances." (D'Arcy, 1985)	Polyneuropathy; polyneuritis; paresthesias; dysesthesias; vitamin B1; folic acid; creatinine; urea
Nitrogen dioxide/NO2/NO(2) [4].		
ICOV	"five regions show the highest NO2 concentrations combined with downwards airflow which prevent an efficient dispersion of air pollution. These results indicate that the long-term exposure to this pollutant may be one of the most important contributors to fatality caused by the COVID-19 virus in these regions and maybe across the whole world." Ogen (2020)	Nitrogen dioxide; NO2; hypertension; diabetes; heart; cardiovascular diseases; coronavirus fatality
WIS	"The objective of this study was to determine whether exposure to NO2, a common indoor air pollutant, modulates immune responses to HDM and influences immune-mediated lung disease ….exposure to a common air pollutant can upregulate specific immune responses and subsequent immune-mediated pulmonary inflammation." Gilmour et al. (1996)	Immune hypersensitivity; respiratory allergy; immune responses; immune-mediated lung disease; immunization; antigen-specific serum IgE; local IgA; IgG; IgE; inflammatory cells; Lymphocyte responsiveness; antigen
IIC	"Particle number, black carbon, NO(2), CO, PM(2.5), and sulfates were associated with ICAM-1 and VCAM-1. An interquartile range increase in 24-h exposure for NO (2) was associated with a 1.7% (95% confidence interval = 0.2%–3.3%) increase in fibrinogen for ozone; a 10.8% (2.2%–20.0%) increase in C-reactive protein for particle number; a 5.9% (3.6%–8.3%) increase in ICAM-1; and for PM(2.5), a 3.7% (1.7%–5.8%) increase in VCAM-1. The air pollution effect was stronger among subjects having higher Alu, lower LINE-1, tissue factor, or TLR-2 methylation status." Bind et al. (2012)	DNA methylation states; fibrinogen; C-reactive protein; intercellular adhesion molecule-1; ICAM-1; vascular cell adhesion molecule-1; VCAM-1; epigene-environment interactions; DNA methylation of Alu; LINE-1; tissue factor (F3); Toll-like receptor 2; TLR-2
DNS	"NO2 inhalation causes the deterioration of spatial learning and memory and tends to promote Aβ deposition in a concentration-dependent manner. Importantly, NO2 aggravated cognitive impairment, amyloid deposition, neuroinflammation and neurodegeneration in APP/PS1 model mice." Yan et al. (2016)	Neurodegeneration; Amyloid β peptide; cognitive defects; APP; BACE1; microglial activation; neuroinflammation; COX-2; PGE2; OX42/CD11b; GFAP; 2-AG; MAGL; AA; KEGG; glutamatergic synapses; neurotrophin signaling; calcium signaling pathway
Omeprazole/proton pump inhibitors [2].		
ICOV	"We found evidence of an independent, dose-response relationship between the use of antisecretory medications and COVID-19 positivity; individuals taking PPIs twice daily have higher odds for reporting a positive test when compared with those using lower-dose PPIs up to once daily, and those taking the less potent histamine-2 receptor antagonists are not at increased risk." Almario et al. (2020)	enteric infections; PPI-induced hypochlorhydria; acid suppression; severe acute respiratory syndrome coronavirus 2; severe acute respiratory syndrome coronavirus 1; histamine-2 receptor antagonists
WIS	"PPIs may cause potentially harmful effects by several mechanisms, including endothelial dysfunction, hypomagnesemia, drug interactions, reduced absorption of selected nutrients, increased gastric microbiota and small intestine bacterial overgrowth, reduced immune response, tubular-interstitial inflammation, increased bone turnover, accumulation of amyloid in the brain." Corsonello et al. (2018)	cardiovascular diseases; kidney impairment; nutritional disorders; fractures; infections; functional decline; endothelial dysfunction; hypomagnesemia; reduced absorption of selected nutrients; gastric microbiota; small intestine bacterial overgrowth; reduced immune response; tubular-interstitial inflammation; bone turnover; amyloid in the brain;
IIC	"Increased risk of microscopic colitis with use of proton pump inhibitors and non-steroidal anti-inflammatory drugs" Masclee et al. (2015)	selective serotonin reuptake inhibitors; angiotensin-converting enzyme (ACE) inhibitors; beta-blockers; PPIs
DNS	"Although neurological side effects secondary to PPIs are rare, several preclinical reports indicate that PPIs might increase Aβ levels, interact with tau protein, and affect the neuronal microenvironment through several mechanisms." Ortiz-Guerrero et al. (2018)	Neurofibrillary tangles; Tau; amyloid β peptide; vitamin B12 deficiency; hyperhomocysteinemia; GSK-3β; PP2A; MAPKs; Cdk-5; IFN-γ; LXR; Abca1; GABA-A receptor; apolipoprotein E; STAT3; I-TAC; α dementia; cognitive impairment
Opioids [1].		
ICOV	"Substance use disorders can also increase the risk of adverse COVID-19 outcomes through immunosuppression ….For example, opioids exert various suppressive effects on both the innate and adaptive immune systems, especially among those who have long used substances (≥90 days in a year). Largely by binding to the mu receptor and modulating various downstream cellular signaling pathways, opioids impair the recruitment and function of virtually all immune cells, such as macrophages, NK cells, granulocytes, and B and T lymphocytes" Baillargeon et al. (2021)	substance use disorder; increased risk of hospitalization; ventilator use; mortality; chronic respiratory disease; cardiovascular disease
WIS	"clinical studies suggest that opioid treatment can be associated with a high risk of immune suppression and the development of inflammatory events, worsening the chronic pain status itself." Malafoglia et al. (2021)	Chronic pain; immune suppression; inflammatory; opioid peptides; opioid receptors; central nervous cells; peripheral nervous cells; immune cells; immune system
IIC	"Morphine dosage must be carefully adapted in patients with renal failure or severe liver failure. The i.v. route is used for morphine titration in the post anesthesia care unit (PACU), or for analgesia in children. Systematic (not on demand) intramuscular or subcutaneous morphine must be administered at intervals not longer than 4 h. Dosage is best determined after i.v. titration in the PACU. Codeine, administered orally, is metabolised into morphine. Codeine has almost no effect in 7% of Caucasians and at least 15% of Asians ….Non-steroidal anti-inflammatory drugs are powerful antinociceptive agents ….They also have a marked morphine sparing effect and reduce therefore the respiratory depression induced by morphine." Mazoit (1998)	renal failure; liver failure; alcoholics; kidney failure; gastrointestinal bleeding; coagulation disorders; allergy; respiratory depression

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Opioids [1].		
DNS	"we found that a subgroup of neurons, as well as glial cells, primarily located in the superficial laminas of the spinal cord dorsal horn and likely to be inhibitory GABAergic neurons, undergo the NMDAR- and caspase-mediated apoptotic process in association with the development of morphine tolerance." Mao et al. (2002)	Opioid tolerance; NMDA receptor; GABA; GAD; GT; neuronal apoptosis; caspase 3; Bax; Bcl-2; GLT-1; PKC; glutamate transporter; neurotoxicity; nociceptive heat sensitivity; neuropathic pain
Organophosphates [4].		
ICOV	"At present, we witness COVID-19 outbreak caused by SARS-CoV-2. Infection triggers cytokine storm coupled with inflammatory manifestations and pulmonary disorders in patients. Since organophosphate-exposure promotes necroinflammation and respiratory troubles hence during current pandemic situation, additional exposure to such chemicals can exacerbate inflammatory outcome and pulmonary maladies in patients, or pre-exposure to organophosphates might turn-out to be a risk factor for compromised immunity." Rajak et al. (2021)	immunotoxic; pathogenic stress; oxidative stress; antiviral immune response; cytokine burst; pyroptosis; broncho-alveolar chambers; respiratory ailments; COVID-19; Infection; cytokine storm; inflammatory manifestations; pulmonary disorders; necroinflammation; respiratory troubles; compromised immunity; immunosuppression
WIS	"Organophosphates ….fuel oxidative stress to impair antiviral immune response in living entities ….promote cytokine burst and pyroptosis in broncho-alveolar chambers leading to severe respiratory ailments ….promotes necroinflammation and respiratory troubles ….exacerbate inflammatory outcome and pulmonary maladies in patients" Rajak et al. (2021)	immunotoxic; oxidative stress; antiviral immune response; cytokine burst; pyroptosis; respiratory ailments; COVID-19; cytokine storm; inflammatory; pulmonary disorders; necroinflammation;
IIC	"the free organophosphorus (FOP) toxic substances content was analyzed using the enzyme inhibition method. The contents of tumor necrosis factor (TNF-α), interleukin 1-β (IL-β) and thromboxane B2 (TXB2) in the plasma and tissue homogenates were determined via radioimmunoassay. … The TXB2 and TNF contents in plasma were significantly higher than those of the control ($P < 0.05$). Except for the intercostal muscle, all of the tissues had significantly higher TXB2 contents than the control. The TNF contents of the liver and lung and the IL-1β contents of the liver and kidney were significantly higher than those of the control ($P < 0.05$)." Hou et al. (2017)	multiple organ dysfunction syndrome; MODS; tumor necrosis factor; TNF-α; interleukin 1-β; IL-β; thromboxane B2; TXB2; lesions; hemorrhage; edema; necrosis; TXB2; TNF; liver; kidney
DNS	"In addition to the well-known inhibitory effects of OPs on acetylcholinesterase, there is an evolving literature to suggest that OPs affect a number of additional targets that lead to oxidative stress, axonal transport deficits, neuroinflammation, and autoimmunity." (Naughton and Terry, 2018)	AChE; neuroinflammation; TNF-α; IL-6; IL-1β; CCL2; GFAP; p-ERK1/2; oxidative stress; ROS; coenzyme Q10; SOD; GSH; GSGG; MAPKs; Cdk-5; PKA; paraoxonase-1; axonal transport deficits; autoimmunity; MBP; MAG; NFP; MAP-2; ATP; α/β-tubulin; 2-AG; 3-NT/Tyrosine; CaMKII; BDNF; Cort; Crhbp; Nptx2; Npy; Pnoc; HDAC6; aerotoxic syndrome; neuropsychiatric effect
Ovariectomy [2].		
ICOV	"Epidemiological data from the SARS-CoV-2 outbreak suggest sex differences in mortality and vulnerability; … acute respiratory distress syndrome (ARDS) … Since stimulation of the Ang(1–7)/Mas axis protects the endothelial barrier in acute lung injury (ALI), … Ovariectomy attenuated protection in female WT mice and reduced Mas-receptor expression. … Improved lung endothelial barrier function protects female mice from ALI-induced lung edema." Erfinanda et al. (2021)	acute respiratory distress syndrome; ARDS; endothelial barrier regulation; angiotensin (Ang)(1–7); Mas receptor; cardiovascular; Ang(1–7)/Mas axis; acute lung injury; Endothelial permeability; weight change; transendothelial electrical resistance; lung edema; protein leaks; Lung weight change; platelet-activating factor; PAF; Mas-receptor expression; thrombin
WIS	"we examined the effect of ovariectomy on T-cell homeostasis and function in adult and aged female rhesus macaques ….in adult female rhesus macaques, ovariectomy increased the frequency of naïve CD4 T cells. In contrast, ovariectomized (ovx) aged female rhesus macaques had increased frequency of terminally differentiated CD4 effector memory T cells and inflammatory cytokine-secreting memory T cells. Moreover, ovariectomy reduced the immune response (T-cell cytokine and IgG production) following vaccination with modified vaccinia ankara in both adult and aged female rhesus macaques compared to ovary-intact age-matched controls ….loss of ovarian steroids, notably estradiol and progesterone, may contribute to reduced immune function in post-menopausal women" Engelmann et al. (2011)	dysregulation; immune function; immune senescence; immune response; T-cell homeostasis; naïve CD4 T cells; terminally differentiated CD4 effector memory T cells; inflammatory cytokine-secreting memory T cells; IgG
IIC	"we found that leukocytes from healthy postmenopausal women were more adhesive to the arterial endothelium than those from premenopausal women regardless of the stimulus used on endothelial cells. Increased circulating levels of IL-8, MCP-1, RANTES, and MIP-1alpha and monocyte CD11b expression were also encountered in postmenopausal vs premenopausal subjects. … Using intravital microscopy, we imaged mesenteric arterioles and found significant increases in arteriolar leukocyte adhesion, cell adhesion molecule expression, and plasma levels of cytokine-induced neutrophil chemoattractant (CINC/KC), MCP-1, and MIP-1alpha in 1-mo ovariectomized rats. Chronic treatment of ovariectomized rats with low dose of 17-beta-estradiol, losartan, both, or benazepril inhibited ovariectomy-induced arteriolar mononuclear leukocyte adhesion by 77%, 58%, 92%, and 65% respectively, partly by inhibition of cell adhesion molecule up-regulation and the increase in circulating chemokines. These results demonstrate that menopause and ovariectomy generate a low grade of systemic inflammation." (Abu-Taha et al., 2009)	systemic inflammation; monocyte adhesion to arterial endothelium; menopause; estrogen depletion; renin-angiotensin system; arterial cells; venous endothelial cells; leukocytes; arterial endothelium; IL-8; MCP-1; RANTES; MIP-1alpha; monocyte CD11b expression; arteriolar leukocyte adhesion; cell adhesion molecule; cytokine-induced neutrophil chemoattractant; CINC/KC; MCP-1; MIP-1alpha; cell adhesion molecule up-regulation; chemokines; estrogen deficiency; systemic inflammation; menopause; cardiovascular diseases

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Ovariectomy [2].		
DNS	"this study determines that OVX (or ovarian hormone deprivation) enhances the induction of CUS on the depression and anxiety behaviors in the body. The possible mechanisms may be related to inducing the activation and polarization of microglial cells in the prefrontal cortex and accelerating the inflammatory response." Ge et al. (2020)	Serum estradiol; serum corticosterone; microglial activation; microglial polarization; Iba-1; chronic unpredictable stress; inflammatory response; IL-1β; IL-6; TNF-α; iNOS; CX3CR1; CX3CL1; CD200; CD200R; TLR4; ARG1; behavior; anxiety; depression
Ozone [4].		
ICOV	"A significant positive association was found for PM2.5, PM10, NO2, and O3 with newly COVID-19 confirmed cases." (Ali, Islam, 2020)	air pollution; PM2.5; nitrogen dioxide; NO2; PM10; SO2; CO; O3; age; pre-existing medical conditions
WIS	"Ozone is highly reactive, eliciting rapid and dose-dependent disruption of the respiratory barrier. It impacts many cell types in the lung and activates specific signaling cascades, eliciting responses including cellular damage, enhanced apoptosis, cytokine production, recruitment of inflammatory cells, and subsequent tissue repair. Oxidative stress is a conserved mechanism that contributes to numerous environmental lung injuries. Ozone, as a principal mediator of oxidative stress in both the intracellular and extracellular compartments, has become a clinically-relevant model to understand the mechanisms underlying biological responses to oxidative stress (6, 7). Oxidation products are either directly toxic and can cause injury to lung tissue or they can function as exogenous ligands via binding to cell surface receptors and thereby triggering intracellular inflammatory and/or apoptotic signaling pathways (8). Thus, ozone-induced oxidant stress modifies several known cell-signaling mechanisms: activation of innate immune signaling pathways, upregulation of antioxidant genes, and enhanced release of damage-associated molecular pattern molecules (DAMPs) (9, 10). Oxidative stress also decreases the clearance of pathogens by impairing antimicrobial function of effector cells including suppressing alveolar macrophage phagocytosis, enhancing macrophage and neutrophil apoptosis, and increasing the susceptibility of epithelial cells to influenza infection." Chung et al. (2021)	difficulty to breathe; shortness of breath; discomfort on breathing; cough; sore-throat; inflammation; upper and lower airways; lung conditions; asthma; COPD; increased school absence; days off work; medication use; visits to doctors and emergency rooms; hospital admissions; respiratory barrier; specific signaling cascades; cellular damage; apoptosis; cytokine production; inflammatory cells; tissue repair; Oxidative stress; lung injuries; intracellular compartment; extracellular compartments; Oxidation products; lung tissue; exogenous ligands; cell surface receptors; intracellular inflammatory; apoptotic signaling pathways; oxidant stress; cell-signaling mechanisms; innate immune signaling pathways; antioxidant genes; damage-associated molecular pattern molecules; DAMPs; effector cells; alveolar macrophage phagocytosis; macrophage apoptosis; neutrophil apoptosis; epithelial cells; influenza infection
IIC	"Interaction effects of temperature and ozone on lung function and markers of systemic inflammation, coagulation, and fibrinolysis: a crossover study of healthy young volunteers" Kahle et al. (2015)	lung function; blood; fibrinolysis; PAI-1; plasminogen activator inhibitor-1; plasminogen; D-dimer; forced expiratory volume
DNS	"oxidative stress caused by low doses of ozone causes dysregulation of inflammatory processes, progressive neurodegeneration, chronic loss of brain repair in the hippocampus, and brain plasticity changes in the rat analogous to those seen in Alzheimer's disease." Rivas-Arancibia et al. (2010)	Oxidative stress; ROS; LPO; doublecortin; Neu-N; p53; microglial activation; phagocytic microglia; Iba-1; GFAP; NF-κB; CNS inflammation; neurogenesis inhibition; neurodegeneration
Perfluorinated alkylates [4].		
ICOV	"Measures of individual exposures to immunotoxic PFASs included short-chain PFBA known to accumulate in the lungs. Elevated plasma-PFBA concentrations were associated with an increased risk of a more severe course of COVID-19." Grandjean et al. (2020)	immunotoxic; PFAS concentrations; perfluorobutanoic acid; PFBA
WIS	"The first guidelines and legal limits for PFAS exposure ….remain higher than suggested by data on human adverse effects, especially on the immune system, that occur at background exposure levels." Grandjean (2018)	toxicity; adverse effects; immune system
IIC	"The peroxisome proliferator-activated receptors (PPAR) … These receptors regulate important physiological processes that impact lipid homeostasis, inflammation, adipogenesis, reproduction, wound healing, and carcinogenesis. … perfluorinated alkyl acids as these compounds, including perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), activate PPARalpha. Exposure of the rodent to PFOA or PFOS during gestation results in neonatal deaths, developmental delay and growth deficits. Studies in PPARalpha knockout mice demonstrate that the developmental effects of PFOA, but not PFOS, depend on expression of PPARalpha." Abbott (2009)	peroxisome proliferator-activated receptors; PPAR; nuclear hormone receptor superfamily; PPARalpha; PPARbeta; PPARgamma; lipid homeostasis; inflammation; adipogenesis; reproduction; wound healing; carcinogenesis; PPAR agonists; neonatal deaths; developmental delay; growth deficits; gamma protein; mRNA expression
DNS	"several epidemiological studies reporting the positive association of PFCs with neurological disorders such as ADHD and Alzheimer's disease, as well as experimental animal studies reporting the underlying mechanism for the neurotoxicity of PFCs" Lee (2018)	Oxidative stress; ROS; PKC; NMDA; Erk1/2; AMPK; IgM immunotoxicity; neurotoxicity; neurodegeneration
PM(10)/PM10 [4].		
ICOV	"PM10 and NO2 were significantly and positively associated with the risk of a COVID-19 diagnosis (hazard ratio (HR) = 1.44 and 1.16, respectively)." Hutter et al. (2020)	COVID-19; nitrogen dioxide; particulate matter
WIS	"inhaled PM10 may induce Th1-shifting immune response in the lung, and that it may affect reproduction (fetus development) by causing lung hypoxia" Park et al. (2021a)	toxicity; total cell number; Th1-dominant immune response; proteins; cell-to-cell communication; IgA; IgE; interval between births of fetuses; number of offspring; neonatal survival rate; sex ratio; stillborn; HIF-1α protein; bronchial epithelial cells; reproduction; lung hypoxia.
IIC	"We also found a significant short-term association between PM10 and fibrinogen (percent change = 0.17%, 95% CI: 0.04%, 0.29%)." Tang et al. (2020)	Inflammation; Tumor necrosis factor-alpha; TNF-α; IL-6; IL-8; fibrinogen; blood coagulation

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PM(10)/PM10 [4].		
DNS	"long-term exposure to PM10 may contribute to pathological Aβ deposition." (Lee et al., 2020)	Amyloid β peptide; Tau; apolipoprotein E; PiB; white matter hyperintensity; cognitive impairment; dementia
PM(2.5)/PM2.5 [4].		
ICOV	"After the wildfire, the numbers of cases and deaths due to COVID-19 both increased respectively by 56.9% and 148.2%. The California wildfire caused an increase in ambient concentrations of toxic pollutants which were temporally associated with an increase in the incidence and mortality of COVID-19." Meo et al. (2021)	Severe Acute Respiratory Syndrome Coronavirus 2; particulate matter; carbon monoxide; Ozone; toxic pollutants
WIS	"PM2.5 causes injuries of lung tissue cells and downregulates immune defense mechanisms in the lung" Ma et al. (2017)	pulmonary immunity; influenza virus response; inflammatory injuries; influenza A infection; pulmonary macrophages; IL-6; IFN-β; pulmonary innate defense system; Kdm6a down-regulation; H3K4 methylation; H3K9 methylation; lung tissue cells; immune defense mechanisms
IIC	"Five biomarkers, including white blood cells (WBC), high sensitive C-reactive protein (hsCRP), tumor necrosis factor-soluble receptor-II (sTNF-RII), interleukin-6 (IL-6), and von Willebrand factor (vWF) were analyzed … revealed positive associations of all biomarkers (except hsCRP) … findings from this study indicated that various PM2.5 sources increase the levels of inflammation and coagulation biomarkers, although the strength and significance of these associations vary depending on the type of PM sources, demographic characteristics, and differ across the different time lags." Altuwayjiri et al. (2021)	white blood cells; WBC; high sensitive C-reactive protein; hsCRP; tumor necrosis factor-soluble receptor-II; sTNF-RII; IL-6; von Willebrand factor; vWF
DNS	"NC residents aged 65+ with long-term exposures to ambient PM2.5 levels exceeding the WHO standard had significantly increased risks of death and hospital admissions for AD. The effects for non-AD dementia and PD were less pronounced." Rhew et al. (2021)	Amyloid β peptide; Tau; α-synuclein; apolipoprotein E; oxidative stress; ROS; SOD; CAT; MAPKs; ER stress; mitochondrial dysfunction; protein homeostasis disturbance; neuroinflammation; COX-2; IL-1β; dopaminergic neuron loss; cognitive decline; glial cell apoptosis; neurodegeneration
Pneumococcal vaccine [2].		
ICOV	"The countries with universal Pneumococcal vaccine (PCV); including PCV1, PCV2, and PCV3 vaccines had significantly higher total mortality ….Our data suggest that serial MCV doses may lead to the non-specific weakening of the immune response to SARS-CoV-2. We believe that more doses of a respiratory vaccine could decrease immunity rather than enhancing it. We call on further investigations on the effect of MCV2 and PCV3 on immunity parameters for respiratory diseases." (Abdulah and Hassan, 2021)	COVID-19; viral infections; Higher income; BCG vaccination; meningococcal conjugate vaccine; PCV3 vaccination; measles-containing vaccine
WIS	"Childhood invasive pneumococcal disease caused by non-7-valent pneumococcal vaccine (PCV7) serotypes under partial immunization in Taiwan" Shen et al. (2013)	invasive pneumococcal disease; Pneumococcal isolates; Pneumonia; empyema; C-reactive protein
IIC	"Severe Inflammatory Response in Myelodysplastic Syndrome and Trisomy 8 Following 23-Valent Polysaccharide Pneumococcal Vaccine Administration" Fujikawa et al. (2021)	pneumonia; sepsis; meningitis; Invasive pneumococcal disease; IPD; blood; cerebrospinal fluid; morbidity; mortality; immunocompromised; inflammatory response; myelodysplastic syndrome; MDS; trisomy 8
DNS	"The association between the pneumococcal conjugate vaccine and febrile seizures is consistent with prior studies, including a recent publication by Duffy et al. that noted an independent risk of febrile seizures with PCV7 [7,13,15]. The authors also evaluated the association between PCV13 and febrile seizures and found an IRR of 1.4 (95% CI 0.27, 7.22)". Baker et al. (2020)	Simple febrile seizures; complex febrile seizures; index seizure code; IRR; fever
Polycyclic aromatic hydrocarbons [4].		
ICOV	"polycyclic aromatic hydrocarbons (PAHs) are among the outdoor air pollutants that are major factors in diseases, causing especially adverse respiratory effects in humans. … Evidence supports a clear association between air concentrations of some pollutants and human respiratory viruses interacting to adversely affect the respiratory system. … the association between air pollutants and the transmission and severity of the effects caused by the coronavirus named SARS-CoV-2, which causes the COVID-19. Although to date, and by obvious reasons, the number of studies on this issue are still scarce, most results indicate that chronic exposure to air pollutants delays/complicates recovery of patients of COVID-19 and leads to more severe and lethal forms of this disease." (Domingo and Rovira, 2020)	Particulate matter; sulfur dioxide; nitrogen oxides; ozone; carbon monoxide; volatile organic compounds; VOCs; polycyclic aromatic hydrocarbons; PAHs; adverse respiratory effects; respiratory viruses; respiratory viral infections
WIS	"Woodsmoke contains a mixture of carcinogenic polycyclic aromatic hydrocarbons (PAHs) and volatile organic compounds. Inhalation of these materials induces local and systemic changes in the immune system which may impair critical cell defense mechanisms ….Our results demonstrated that exposure to PAHs leads to cell activation and deteriorates mitochondrial function of the macrophage thus facilitating growth of *M. tuberculosis*." Sada-Ovalle et al. (2018)	respiratory tract; immune system; cell defense mechanisms; immune cells; macrophages; *Mycobacterium tuberculosis*; THP-1; monocyte-derived macrophages; cell activation; mitochondrial function
IIC	"Polycyclic aromatic hydrocarbons induce endothelial injury through miR-155 to promote atherosclerosis" He et al. (2021)	atherosclerotic cardiovascular disease; miR-155; vascularization; permeability; miR-155 expression in HUVECs; permeability; proliferation; vascular lumen number; transcriptome sequencing; 63 genes; complement cascades; coagulation cascades; cytokine-cytokine receptor interaction; TNF signaling pathway; NF-kappa B signaling pathway; SERPIND1

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Polycyclic aromatic hydrocarbons [4].		
DNS	"this study suggests that exposure to PAHs leads to cortical thinning in the elderly in the absence of known neurological diseases. The affected brain regions included frontal, parietal, temporal, and insular lobes. The volumes of the caudate and pallidum as well as verbal learning and memory function also decreased in relation to high exposure to PAHs. These results add to the literature on the neurotoxicity of PAHs and support a hypothesis of neurodegeneration in adults induced by exposure to PAHs." Cho et al. (2020)	Norepinephrine; dopamine; aspartic acid, GABA; 2-naphthol; 1-hydroxypyrene; 1-hydroxyphenanthrene; 2-hydroxyfluorene; brain cortical thinning; neuropsychological dysfunction; neurodegeneration
Pregabalin [2].		
ICOV	"Some analgesics, particularly pregabalin ….were positively associated with COVID-19 incidence" Blanch-Rubio et al. (2020)	COVID-19; osteoporosis; non-inflammatory rheumatic conditions; osteoarthritis; fibromyalgia
WIS	"Pregabalin induces hepatic hypoxia and increases endothelial cell proliferation in mice" Criswell et al. (2012)	nongenotoxic hemangiosarcoma; serum bicarbonate; respiratory rate; blood pH; venous oxygen saturation; vascular endothelial growth factor; basic fibroblast growth factor; hepatic vascular endothelial growth factor receptor 2; iron-laden macrophages; platelet count; platelet activation; erythropoiesis; macrophage activation; tissue growth factors; hypoxia; endothelial cell (EC) proliferation; antioxidant; antiangiogenic
IIC	"Pregabalin (PGB) … The level of fast-twitch skeletal muscle troponin I and CK-MM activity were evaluated in blood as an indicator of muscle injury. … In the acute and sub-acute toxicity assay IP injection of PGB significantly increased the activity and levels of CK-MM and fsTnI compared to the control group. Sub-acute exposure to PGB caused damages that include muscle atrophy, infiltration of inflammatory cells and cell degeneration." Moshiri et al. (2017)	neuropathic pain; partial seizures; generalized anxiety disorder; fibromyalgia; sleep disorders; muscular system of mice; skeletal muscle; fast-twitch skeletal muscle troponin I; CK-MM activity; CK-MM; fsTnI; muscle atrophy; inflammatory cells; cell degeneration; muscle atrophy
DNS	"PGB dependence induces neurotoxic effects mainly in the form of neuronal apoptosis, gliosis, and oxidative stress injury of the frontal cortex. The PGB-induced neurotoxic effects persisted after withdrawal. The influence of these neurotoxic effects and their relevance to the cognitive or neurologic disorders in PGB-dependent individuals warrants further research." Elgazzar et al. (2021)	GABA; apoptosis; Bcl-2; p38; VEGF; iNOS; nestin; NO; neurotoxicity; memory deficit; hypoxic, ischemic, neurodevelopmental disorders; cognitive disorders
Radiotherapy [2].		
ICOV	"The results of the current study demonstrated a possible association between recent receipt of oncologic treatment and a higher risk of death among patients with carcinoma who are hospitalized with COVID-19." (Song et al., 2021)	COVID-19; recent receipt of chemotherapy; surgery; radiotherapy; recent receipt of oncologic treatment
WIS	"Two weeks after irradiation the phagocytic capacity and oxygen superoxide anion generation decreased by 61 and 70%, respectively, compared with controls. This tendency persisted after 4 weeks post irradiation, the decrease in both functions being 50 and 74%, respectively. It is suggested that the altered function of peritoneal macrophages following irradiation may further compromise the immune defense in patients receiving abdominal radiotherapy." Salman et al. (1999)	immune defense; peritoneal macrophages; immune system; phagocytic activity; oxygen superoxide anion;
IIC	"oral epithelial cell apoptosis and pro-inflammatory cytokines secretion induced by radiotherapy via the miR-9-3p/NFATC2/NF-κB axis" Liang et al. (2022)	Oral mucositis; poor quality of life; RNA sequencing; gene nuclear factor of activated T cells c2; NFATC2; human oral epithelial cells; HOECs; apoptosis; pro-inflammatory factors secretion; cytokines level; regulatory miRNA of NFATC2; miR-9-3p; phosphorylation of p65; NF-κB pathway; miR-9-3p/NFATC2/NF– NF-κB axis
DNS	"Radiation primarily causes coagulation necrosis of the white matter tracts and cerebral vasculature by axonal demyelination and damage to vascular endothelial cells30. Leukoencephalopathy occurs from the overproduction of myelin in oligodendrocytes and occurs as a late toxicity ….Demyelination can also occur in spinal cord and nerve roots. Neurodegeneration may occur directly from radiation-induced stress as well as a by-product of detrimental effects on the supporting astrocytes, and supporting astrocytes may undergo reactive gliosis. However, the most severe form of injury is radionecrosis, producing a brisk neuroinflammatory reaction ….Neuroinflammation is a prominent feature of many CNS diseases including stroke, Alzheimer's disease, Parkinson's disease, and mild cognitive impairment, and has also been hypothesized to contribute to radiation-induced cognitive losses." Smart (2017)	Choline/creatine; choline/N-acetylaspartate; NMDA receptor; oxidative stress; ROS; AChE; sirtuin 2 deacetylase; axonal demyelination; neuroinflammation; white matter coagulation necrosis; neurotransmitter modulation; cognitive impairment
Red meat [1].		
ICOV	"a 1% increase in supplementation of animal products and meat increased the odds of having a zero death by 1.076-fold (OR 1.076, 95% CI 1.01–1.15) and 1.13-fold (OR 1.13, 95% CI 1.0–1.28), respectively ….populations that consume more meat, vegetal products, sugar and sweeteners, sugar crops, animal fats, and animal products were associated with more death and less recoveries in patients" Kamyari et al. (2021)	immune system; immunometabolism; chronic disease; infectious diseases; nutrition; obesity; pulses; animal products; meat; Tree nuts; vegetables; eggs; cereals; sugar; sweeteners; sugar crops; animal fats; unbalanced diets
WIS	"N-glycolylneuraminic acid, a non-human sialic acid sugar present in red meat, becomes incorporated in the cell membrane, triggering the immune response with associated inflammation and reactive oxygen species, which can contribute to DNA damage, tumor promotion, and cancer." Turesky (2018)	colorectal cancer; N-nitroso compounds; polycyclic aromatic hydrocarbons; heterocyclic aromatic amines; lipid peroxidation products; DNA adducts; mutations; carcinogenesis; cell membrane; immune response; inflammation; reactive oxygen species; DNA damage; tumor promotion; cancer

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Red meat [1].		
IIC	"Between 1993 and 2002, 88 new patients with inflammatory polyarthritis were identified and matched with 176 controls. Among patients, the level of red meat intake was higher (P = 0.04) and that of vitamin C was lower (P = 0.03) compared with intake among controls, but no difference in total energy intake was observed. Patients were more likely to be smokers. After adjusting for total energy intake, smoking, and other possible dietary confounders, subjects with the highest level of consumption of red meat (OR 1.9, 95% CI 0.9–4.0), meat and meat products combined (OR 2.3, 95% CI 1.1–4.9), and total protein (OR 2.9, 95% CI 1.1–7.5) were at an increased risk for inflammatory polyarthritis. " Pattison et al. (2004)	inflammatory polyarthritis; cancer; total energy intake; smoking;
DNS	"In the case of red meat, a positive association between red meat consumption and PD may be explained by the heme content that may act as a toxin when not digested properly." Seidl et al. (2014)	Hemin; heme; iron deposit; mitochondrial damage; HO-1, ROS; neurodegeneration
Rituximab [2].		
ICOV	"High rates of severe disease and death due to SARS-CoV-2 infection in rheumatic disease patients treated with rituximab: a descriptive study" Loarce-Martos et al. (2020)	rheumatic and musculoskeletal disease; RMD; severe acute respiratory syndrome coronavirus 2; infection; rheumatoid arthritis; systemic vasculitis; Sjögren syndrome; systemic lupus erythematosus; pulmonary involvement; bilateral pneumonia; respiratory insufficiency; hyperinflammation
WIS	"rituximab may generate immune complexes with degraded components of B cells and/or anti-rituximab antibody, and play an important role in triggering leukocytoclastic vasculitis. Indeed, we revealed the presence of C3 deposition for the first time in our report, which supports our hypothesis. In addition, our observation of liquefaction degeneration and infiltrating lymphocytes into the epidermis are both infrequent in the case of IgA vasculitis and other types of vasculitis." Abe et al. (2019)	B-cell lymphoproliferative disorders; B cells; immunoreactions; cutaneous leukocytoclastic vasculitis; follicular lymphoma; purpuric lesions; Liquefaction degeneration; lymphocyte infiltration; IgG; IgM; IgA; complement C3; perinuclear antineutrophil cytoplasmic antibody; skin lesions; immune complexes; IgA vasculitis
IIC	"39-year-old patient with precursor B-cell acute lymphoblastic leukemia who was started on rituximab infusion. The patient developed a cytokine-release syndrome with haemodynamic instability, followed by rapid-onset cytopenias and disseminated intravascular coagulation abnormalities characterised by coagulopathy with fibrinolysis and mucocutaneous bleeding." Rafei et al. (2017)	haematological conditions; autoimmune conditions; cytokine release; cytopenias; thrombocytopenia; leucopenia; coagulopathy; B-cell; acute lymphoblastic leukemia; cytokine-release syndrome; haemodynamic instability; coagulopathy; fibrinolysis; mucocutaneous bleeding; thrombocytopenia; disseminated intravascular coagulation
DNS	"Among 465 patients treated with rituximab for active RA refractory to MTX, one case each of a cerebrovascular infarction, convulsion, epilepsy, and serotonin syndrome were reported. Extremely rare cases of fatal ischemic and hemorrhagic strokes have been reported [9]. Patients have also presented with JC virus reactivation, leading to progressive multifocal leukoencephalopathy [68]. These patients presented within 1 year of rituximab treatment for lymphoid malignancy or autoimmune disorders but had also received either immunosuppressive therapy or stem cell transplants. JC virus can be identified in the cerebrospinal fluid, and the diagnosis of progressive multifocal leukoencephalopathy is an indication to stop rituximab". Kasi et al. (2012)	CD20; complement-dependent cytotoxicity; apoptosis; antibody-dependent phagocytosis
Sedentary/physical inactivity [1].		
ICOV	"There were 760 COVID-19 cases. After adjustment for age, sex and mutually for each lifestyle factor, physical inactivity (Relative risk, 1.32, 95% confidence interval, 1.10, 1.58), smoking (1.42; 1.12, 1.79) and obesity (2.05; 1.68, 2.49) but not heavy alcohol consumption (1.12; 0.93, 1.35) were all related to COVID-19." Hamer et al. (2020)	smoking; physical inactivity; obesity; excessive alcohol intake; Body mass index; C-reactive protein; inflammation; severe infection
WIS	"Physical exercise contributes to cisplatin-induced nephrotoxicity protection with decreased $CD4^+$ T cells activation" Miyagi et al. (2018)	cancer; acute kidney injury; inflammatory cytokines; immune cells; CD4 + T cells; creatinine; Kim-1; brown adipose tissue weight; Tregs; $CD4^+CD25^+$ cells; $CD69^+$; $CD25^+$; TNF; IL-10
IIC	"midarm muscle circumference (MAMC) and fat-free mass index (FFMI). … Physical inactivity, insulin resistance, C-reactive protein, von Willebrand factor and fibrinogen were associated with significantly increased odds of low MAMC and FFMI after adjustment for body mass index, lifestyle characteristics and morbidity." Atkins et al. (2014)	low muscle mass; metabolic risk factors; inflammation; endothelial dysfunction; coagulation; midarm muscle circumference; MAMC; fat-free mass index; FFMI; Physical inactivity; insulin resistance; C-reactive protein; von Willebrand factor; fibrinogen; body mass index; lifestyle characteristics; morbidity; dietary variables; smoking; alcohol intake; D-dimer, IL-6; homocysteine
DNS	"Many studies have shown that PA can reverse at least some of the unwanted effects of sedentary lifestyle, and can also contribute in delaying brain aging and degenerative pathologies such as Alzheimer's Disease, diabetes, and multiple sclerosis. Most importantly, PA improves cognitive processes and memory, has analgesic and antidepressant effects, and even induces a sense of wellbeing, giving strength to the ancient principle of "mens sana in corpore sano" (i.e., a sound mind in a sound body)." Di Liegro et al. (2019)	BDNF; GDNF; VEGF; DNMT3B; ABCA1; IGF-1R; erythropoietin; PGC-1α; oxidative stress; ROS; HDACs; CTSB; GF21; Irisin/FNDC5; lactate; c-Fos; Wnt3; GSK-3β; GLUT4; IGF-1; KYN; miR-483, miR-200; miR-21; miR-34A; dopamine; MAO; NMDA; CaMKII; apolipoprotein E; autophagy; SIRT1; TFEB; DRP1
Selenium deficiency [1].		
ICOV	"there is evidence of the potential protective and therapeutic roles of vitamin C, D, zinc, and selenium in COVID-19." Pedrosa et al. (2022)	pathogenicity; COVID-19; essential nutrients; viraemic; hyperinflammatory; Micronutrients; vitamin C; vitamin D; zinc; selenium; antioxidant; anti-inflammatory; antithrombotic; antiviral; immuno-modulatory; innate immunity; adaptive immunity; nutritional risk;

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Selenium deficiency [1].		
WIS	"Selenium Deficiency Attenuates Chicken Duodenal Mucosal Immunity via Activation of the NF-κb Signaling Pathway" Liu et al. (2016)	Selenium deficiency; intestinal mucosal inflammation; nuclear transcription factor kappa-B; NF-κB; inflammatory response; chicken duodenal mucosa; secretory immunoglobulin A; SIgA; inflammatory cytokines; oxidized glutathione; glutathione peroxidase; glutathione activities; p50; p65; p65 DNA-binding; phosphorylation of IκB-α; phosphorylation of kappa-B kinase subunit alpha; IKKα; IKKα; IκB-α; interleukin-1β; IL-1β; IL-17A; tumor necrosis factor-α; TNF-α; interferon gamma; IFN-γ; anti-inflammatory cytokines; TGF-β1; IL-10; oxidized glutathione activity; glutathione peroxidase; regulation function of redox
IIC	"Selenium Deficiency Induces Pathological Cardiac Lipid Metabolic Remodeling and Inflammation" Tang et al. (2022b)	Selenium disequilibrium; cardiac diseases; cardiac response; cardiac oxidative stress; glutathione; thioredoxin; thioredoxin domain-containing protein S-nitrosylation; Energy production; free fatty acids; tricarboxylic acid cycle; respiratory chain proteins; S-nitrosylation; diacylglycerol; phosphatidylcholine; phosphatidylethanolamine; oxidation; malondialdehyde; palmitic acid; ceramide synthesis; inflammation; cytosolic DNA-sensing pathways; interferon regulatory factor 7; nuclear factor kappa B; lipid metabolic vulnerability; redox imbalance; cardiac disease treatment.
DNS	"Se-deficient MA-treated mouse is a relevant model of Parkinsonism, and that optimal level of Se plays a crucial role in preventing nigral dopaminergic toxicity induced by MA" Kim et al. (2000)	antioxidant; selenium; methamphetamine; MA; dopaminergic cell damage; substantia nigra; SN; tyrosine hydroxylase-like immunoreactivity; TH-IR; dopamine; DA; metabolites; 3, 4-dihydroxyphenylacetic acid; DOPAC; homovanilic acid; HVA; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPTP; Parkinsonism; nigral dopaminergic toxicity; thermoregulation
Silica [4].		
ICOV	"Mineworkers continue to experience high levels of silica exposure. The prevalences of silicosis, HIV and pulmonary TB, remain high. Interstitial lung disease, pulmonary TB, and HIV have all been associated with poorer outcomes of SARS-CoV-2 infections." (Naidoo and Jeebhay, 2021)	Migrant work; living in crowded hostels; working in narrow poorly ventilated shafts; silica exposure; silicosis; HIV; pulmonary TB; Interstitial lung disease;
WIS	"Acute Exposure to Crystalline Silica Reduces Macrophage Activation in Response to Bacterial Lipoproteins" Beamer et al. (2016)	alveolar macrophages; immunotoxicity; immunity; pattern recognition receptors; PRRs; bone marrow-derived macrophages; TLR2; CD204; Pam2CSK4; Pam3CSK4; IL-1β; IL-6
IIC	"SiNPs could induce inflammation-coagulation response and thrombotic effects via JAK1/TF signaling pathway." Duan et al. (2018)	endothelial cells; swollen mitochondria; autophagosome; cytoskeleton organization; vascular endothelial cells; procoagulant cytokines; IL-6; IL-8; MCP-1; PECAM-1; TF; vWF; Tg(mpo:GFP); Tg(fli-1:EGFP); inflammation; blood flow; blood velocity; blood hypercoagulable; thrombotic; erythrocyte aggregation; microarray analysis; JAK1/TF signaling pathway; qRT-PCR assays; Western blot assays; il6st; jak1; f3b
DNS	"SiNPs may cause adverse effects in brain including neurotoxicity, neuroinflammation, neurodegeneration and enhancing levels of amyloid beta protein (Aβ); all pathological hallmarks of Alzheimer's disease." Ye et al. (2019)	Amyloidogenesis; amyloid β peptide; endolysosome calcium store; endolysosome accumulation; endolysosome pH; neuro-toxcity; GFAP; MAP2; NeuN; autophagy
Smoking [1].		
ICOV	"Smoking was associated with severe or critical outcomes and increased the risk of admission to ICU and mortality in COVID-19 patients ….This association was more significant for former smokers than in current smokers. Current smokers also had a higher risk of developing severe COVID-19 compared with non-smokers." Zhang et al. (2021)	COVID-19 pneumonia; Smoking; mechanical ventilation; age; hypertension; diabetes; chronic obstructive pulmonary disease; COPD
WIS	"plasma samples from 30 heavy smokers (16 men and 14 women) had significantly higher CRP, fibrinogen, IL-6 and CEA levels than 36 non-smoking controls. Whole blood samples from smokers, incubated for 7 h at 37 °C in the absence of any exogenous stimuli, secreted significantly higher levels of IL-8 and a number of other cytokines/chemokines than non-smokers. When challenged for 7 h with *E. coli*, whole blood samples from smokers secreted significantly lower levels of many inflammatory cytokines/chemokines. However, when stimulated with HSV-1, significantly higher levels of both PGE2 and many cytokines/chemokines were secreted from smokers' blood samples than from controls. In terms of blood cell composition, red blood cells, hematocrits, hemoglobin levels, MCV, MCH, MCHC, Pct and RDW levels were all elevated in smokers, in keeping with their compromised lung capacity. As well, total leukocytes were significantly higher, driven by increases in granulocytes and monocytes. In addition, smokers had lower NK cells and higher Tregs than controls, suggesting that smoking may reduce the ability to kill nascent tumor cells." Elisia et al. (2020)	inflammatory markers;, innate immune responses; adaptive immune responses; CRP; fibrinogen; IL-6; CEA; IL-8; cytokines; chemokines; PGE2; red blood cells; hematocrits; hemoglobin; MCV; MCH; MCHC; Pct; RDW; leukocyte; granulocytes; monocytes; NK cells; Tregs; nascent tumor cells
IIC	"Water-pipe smoking (WPS) . WPS aggravated in vivo thrombosis by shortening the thrombotic occlusion time in pial arterioles and venules. The number of circulating platelets was reduced by WPS suggesting the occurrence of platelet aggregation in vivo. Elevated concentrations of fibrinogen and plasminogen activator inhibitor-1 were seen after the exposure to WPS. Blood samples taken from mice exposed to WPS and exposed to adenosine diphosphate showed more platelet aggregation. The heart concentrations of IL-6 and TNFα were augmented by WPS. Likewise, heart levels of LPO, reactive oxygen species and the antioxidants catalase and GSH were increased by WPS." Nemmar et al. (2015)	leukocytes; C-reactive protein; TNFα; IL-6; lipid peroxidation; LPO; glutathione; GSH; catalase; thrombosis; thrombotic occlusion time; pial arterioles; venules; circulating platelets; platelet aggregation; fibrinogen; plasminogen activator inhibitor-1; Blood samples; heart levels of LPO; reactive oxygen species; antioxidants; systolic blood pressure; heart rate; procoagulatory effects; cardiac inflammation; oxidative stress

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Smoking [1].		
DNS	"Evidence from epidemiological studies and meta-analyses have indicated that cigarette smoking is significantly associated with the risk of neurodegenerative disorders,1–3 including Alzheimer disease (AD) and dementia." Liu et al. (2020c)	Amyloid β peptide (Aβ42); neuroinflammation; TNFα; BDNF; oxidative stress; SOD; NOS; neurodegeneration
Sodium intake [1].		
ICOV	"Besides habitual dietary salt intake, more acute changes in sodium balance might also influence ACE2 receptor expression. Intermittent sodium loss, either due to diarrhea, vomiting or perspiration could put patients that acquire COVID-19 infection at higher risk for development of a more severe or fatal course of disease." Post et al. (2020)	infection; high sodium intake; Human pathogenic coronaviruses; angiotensin-converting enzyme 2 receptor; ACE2; epithelial cells; lung; intestine; kidney; blood vessels; tissue expression; low sodium balance; cellular damage; virus load; COVID-19 infection; anti-inflammatory; acid aspiration-induced acute respiratory distress syndrome; diarrhea; vomiting; perspiration
WIS	"Cells of the innate immune system including monocyte/macrophages and dendritic cells can promote blood pressure elevation via effects mostly on kidney and vascular function. Moreover, convincing evidence shows that T and B cells from the adaptive immune system are involved in hypertension and hypertensive end-organ damage. Skin monocyte/macrophages, regulatory T cells, natural killer T cells, and myeloid-derived suppressor cells have been shown to exert blood pressure controlling effects. Sodium intake is undoubtedly indispensable for normal body function but can be detrimental when taken in excess of dietary requirements. Sodium levels also modulate the function of monocyte/macrophages, dendritic cells, and different T cell subsets. Some of these effects are mediated by changes in the microbiome and metabolome that can be found after high salt intake." Wenzel et al. (2021)	hypertension; Inflammation; innate immune system; monocyte; macrophages; dendritic cells; blood pressure; T cells; B cells; adaptive immune system; hypertensive end-organ damage; regulatory T cells; natural killer T cells; myeloid-derived suppressor cells; immune response
IIC	"Tissue sodium accumulation in salt-sensitive individuals due to endothelial glycocalyx dysfunction causes macrophage infiltration, vascular inflammation, and local changes in angiotensin-2 and aldosterone concentrations. This inflammatory cascade leads to factor XII-related coagulation disorders with neutrophil extracellular trap formation (NETosis)." (Targonski et al., 2020)	sodium; inflammation; hypertension; hemodynamic effects of drugs; vascular resistance; sodium balance; water retention; hemodynamic parameters; endothelial glycocalyx dysfunction; macrophage infiltration; vascular inflammation; angiotensin-2; aldosterone concentrations; factor XII-related coagulation disorders; neutrophil extracellular trap formation; NETosis; microcirculation impairment; central hemodynamic parameters; hypertension; inflammation; coagulation disorders; vascular health; cardiac diastolic function
DNS	"lower dietary sodium intake over three years was associated with decreased rates of cognitive impairment, especially in elderly subjects with low levels of physical activity" Liu et al. (2014)	Oxidative stress; ROS; SOD; CAT; GSH; T-AOC; spatial memory; memory decline; cognitive dysfunction
Steroid use [2].		
ICOV	"Penalised regression models selected income, cardiovascular disease, hypertension, diabetes, cystatin C, and oral steroid use as jointly contributing to COVID-19 mortality risk" Elliott et al. (2021)	education; income; housing; employment; smoking; drinking; body mass index; lipids; cystatin C; vitamin D; comorbidities; medications; air pollution; healthcare worker; current smoker; cardiovascular disease; hypertension; diabetes; autoimmune disease; oral steroid use; income; cardiovascular disease; hypertension; diabetes; cystatin C; oral steroid use; Black ethnicity; body mass index; low vitamin D; air pollutants; renin-angiotensin-aldosterone system inhibitors
WIS	"Reduced Antiviral Interferon Production in Poorly Controlled Asthma Is Associated With Neutrophilic Inflammation and High-Dose Inhaled Corticosteroids" Simpson et al. (2016)	Asthma; inflammatory disease; type I interferon; mononuclear cells; IFN-α; IFN-β; sputum cell count; IL-1β; Peripheral blood mononuclear cells; PBMCs; Sputum neutrophil; neutrophilic airway inflammation
IIC	"We present a case of a healthy 9-year-old boy with an exuberant, inflammatory, Demodex-associated pustular eruption of the face, induced by the use of a high-potency topical steroid and successfully treated with oral ivermectin." Guzman et al. (2020)	demodicosis; skin diseases; immunocompetent; erythematotelangiectatic; papulopustular rosacea; Demodex folliculorum; blepharitis; inflammatory; Demodex; pustular eruption of the face
DNS	"There is growing evidence that non-medical use of AAS has a neurodegenerative potential. Although the nature of this effect is still largely not clarified, recent animal studies have shown the recurrence of neurotoxic effects of AAS, ranging from neurotrophin unbalance to increased neuronal susceptibility to apoptotic stimuli" Pomara et al. (2015)	Androgen receptors; estrogen receptors; SRE; GABA-A receptor; GABA-B receptor; excitotoxic neuronal death; neurotrophin imbalance; NMDA; AMPA; NGF; steroid hormone binding globulin (SHBG); SHBG receptor; PKA; IP3; RAS; MEK; Erk; [Ca2+]i; oxidative; ROS; RNS; apoptosis; caspase 3; caspase 9; APAF-1, cytochrome C; FAS/CD95 ligand; caspase 8; Bid; neuroinflammation; TNF-α; InsP3R; NO
Substance abuse [1].		
ICOV	"The findings suggest that COVID-19 patients with substance use disorders are at increased risk for adverse outcomes." Baillargeon et al. (2021)	substance use disorder; increased risk of hospitalization; ventilator use; mortality; chronic respiratory disease; cardiovascular disease
WIS	"There is a long-recognized relationship between addictive drugs and increased levels of infections ….Recent studies of the effects of opiates or marijuana on the immune system have demonstrated that they are receptor mediated, occurring both directly via specific receptors on immune cells and indirectly through similar receptors on cells of the nervous system ….cocaine and nicotine have similar immunomodulatory effects, which are also apparently receptor mediated." Friedman et al. (2003)	infections; immunomodulation; immune system; immune cells; receptor mediated; infectious diseases; AIDS.
IIC	"external male genitals (EMG) … The study results are indicative of a high frequency rate of pathologic changes of the EMG in persons, who abused alcohol and narcotics at lifetime. The inflammatory, fibrosing and atrophic changes of the EMG as well as a reduced vascular permeability can be a cause for erection malfunction." (Dmitriyeva and Sherstyuk, 2003)	external male genitals; EMG; high frequency rate of pathologic changes of the EMG; inflammatory; fibrosing; atrophic; vascular permeability; erection malfunction

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Substance abuse [1].		
DNS	"Substance abuse and addiction are the most costly of all the neuropsychiatric disorders. In the last decades, much progress has been achieved in understanding the effects of the drugs of abuse in the brain. However, efficient treatments that prevent relapse have not been developed. Drug addiction is now considered a brain disease, because the abuse of drugs affects several brain functions. Neurological impairments observed in drug addicts may reflect drug-induced neuronal dysfunction and neurotoxicity. The drugs of abuse directly or indirectly affect neurotransmitter systems, particularly dopaminergic and glutamatergic neurons." Cunha-Oliveira et al. (2008)	5-HT2A receptors; serotonin transporter; VMAT-2; dopamine; glutamate; NMDA receptors; D2 dopamine receptor; MAO; oxidative stress; ROS; MDA; SOD; CAT; GST; GPx; GSH; mitochondrial DNA deletions; 8-OhdG; caspase 3; caspase 9; caspase 2; cytochrome c; p53; Bax; Bcl-2; c-Jun; mitochondrial dysfunction; mitochondrial membrane potential; neurogenesis inhibition; MAPK; PKA; dopamine metabolism; ATP/ADP
Sulfur dioxide [4].		
ICOV	"Air pollutants such as PM10, PM2.5, SO2, NO2, and CO showed a significant correlation with the COVID-19 epidemic." (Ali, Islam, 2020)	air pollution; PM2.5; nitrogen dioxide; NO2; PM10; SO2; CO; O3; age; pre-existing medical conditions
WIS	"Exposure to sulfur dioxide (SO2) increases asthma risk. Inflammatory and immune responses are typical in asthma disease ….we sought to investigate the molecular mechanisms underlying the NF-κB inflammatory pathway and the Th1/Th2 imbalance in asthmatic rats exposed to SO2 ….SO2 affects the airway inflammatory and immune responses of the asthmatic rats and enhances the susceptibility to OVA by aggravating inflammatory responses in lungs, up-regulating pro-inflammatory cytokine expression, and causing the Th1/Th2 imbalance, which might contribute to the increased risk of asthma disease." Li et al. (2014)	asthma; Inflammatory; immune responses; NF-κB; Th1/Th2; immune genes; inflammatory cell counts; IKKβ mRNA; TNF-α; IL-6; IL-4; IFN-γ; IgE; Foxp3; regulatory T cells
IIC	"Anti-inflammatory and anti-fibrotic treatment in a rodent model of acute lung injury induced by sulfur dioxide" Wigenstam et al. (2018)	tissue injury; lung inflammation; airway hyperresponsiveness; AHR; pulmonary fibrosis; collagen; lung tissue; inflammatory response in airways
DNS	"Sulfur dioxide (SO(2)) pollution in atmospheric environment is involved in neurotoxicity and increased risk for hospitalization and mortality of many brain disorders" Sang et al. (2011)	Inflammation; synaptic plasticity; PGE2; COX1; COX2; EP2/4; NF-κB; neuronal apoptosis; caspase 3; Gs-AC-cAMP; PKA; NMDA receptor; NR2B; Gq-PLCIP 3; PKC; c-AMP
TCDD [2,3,7,8-tetrachlorodibenzodioxin (TCDD)] [4].		
ICOV	"Countries like Northern Italy, France, Spain, and UK have suffered from 5 times more deaths from the corona virus infection than neighboring countries like Germany, Switzerland, Austria, and Denmark related to the size of their respective populations. There is a striking correlation between the level of environmental pollutants including pesticides, dioxins, and air pollution such as NO2 known to affect immune function and healthy metabolism with the rate of mortality in COVID-19 pandemic in these European countries. There is also a correlation with the use of chlorination of drinking water in these regions." Bornstein et al. (2020)	SARS-CoV-2; environmental pollutants; pesticides; dioxins; air pollution; NO2; immune function; healthy metabolism; chlorination of drinking water; metabolic inflammation; altered vascular perfusion; neurodegeneration
WIS	"2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a well-known immunotoxic environmental pollutant ….After TCDD treatment, we observed an inhibited cell adherence, probably attributed to the suppressed mRNA levels of adhesion molecules ICAM-1, VCAM-1 and CD11b, and a decrease in cell pseudopodia and expression of F-actin. The inflammatory cytokines TNF-α, IL-10 and other 8 cytokines/chemokines regulating granulocytes/T cells and angiogenesis were disrupted by TCDD. Alternative splicing event was found to be a sensitive target for TCDD. Using WGCNA, we identified 10 hub genes (TNF, SRC, FGF2, PTGS2, CDH2, GNG11, BDNF, WNT5A, CXCR5 and RUNX2) highly relevant to these observed phenotypes, suggesting AhR less important in the effects TCDD have on THP-1 macrophages than in other cells." Li et al. (2021b)	immunotoxic; immune functions; THP-1-derived macrophages; cell adhesion; morphology; cytokines; chemokines; ICAM-1; VCAM-1; CD11b; cell pseudopodia; F-actin; inflammatory cytokines; TNF-α; IL-10; granulocytes; T cells; angiogenesis; hub genes; TNF; SRC; FGF2; PTGS2; CDH2; GNG11; BDNF; WNT5A; CXCR5; RUNX2; AhR
IIC	"Occurrence of disseminated intravascular coagulation in 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced pneumonia in the rat" Calkosinski et al. (2013)	disseminated intravascular coagulation; DIC; laboratory diagnostics of blood; hematologic indicators; RBC; HCT; HGB; inflammatory reaction; erythrocyte hemolysis; inflammatory focus; erythrocyte elimination from circulation; leukocyte; hepatization
DNS	"One of the important public health concerns related to TCDD is its adverse effect on the neural system. Recent studies have demonstrated that TCDD causes significant neurodevelopmental and neurobehavioral deficits in rodents" Wan et al. (2014)	Oxidative stress; ROS; γ-H2AX; p16; p21; p-Rb; SOD-1; SOD-2; GPx; FOXO1; FOXO3a; p27; p53; autophagy; autophagy; Beclin-1; Atg5; PKC; premature senescence; aryl hydrocarbon receptor; mitochondrial redox stress; 8-oxo-dG
Unmarried [5].		
ICOV	"By means of individual-level survival analysis we demonstrate that being male, having less individual income, lower education, not being married all independently predict a higher risk of death from COVID-19 and from all other causes of death." Drefahl et al. (2020)	male; less individual income; lower education; not being married; immigrant from a low- or middle-income country
WIS	"Single patients reporting lower Ps-fr showed the strongest association between stress and infections, while the weakest association was found in patients in a committed relationship with a higher level of Ps-fr." Roy et al. (2021)	immune function; Stress; innate immune markers; T cells; NK cells; neutrophils; Infections; social support; Ps-fr
IIC	"Our study evidences a seasonal trend and confirms unmarried, particularly divorced status, as important risk factor for acute pelvic inflammatory disease." Xholli et al. (2014)	pelvic inflammatory disease' PID; Periodogram analysis; environmental factors; temperature; photoperiod; seasonal rhythm; rhythm of temperature; rhythm of photoperiod; unmarried; divorced women; divorced status

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Unmarried [5].		
DNS	"Studies using clinical examination for dementia ascertainment produced higher pooled estimates for the effect of being widowed (1.20 (1.02–1.41) versus 1.12 (1.07–1.18)) or lifelong single (1.42 (1.07–1.90) versus 1.23 (1.17–1.29)), and this difference nearly reached significance for the comparison of single and married people ($p = 0.06$)." (Chen and Mok, 2018)	Dementia; vascular dementia; Alzheimer's disease; baseline cognitive function
Vitamin A deficiency [1].		
ICOV	"Deficiencies of micronutrients, especially vitamins A, B complex, C, and D, zinc, iron, and selenium, are common among vulnerable populations in general and among COVID-19 patients in particular and could plausibly increase the risk of mortality." Akhtar et al. (2021)	severe acute respiratory syndrome coronavirus 2; micronutrient supplementation; immune system; immune-boosting agents; undernutrition; micronutrient deficiencies; vitamin A; vitamin B complex; vitamin C; vitamin D; zinc; iron; selenium
WIS	"Naive VAD mouse lungs exhibited dysregulated immune function. Neutrophils were enhanced in frequency and there was a significant reduction in RANTES (regulated on activation of normal T cells expressed and secreted), a chemokine instrumental in T-cell homing and recruitment. After influenza virus infection, VAD mice experienced failures in $CD4^+$ T-cell recruitment and B-cell organization into lymphoid structures in the lung. VAD mice exhibited higher viral titers than controls and slow viral clearance. There were elevated levels of inflammatory cytokines and innate cell subsets in the lungs. However, arginase, a marker of alternatively activated M2 macrophages, was rare. When influenza-infected VAD animals were exposed to bacteria, they experienced a 100% mortality rate." Penkert et al. (2021)	bacterial coinfections; influenza; inflammatory cytokines; cellular immune responses; viral clearance; dysregulated immune function; Neutrophils; RANTES; $CD4^+$ T-cell; B-cell; lymphoid structures; viral titers; inflammatory cytokines; innate cell subsets; arginase; M2 macrophages; immune response
IIC	"Retinoids, a family of vitamin A metabolites or analogs, … Vitamin A deficiency and mutations of retinoid nuclear receptors cause abnormalities in fetal kidneys, which might predispose to adult diseases such as hypertension. … Retinoids target mesangial cells, podocytes, tubular epithelial cells, interstitial fibroblasts, as well as lymphocytes and macrophages. The anti-inflammation, anti-coagulation effects, and the proliferation- and immunity-modulating actions of retinoids, have been widely appreciated. Our recent in vitro data revealed a direct antifibrotic effect and a cytoprotective effect of retinoids in various renal cell types." Xu et al. (2004)	Retinoids; vitamin A metabolites; cell proliferation; cell differentiation; cell apoptosis; kidney; renal diseases; Vitamin A deficiency; retinoid nuclear receptors; fetal kidneys; hypertension; mesangial cells; podocytes; tubular epithelial cells; interstitial fibroblasts; lymphocytes; macrophages; anti-inflammation, anti-coagulation; immunity; retinoids; antifibrotic effect; cytoprotective effect; renal cell; lipid accumulation; smooth muscle cells; macrophages; proinflammatory molecules
DNS	"nutritional VAD in rats induces anatomic and metabolic changes comparable to those observed in brains exhibiting neurodegenerative disorders." Ghenimi et al. (2009)	Nutritional disturbances; serum retinol; MRI; global cerebral volume; hippocampal CTThV; NAA/Cr; MIns/Cr; Cho/Cr; Tau/Cr; amyloid β peptide; retinaldehyde dehydrogenase 2; RARα/β; hippocampal atrophy; brain atrophy; neurodegenerative disorders
Vitamin B12 deficiency [1].		
ICOV	"B12 deficiency is a potential modifiable risk factor in our fight against COVID-19." Wee (2021)	diabetes; vitamin B12 deficiency; immunologically; microbiologically; haematologically; endothelial cell signalling
WIS	"the elevation of the $CD4^+CD8^-$/CD4-$CD8^+$ ratio by vitamin B12-deficiency was confirmed in rats. The serum C3, IgM and IgG concentrations were lower in the vitamin B12-deficient group than in the control group. These findings suggest that vitamin B12 plays a role in maintaining the immune function in rats" Funada et al. (2000)	cell-mediated immune functions; humoral immune functions; splenocytes; CD4; CD8; serum C3; IgM; IgG; $CD4^+CD8^-$/CD4-$CD8^+$ ratio;
IIC	"Homocysteine is a sulfur-containing amino acid whose metabolism stands at the intersection of two pathways: remethylation to methionine, which requires folate and vitamin B12 (or betaine in an alternative reaction) … Mild hyperhomocysteinemia seen in fasting condition is due to mild impairment in the methylation pathway (i.e. folate or B12 deficiencies or MTHFR thermolability). … High levels of homocysteine induce sustained injury of arterial endothelial cells, proliferation of arterial smooth muscle cells and enhance expression/activity of key participants in vascular inflammation, atherogenesis, and vulnerability of the established atherosclerotic plaque. … the effect of elevated homocysteine appears multifactorial affecting both the vascular wall structure and the blood coagulation system." Guilland et al. (2003)	hyperhomocysteinemia; vascular disease; Homocysteine; pathways: remethylation; methionine; folate; vitamin B12; betaine; transsulfuration; cystathionine; vitamin B6; S-adenosylmethionine; methylenetetrahydrofolate reductase; MTHFR; cystathionine beta-synthase; CBS; homocysteine metabolism; enzymes; methyl cobalamine synthesis; homocysteine methylation; methylation pathway; heterozygous cystathionine-beta-synthase defect; B6 deficiency; homocystinuria; hyperhomocysteinemia; arterial thrombotic events; venous thromboembolism; arteriosclerosis; homocysteine; vascular changes; arterial endothelial cells; arterial smooth muscle cells; vascular inflammation; atherogenesis; atherosclerotic plaque; reactive oxygen species; endothelium; relaxing factor; nitric oxide; transcription factors; signal transduction; oxidation; low-density lipoproteins; endothelium-dependent vasodilatation; vascular wall structure; blood coagulation system
DNS	"Vitamin B12 deficiency is common in aging and causes a number of neurological conditions including cognitive and psychiatric disturbances, gait instability, neuropathy, and autonomic dysfunction" Luthra et al. (2020)	Mild cognitive impairment; multiple systems atrophy; progressive supranuclear palsy; Lewy bodies; frontotemporal dementia; LRRK2; α-synuclein; amyloid β peptide; B12 levels
Vitamin C deficiency [1].		
ICOV	"the present review aims to provide a comprehensive overview of the roles of zinc and vitamins C and D in the immune response to viral infections ….The evidence found in the literature shows that deficiency of one or more of these three elements compromises the immune response, making an individual more vulnerable to viral infections and to a worse disease prognosis. Thus, during the COVID-19 pandemic, the adequate intake of zinc and vitamins C and D may represent a promising pharmacological tool due to the high demand for these nutrients in the case of contact with the virus and onset of the inflammatory process." Name et al. (2020)	immune system; immune response; zinc; vitamin C; vitamin D; immunomodulatory; physical tissue barriers; viral infection; inflammatory

(*continued on next page*)

Table 1 (*continued*)

Vitamin C deficiency [1].		
WIS	"Vitamin C deficiency results in impaired immunity and higher susceptibility to infections." (Carr and Maggini, 2017)	antioxidant; immune defense; innate immune system; adaptive immune system; epithelial barrier function; oxidant scavenging activity; oxidative stress; phagocytic cells; neutrophils; chemotaxis; phagocytosis; reactive oxygen species; microbial killing; apoptosis; macrophages; necrosis; NETosis; tissue damage; lymphocytes; cells; T-cells; gene regulating; immunity; infections; inflammation; respiratory infections; systemic infections; metabolic demand
IIC	"Bloods showed mild thrombocytopenia and anaemia with markedly raised inflammatory markers. Coagulation studies consistent with inflammation rather than disseminated intravascular coagulation. She was found to have Klebsiella bacteraemia secondary to urinary source. Skin biopsy showed dermal hemorrhage without vessel inflammation. Vitamin C levels were low confirming the diagnosis of scurvy." (Inglis and Tan, 2020)	lower limb bruising; colon cancer; malignant sacral mass; spinal cord; left-sided foot drop; macular ecchymoses; petechiae; lower limbs; ankle-foot orthosis; thrombocytopenia; anaemia; inflammatory markers; inflammation; disseminated intravascular coagulation; *Klebsiella* bacteraemia; skin biopsy; dermal hemorrhage; vessel inflammation; Vitamin C levels; scurvy
DNS	"intracellular vitamin C deficiency plays an important role in accelerating amyloid pathogenesis, particularly during early stages of disease development, and that these effects are likely modulated by oxidative stress pathways." Dixit et al. (2015)	SVCT; BACE1; amyloid β peptide; APP; PSEN1; oxidative stress; MDA, protein carbonyl; isoprostanes; F2-isoprostanes; GFAP; GSH; GSSG; vitamins C level; cognitive decline
Vitamin D deficiency [1].		
ICOV	"Two causal modeling studies and several analyses of variance strongly supported the hypothesis that vitamin D deficiency is a causal, rather than a bystander, factor in COVID-19 outcomes." Benskin (2020)	vitamin D deficiency; innate immune system; viral infections; X-chromosome; Renin-Angiotensin System; cytokine storm; immune system overreaction; obese; hypertension; cardiovascular disease; diabetes; dengue fever; virus replication;
WIS	"Vitamin D can regulate the antiviral immune response in the respiratory tract in order to provide an effective defense against respiratory viral infections and prevention from excessive inflammatory response and tissue damage. In addition, this vitamin has preventive effects against respiratory viral infections." Vaghari-Tabari et al. (2021)	Respiratory viral infections; Influenza viruses; unregulated immune response; inflammation; tissue damage; antiviral immune response; immune regulation; COVID-19
IIC	"Patients with sepsis have a high mortality rate as well as a high prevalence of vitamin D deficiency. In addition, septic patients have decreased vitamin D binding protein levels which further exacerbates vitamin D deficiency. Therapy with vitamin D in animal models of sepsis improves blood coagulation parameters in disseminated intravascular coagulation and modulates levels of systemic inflammatory cytokines including TNF-α and IL-6. Vitamin D can enhance the induction of the antimicrobial peptides cathelicidin and β-defensin which are found on mucosal and epithelial surfaces and act as the body's first line of defense against viral and bacterial pathogens." Watkins et al. (2011)	vitamin D; bone homeostasis; calcium homeostasis; innate immune system; adaptive immune system; vitamin D receptors; 1, 25-dihydroxyvitamin D; sepsis; vitamin D binding protein levels; blood coagulation; disseminated intravascular coagulation; inflammatory cytokines; TNF-α; IL-6; antimicrobial peptides; cathelicidin; β-defensin; mucosal surfaces; epithelial surfaces
DNS	"Prospective studies and meta-analyses have demonstrated that low serum or plasma vitamin D levels increased the risk of dementia [15, 16], cognitive impairment [12, 13], impaired motor functions [17, 18], and memory decline [19] which are all characteristics of neurodegenerative diseases. Additionally, evidence from cross-sectional studies has shown the impact of vitamin D deficiency on falls and balance in Parkinson's disease (PD)" Koduah et al. (2017)	Amyloid β peptide; cognitive decline; neuroinflammation; apolipoprotein E; IL-17; immunomodulation; 1α-hydroxylase activity; dopaminergic neurons; vitamin D level; vitamin D receptor polymorphisms
Vitamin K deficiency [1].		
ICOV	"Early in acute COVID-19, both vitamin K and vitamin D deficiency were independently associated with worse COVID-19 disease severity, suggesting a potential synergistic interplay between these 2 vitamins in COVID-19″ Desai et al. (2021)	vitamin K; vitamin D; COVID-19; dephosphorylated uncarboxylated matrix Gla protein; dp-ucMGP; 25-hydroxyvitamin D; 25(OH)D
WIS	"Temporal association between serious bleeding and immunization: vitamin K deficiency as main causative factor" Susanah et al. (2020)	Bleeding; immunization; AEFI; acquired disorders; hereditary disorders; acquired prothrombin complex deficiency; APCD; vitamin K deficiency bleeding; VKDB
IIC	"Vitamin K deficiency was more common in patients with higher CD activity, in CD patients with higher mass Z-scores, and less common among children with CD treated with infliximab" Nowak et al. (2014)	vitamin K deficiency; inflammatory bowel disease; IBD; Crohn's disease; CD; ulcerative colitis; UC; protein induced by vitamin K absence-II; PIVKA-II; ELISA; mass Z-scores; infliximab
DNS	"Levels of proteins induced by vitamin K absence for factor II (PIVKA-II) reflect hypocarboxylated prothrombin and can be used to detect subclinical vitamin K deficiency." Dahlberg et al. (2017)	Vitamin K; carboxylation; hepatic coagulation proteins; Vitamin K absence for factor II; PIVKA-II; hypocarboxylated prothrombin; coagulation; brain tumor resection; prothrombin times; PT-INR; body mass index; BMI
Western Diet [1].		
ICOV	"The high rate of consumption of diets high in saturated fats, sugars, and refined carbohydrates (collectively called Western diet, WD) worldwide, contribute to the prevalence of obesity and type 2 diabetes, and could place these populations at an increased risk for severe COVID-19 pathology and mortality. WD consumption activates the innate immune system and impairs adaptive immunity, leading to chronic inflammation and impaired host defense against viruses." (Butler, Barrientos, 2020)	obesity; type 2 diabetes; COVID-19; mortality; innate immune system; adaptive immunity; chronic inflammation; host defense; viruses; peripheral inflammation; dementia; neurodegenerative; neuroinflammatory

(*continued on next page*)

Table 1 (*continued*)

Western Diet [1].		
WIS	"Western diet-induced dysbiosis of the gut microbiota has been shown to negatively impact human digestive physiology, to have pathogenic effects on the immune system, and, in turn, cause exaggerated neuroinflammation. Given the tremendous amount of evidence linking neuroinflammation with neural dysfunction, it is no surprise that the Western diet has been implicated in the development of many diseases and disorders of the brain, including memory impairments, neurodegenerative disorders, and depression." Olmo et al. (2021)	commensal microbial species; gut health; human gut microbiota; microbes; immune system; dysbiosis; neuroinflammation; neural dysfunction; memory impairments; neurodegenerative disorders; depression
IIC	"In association with hepatic steatosis, plasma thrombin-antithrombin levels and hepatic fibrin deposition increased significantly in C57Bl/6J mice fed a Western diet for 3 months." Kassel et al. (2011)	Nonalcoholic fatty liver disease; NAFLD; obesity; metabolic syndrome; cardiovascular disease; liver-related morbidity and mortality; thrombin; coagulation cascade activation; thrombin receptor; protease-activated receptor 1; PAR-1; hematopoietic cell; tissue factor; TF; hepatic steatosis; thrombin-antithrombin levels; hepatic fibrin deposition; hepatic inflammation; monocyte chemoattractant protein-1 expression; macrophage accumulation; liver triglyceride accumulation; CD36 expression; inflammation; steatosis; livers; low-density lipoprotein receptor; hematopoietic cell TF; hepatic fibrin deposition
DNS	"A western diet can cause nutrient deficiency and inflammation that could impact cognition directly. However, a western diet in combination with physical inactivity can lead to obesity that increases risk of cognitive decline and AD." Graham et al. (2016)	Obesity; TREM2; APP; PS1; IBA; GFAP; amyloid β peptide; cognitive decline; neuroinflammation; IL-1β; IL-10; neuronal cell loss; NeuN; microglia responses; monocyte responses
Zinc deficiency [1].		
ICOV	"Our study demonstrates a correlation between serum zinc levels and COVID-19 outcome. Serum zinc levels lower than 50 g/dL at admission correlated with worse clinical presentation, longer time to reach stability, and higher mortality. Our in vitro results indicate that low zinc levels favor viral expansion in SARS-CoV-2 infected cells" Vogel-Gonzalez et al. (2021)	infection; immune responses; antiviral; viruses; zinc deficiency; chronic diseases; severe coronavirus disease 2019; serum zinc content; SZC; Vero E6 cell line; serum zinc levels; viral expansion; infected cells
WIS	"zinc status is a critical factor that can influence antiviral immunity, particularly as zinc-deficient populations are often most at risk of acquiring viral infections such as HIV or hepatitis C virus." Read et al. (2019)	immune function; human proteome; antiviral immunity; viral infections; HIV; hepatitis C virus; herpes simplex virus; common cold
IIC	"Zinc deficiency is associated with impairment of numerous metabolic processes, reduced resistance to infections due to impaired immune functions, changes in skin and its appendages and disorders of wound healing and haemostasis." Grungreiff et al. (2020)	metabolic; immunological; regulatory function; zinc ion; $Zn^{2+;}$ proteins; cellular zinc homeostasis; metabolic processes; infections; immune functions; skin; appendages; wound healing; haemostasis; ischemic heart attacks; myocardial infarction; haemorrhagic strokes; micronutrients; vitamin B12; vitamin D; amino acids; zinc; albumin; zinc deficiency; blood vessels; blood coagulation
DNS	"zinc deficiency has been shown to affect neurogenesis and increase neuronal apoptosis, which can lead to learning and memory deficits. Altered zinc homeostasis is also suggested as a risk factor for depression, Alzheimer's disease (AD), aging, and other neurodegenerative disorders." Szewczyk (2013)	ZnT; Zip; metallothioneins; GPR39; oxidative stress; ROS; NOS; NADPH oxidase; CaM; CaMKII; CREB; TrkB; BDNF; MMPs; amyloid β peptide; apolipoprotein E; APP; BACE-1; apoptosis

Notes.

Table 1 contains eighty sub-tables, one sub-table for each CF. The heading for each sub-table is the CF that was validated followed by the category (CAT) to which the CF is assigned (1 = lifestyle; 2 = iatrogenic; 3 = biotoxin; 4 = occupational/environmental; 5 = psychosocial/socioeconomic). The sub-tables are listed in alphabetical order of the CFs. Thus, the first sub-table listed has the overall heading Advanced glycation end products [1], where Advanced glycation end products was the CF validated, and [1] was the category to which the CF was assigned.

Each sub-table of Table 1 contains three columns. The first column (TARG) is one of the four CF targets being addressed (ICOV-Impact COVID-19; WIS-Weaken Immune System; IIC-Increase Inflammation/Coagulation; DNS-Damage Neural System). The second column (QUOTES/REFERENCES) contains the narrative describing the link between the CF and the target of interest (QUOTES), followed by the reference from which the narrative was extracted. The third column (BIOMARKERS) contains the general and specific biomarkers from the cited reference's abstract.

T = Target Code: ICOV-Impact COVID-19; WIS-Weaken Immune System; IIC-Increase Inflammation/Coagulation; DNS-Damage Neural System.

CAT=Category Code: 1-Lifestyle; 2-Iatrogenic; 3-Biotoxin; 4-Occupational/Environmental; 5-PsychoSocial/SocioEconomic.

Table 2
Sample Biomarkers for each Target Category

BIOMARKER	DIRECT COV-19	WEAKEN IMMUNE SYSTEM	INCR COAG AND INFLAMM	INCR NEURO DEGEN
ACE2	*			
CO	*			
cystatin C	*			
cytokine storm	*			
epithelial cells	*			
ferritin	*			
hyperinflammation	*			
IL2R	*			
immune dysregulation	*			
methemoglobin	*			
reduced barrier function	*			
respiratory dysfunction	*			
serum cytokines	*			
thrombin	*			

(*continued on next page*)

Table 2 (*continued*)

BIOMARKER	DIRECT COV-19	WEAKEN IMMUNE SYSTEM	INCR COAG AND INFLAMM	INCR NEURO DEGEN
vitamin B12 deficiency	*			
vitamin C	*			
vitamin D	*			
white blood cell count	*			
advanced glycation end products		*		
antibodies		*		
B cells		*		
CD4		*		
CD8 T cell		*		
cell death		*		
chemokines		*		
dysbiosis		*		
Foxp3		*		
gut microbiota		*		
hemoglobin		*		
ICAM-1		*		
IgA		*		
IgE		*		
IgG		*		
IgM		*		
IL-10		*		
IL-1β		*		
IL-4		*		
immune activation		*		
immunoglobulin		*		
immunosuppression		*		
inflammatory response		*		
interferon-γ		*		
leukocyte		*		
lymphocytes		*		
metabolic dysregulation		*		
Monocytes		*		
naive T-cells		*		
natural killer T cells		*		
necrosis		*		
neutrophils		*		
NK cells		*		
PD-1		*		
peripheral blood mononuclear cells		*		
phagocytes		*		
phagocytosis		*		
platelets		*		
reactive oxygen species		*		
regulatory T cells		*		
skin lesions		*		
T-cells		*		
Th1/Th2		*		
THP-1-derived macrophages		*		
thymocytes		*		
tissue damage		*		
TLR2		*		
TLRs		*		
TNF		*		
Tregs		*		
antithrombin III			*	
aPTT			*	
arterial endothelial cells			*	
aspartate aminotransferase			*	
AT-III			*	
autophagosome			*	
blood flow			*	
body mass index			*	
catalase			*	
CD3+T lymphocytes			*	
cell adhesion molecule			*	
coagulation			*	
complement activation			*	
C-reactive protein			*	
cytokines			*	
D-dimer			*	
disseminated intravascular coagulation			*	
endothelial barrier			*	
endothelial dysfunction			*	
erythrocyte aggregation			*	
Factor X			*	
fibrin formation			*	

(*continued on next page*)

Table 2 (*continued*)

BIOMARKER	DIRECT COV-19	WEAKEN IMMUNE SYSTEM	INCR COAG AND INFLAMM	INCR NEURO DEGEN
fibrinogen			*	
fibrinolytic factors			*	
glutathione			*	
hematopoietic cell TF			*	
hepatic dysfunction			*	
homocysteine			*	
hs-CRP			*	
hyperhomocysteinemia			*	
hypertension			*	
IFN-γ			*	
IL-6			*	
il6st			*	
IL-8			*	
inflammation			*	
inflammatory cytokines			*	
intercellular adhesion molecule-1			*	
JAK1/TF signaling pathway			*	
lipid accumulation			*	
low-density lipoproteins			*	
macrophages			*	
magnesium			*	
malondialdehyde			*	
mast cells			*	
MCP-1			*	
micronutrients			*	
MIP-1alpha			*	
miR-155			*	
monocyte chemoattractant protein-1			*	
mRNA			*	
multi-organ failure			*	
nitric oxide			*	
oxidative stress			*	
p38MAPK			*	
PAI-1			*	
permeability			*	
plasminogen activator inhibitor type 1			*	
platelet aggregation			*	
PPAR			*	
procoagulant cytokines			*	
pro-inflammatory cytokines			*	
proteins			*	
prothrombin time			*	
Retinoids			*	
sodium			*	
T cells			*	
thrombocytopenia			*	
thrombosis			*	
tissue plasminogen activator			*	
TNF-α			*	
tPA			*	
triglycerides			*	
tumor necrosis factor-alpha			*	
vascular cell adhesion molecule-1			*	
vascular endothelial cells			*	
vascular endothelial growth factor			*	
von Willebrand factor			*	
white blood cells			*	
zinc			*	
5-HT				*
8-OhdG				*
Abca1				*
AChE				*
Akt				*
AMPA				*
amyloid β peptide				*
apolipoprotein E				*
ARG1				*
ATP				*
BACE1				*
Bax				*
Bcl2				*
BDNF				*
Beclin-1				*
Ca2+				*
CaMKII				*
caspase 3				*

(*continued on next page*)

Table 2 (*continued*)

BIOMARKER	DIRECT COV-19	WEAKEN IMMUNE SYSTEM	INCR COAG AND INFLAMM	INCR NEURO DEGEN
caspase 8				*
caspase 9				*
CAT				*
CCL2				*
Cdk-5				*
c-Fos				*
cholesterol				*
choline				*
cognitive impairment				*
COX-2				*
creatinine				*
CREB				*
cytochrome C				*
DNA damage				*
dopamine				*
endolysosome pH				*
ERK				*
GABA				*
GFAP				*
glutamate				*
GPx				*
GSH				*
GSK-3β				*
GSSG				*
HDACs				*
hippocampal atrophy				*
HMGB1				*
HO-1				*
Hsp70				*
hyperphosphorylated Tau				*
Iba-1				*
IGF-1R				*
IL-1				*
IL-17				*
iNOS				*
MAO				*
MAP2				*
MAPK				*
MDA				*
memory decline				*
microglial activation				*
mitochondrial dysfunction				*
MMPs				*
NADPH oxidase				*
NeuN				*
neurodegeneration				*
neuroinflammation				*
NF-κB				*
NMDA				*
NMDA receptor				*
NOS				*
Nrf2				*
p53				*
PARP				*
PGE2				*
PKA				*
PKC				*
protein carbonyl				*
RAGE				*
RNS				*
ROS				*
serotonin				*
SOD				*
Tau				*
VEGF				*

APPENDIX 3. FACTOR MATRIX AND HIERARCHICAL CLUSTERING TAXONOMY

Table 3
Factor Matrix of key abstract phrases

FACTOR 1 - MITOCHONDRIAL DYSFUNCTION mitochondrial (H); apoptosis (H); mitochondrial membrane potential (H); cell death (H); membrane (H; 32-M); reactive oxygen species (H; 10-H); cytochrome *c* (H); caspase-3 (H); mitochondria (H); Bcl-2 (H); cytochrome (H); Bax (H; 27A-H); neuronal cell (H); N-acetyl-L-cysteine (H); mitochondrial dysfunction (H); ATP (M); cadmium (M); mitochondrial function (M); death (M); pro-apoptotic (M); neuronal (M; 3-H; 24-M); protein (M; 22-M); intracellular (M); phosphorylation (M); cell apoptosis (M); caspase (M); mitogen-activated protein kinase (M); cytotoxicity (M); oxidative stress (M; 10-H); mTOR (M); heavy metal (M); DNA fragmentation (M); Akt (M); caspase-9 (M); membrane integrity (M).

FACTOR 2 - INSULIN RESISTANCE insulin (H); glucose (H); insulin resistance (H); metabolic dysfunction (H); impaired glucose tolerance (H); obesity (H); metabolism (H; 12-M); diabetes (H); insulin sensitivity (H); hyperglycemia (H); adipose tissue (H; 27-M); blood glucose (H); fasting glucose (H); fat (H); glucose intolerance (H); glucose levels (M); triglyceride (M; 18-H); high-fat diet (M); Syndrome (M); western diet (M; 7-M); weight gain (M; 27-M); lipid (M; 10-H; 18-M); weight (M; 27-H); glucose metabolism (M); lipid metabolism (M; 12-M); fructose (M); plasma glucose (M); dyslipidemia (M); body weight (M; 27-H).

FACTOR 3 - COGNITIVE DECLINE memory (H); learning and memory (H); cognitive (H); learning (H); cognitive decline (H); hippocampus (H); brain (H; 24-M; 25-M); Alzheimer's disease (H); neuronal (H; 1-M; 24-M); cognitive function (H); neurodegenerative diseases (H; 27-M); spatial learning (H); memory deficits (H); spatial memory (H); synaptic (H); Tau (H); cortex (M; 26-H); Abeta (M); neuroinflammation (M); memory function (M); neurotoxicity (M; 24-M); BDNF (M).

FACTOR 4 - PROINFLAMMATORY CYTOKINES cytokines (H); IFN-gamma (H); Th2 (H; 26-M); IL-4 (H); T cells (H; 14-M; 23-H); IL-10 (H); tumor necrosis factor-alpha (H; 10-M; 22-M; 30-M); $CD4^+$ (H; 23-M); Th1 (H); pro-inflammatory cytokines (H); IL-6 (H); interleukin (H); inflammation (H; 8-M; 22-M); lymphocytes (H; 30-M); Th1/Th2 (H); $CD8^+$ (H; 23-M); IL-2 (H); spleen (M); regulatory T cells (M); cytokine production (M); immune response (M; 23-M; 31-M); necrosis (M; 28-M); T lymphocytes (M); IL-1beta (M; 22-M); IL-12 (M); Th17 (M); cytokine secretion (M); thymus (M); tumor (M; 15-H); splenocytes (M); interferon (M); cell activation (M).

FACTOR 5 – COAGULATION coagulation (H; 20-M); plasminogen activator (H); fibrinogen (H); fibrinolysis (H); prothrombin (H); PAI-1 (H); von Willebrand factor (H; 20-M); C-reactive protein (M); thrombotic (M); coagulation factors (M); platelet aggregation (M); plasma (M); thrombin (M); thrombosis (M; 20-M); platelets (M); nanoparticles (M; 8-M; 26-M; 28-M); blood coagulation (M); Silica nanoparticles (M; 26-M; 28-M); cardiovascular system (M; 11-M); plasma levels; inflammation (4-H; 8-M; 22-M); vitamin K deficiency (16-M).

FACTOR 6 - AIR POLLUTION, EMPHASIZING PARTICULATE MATTER particulate matter (H; 19-H); PM2.5 (H; 19-M); air pollution (H; 19-H); PM10 (H; 19-M); pollution (H; 19-M); nitrogen (H; 19-M); PM2.5-10 (H; 19-M); nitrogen dioxide (H; 19-M); sulfur dioxide (H); sulfur (H); ozone (H); carbon monoxide (H; 11-M); carbon (M); ambient particulate matter (M); nitrogen oxides (M); serotonin (M; 19-H); selective serotonin reuptake inhibitors (M; 19-H); antidepressants (19-H); monoamine (19-H); tricyclic antidepressants (19-H); tramadol (19-H); respiratory diseases; morphine (19-H); respiratory (8-M; 26-M); bronchial; analgesic (19-H); dopamine (19-M); stroke; opioid (19-H); asthma (26-H); inflammation (4-H; 8-M; 22-M).

FACTOR 7 - GUT DYSBIOSIS gut (H); microbiota (H); Gut microbiota (H); dysbiosis (H); microbiome (H); intestinal (H); gut microbiome (H); rRNA (H); intestinal microbiota (H); fecal (H); intestinal barrier function (M); western diet (M; 2-M); fatty acids (M); intestinal permeability (M); bacteria (M); gastrointestinal (M); antibiotic (M); permeability.

FACTOR 8 - PULMONARY DAMAGE lung (H); Pulmonary (H); alveolar (H); Alveolar macrophages (H); lung tissue (H); bronchoalveolar (H); macrophages (H); lung injury (H); silica (H; 26-M; 28-M); silicosis (H); pulmonary fibrosis (H); lung inflammation (H); intratracheal (H); inflammation (M; 4-H; 22-M); chronic obstructive pulmonary disease (M); fibrosis (M); epithelium (M); lung disease (M); respiratory (M; 26-M); lung function (M); inflammatory cells (M; 22-M); pulmonary function (M); tissue (M); nanoparticles (M; 5-M; 26-M; 28-M); titanium dioxide (M); neutrophil (M).

FACTOR 9 - KIDNEY DYSFUNCTION kidney (H); renal (H); urea (H); creatinine (H); urea nitrogen (H); nephrotoxicity (H); glomerular filtration rate (H); acute kidney injury (H); kidney function (H); renal tissue (H); renal disease (H; 28-M); chronic kidney disease (H); renal function (M); liver and kidney (M); albumin (M); urine (M); urinary (M); Kidney transplant; hemodialysis (28-M); dialysis (28-M); Bcl-2 (H; 1-H).

FACTOR 10 - OXIDATIVE STRESS glutathione (H); superoxide dismutase (H); catalase (H); lipid peroxidation (H); oxidative stress (H; 1-M); antioxidant enzymes (H); malondialdehyde (H); enzyme (H); lipid (H; 2-M; 18-M); oxidation (H); dismutase catalase (H); antioxidants (H); reactive oxygen species (H; 1-H); oxidative damage (M); antioxidant capacity (M); antioxidant defense (M; 32-M); DNA damage (M; 30-H); hydrogen peroxide (M); Protein Carbonyl (M); total antioxidant (M); protein oxidation (M; 32-M); cardiotoxicity (M); creatine (M); DNA (M; 13-M; 30-H); tumor necrosis factor-alpha (M; 4-H; 22-M); Nrf2 (M); nitric oxide (M; 20-H); vitamin C (M); lactate dehydrogenase (M); intraperitoneally; vitamin E; free radical.

FACTOR 11 - CARDIAC DYSFUNCTION cardiac (H); heart (H); ventricular (H); left ventricular (H); myocardial (H); heart failure (H); cardiovascular (H; 20-M); cardiac function (H); cardiac dysfunction (H); ejection fraction (H); ischemic heart (H); arrhythmias (M); heart rate (M); myocardial infarction (M); congestive heart failure (M); heart disease (M); cardiomyocytes (M); cardiovascular disease (M; 20-M); ischemic (M); carbon monoxide (M; 6-H); cardiovascular system (M; 5-M); troponin (M); cardiomyopathy (M); hypertrophy (M).

FACTOR 12 - LIVER DISEASE liver disease (H); steatosis (H); non-alcoholic fatty liver disease (H); liver (H; 28-M); hepatic (H; 28-M); hepatic steatosis (H); steatohepatitis (H); hepatocellular (H; 15-M); hepatocellular carcinoma (M; 15-M); alanine aminotransferase (M; 28-H); chronic liver disease (M); liver injury (M; 28-H); lipid metabolism (M; 2-M); metabolism (M; 2-H); carcinoma (M; 15-H); hepatocytes (M; 28-M); protein-1 (M); aminotransferase (M; 28-H); diet-induced; liver tissue; liver function (28-M); liver failure.

FACTOR 13 - CHRONIC ARYL HYDROCARBON RECEPTOR ACTIVATION Aryl hydrocarbon receptor (H); hydrocarbons (H); 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (H); gene (H; 22-M); methylation (H); DNA methylation (H); epigenetic (H); Polycyclic aromatic hydrocarbons (H; 30-M); xenobiotic (H); receptor (H); gene expression (M); DNA (M; 10-M; 30-H); mRNA (M; 22-H; 26-M); histone (M); collagen (M; 5-M); ligands (M); muscle actin (M); Environmental pollutant (M); dioxin.

FACTOR 14 - BONE MARROW TRANSPLANTATION bone marrow (H); bone marrow transplantation (H); GVHD (H); bone (H; 16-H); Graft-versus-host disease (H); myeloid (H); myeloid leukemia (H); leukemia (H); hematopoietic (H); malignancies (H; 15-M); marrow cells (M); T cells (M; 4-H; 23-H); lymphoma (M); lymphoproliferative (M); hematologic (M); stem cell (M); B-cell (M; 31-H); immunosuppression (M); $CD3^+$; anemia (21-M); T-cell receptor.

FACTOR 15 - COLORECTAL CANCER cancer (H); colorectal cancer (H); colon (H; 21-H); tumor (H; 4-M); meat intake (H); colon cancer (H); carcinoma (H; 12-M); rectal (H); radiotherapy (M); metastasis (M); chemotherapy (M); processed meat (M); breast cancer (M); lung cancer (M); carcinogenesis (M; 30-M); carcinogenic (M; 30-M); hepatocellular carcinoma (M; 12-M); marital status (M); malignancies (M; 14-H); DNA adducts (M; 30-M); hepatocellular (M; 12-H); adenocarcinoma.

FACTOR 16 - BONE LOSS Osteoporosis (H); bone mineral density (H; 21-M); bone (H; 14-H); fracture (H); bone mass (H); osteoblast (H); bone loss (H); Osteocalcin (H; 21-M); bone formation (H); Glucocorticoid (H); vitamin K deficiency (M); dexamethasone (M); phosphatase (M; 31-M); parathyroid hormone (M); femoral head (M).

FACTOR 17 - THYROID DYSFUNCTION thyroid (H); thyroid hormone (H); thyroid function (H); thyroid gland (H); hormone (H); thyroxine (H); gland (H); endocrine (H); endocrine disruptors (M); fertility (M).

FACTOR 18 - ABNORMAL CHOLESTEROL LEVELS lipoprotein (H); cholesterol (H); low-density lipoprotein (H); high-density lipoprotein (H); lipoprotein cholesterol (H); total cholesterol (H); triglyceride (H; 2-M); hypercholesterolemia (H); cholesterol levels (H); atherosclerosis (20-H); lipid (M; 2-M; 10-H); atherogenesis (M; 20-M); apolipoprotein (M); high cholesterol (M); lipid profiles; aorta (20-H).

FACTOR 19A – ANTIDEPRESSANTS serotonin (H; 6-M); antidepressants (H); selective serotonin reuptake inhibitors (H; 6-M); tricyclic antidepressants (H); monoamine (H); tramadol (H); morphine (H); analgesic (H); opioid (H); antipsychotic drugs (H); depression (M); hypotension (M); dopamine (M); Clozapine (M); risperidone; cardiovascular effects; psychosis; neurotransmitters.

FACTOR 19B - AIR POLLUTION, EMPHASIZING PARTICULATE MATTER air pollution (H; 6-H); particulate matter (H; 6-H); PM2.5 (M; 6-H); PM10 (M; 6-H); pollution (M; 6-H); nitrogen dioxide (M; 6-H); PM2.5-10 (M; 6-H); nitrogen (M; 6-H); carbon monoxide (6-H); sulfur dioxide (6-H); carbon (6-M); sulfur (6-H); ozone (6-H); ambient particulate matter (6-M); nitrogen oxides (6-M); ischemic (11-M); methylation (13-H); heart disease (11-M); lung (8-H).

(*continued on next page*)

Table 3 (*continued*)

FACTOR 20 - ENDOTHELIAL DYSFUNCTION endothelial (H); vascular (H); endothelial cells (H); endothelial dysfunction (H); endothelium (H); aorta (H); vascular endothelial (H); arterial (H); nitric oxide (H; 20-M); atherosclerosis (H); inducible nitric oxide synthase (M; 22-M); endothelial function (M); endothelial nitric oxide synthase (M); cardiovascular (M; 11H); von Willebrand factor (M; 5-H); vessels (M); vasculature (M); smooth muscle cells (M); vascular dysfunction (M); blood vessels (M); atherogenesis (M; 18-M).
FACTOR 21 - INFLAMMATORY BOWEL DISEASE Inflammatory Bowel Disease (H); colitis (H); ulcerative colitis (H); Bowel (H); Crohn's disease (H); iron deficiency (H; 15-M; 16-M); iron deficiency anemia (H); iron (H; 15-M; 16-M); colon (H; 15-H); anemia (M).
FACTOR 22 - SELENIUM DEFICIENCY Se deficiency (H); Selenium (H); selenoproteins (H); mRNA (H; 13-M; 26-M); NF-kappaB (H); trace element (H); Heat shock (H; 31-H); HSP70 (H; 31-M); mRNA and protein levels (M); COX-2 (M); protein (M; 1-M); shock (M; 31-M); inducible nitric oxide synthase (M; 20-M); tumor necrosis factor-alpha (M; 4-H; 10-M; 30-M); protein expression (M); inflammatory response (M); inflammation (M; 4-H; 8-M); IL-1beta (M; 4-M); inflammatory cells (M; 8-M).
FACTOR 23 - VIRAL INFECTIONS virus (H); infection (H); Herpes simplex virus (H); encephalitis (H); Cytomegalovirus (H); T cells (H; 4-H; 14-M); corneal (H); keratitis (H); $CD8^+$ (M; 4-H); immune response (M; 4-M; 31-M); $CD4^+$ (M; 4-H); Epstein-Barr virus (M); immunodeficiency (M); viral infections (M); immunity (M); immunocompetent (M); COVID-19 (M); ocular (M); inflammatory diseases.
FACTOR 24 - NEUROLOGICAL DYSFUNCTION neurological (H); neuropathy (H); nervous system (H); brain (M; 3-H; 26-M); central nervous system (M); dizziness (M); Methyl bromide (M); cerebral (M); cerebellum (M); ataxia (M); pain (M); poisoning (M); neuronal (M; 1-M; 3-H); nerve (M); headache (M); olfactory (M); Pregabalin (M); atrophy (M); vomiting (M); brain injury (M); neurotoxicity (M; 3-M).
FACTOR 25 - PERFLUORINATED ALKYLATES perfluorinated alkylate substances (M); perfluorooctanoic acid (M); tetanus (M); perfluorooctane sulfonate (PFOS) (M); diphtheria (M); immunotoxicity (M); immune suppression (M); antibodies (M; 31-M).
FACTOR 26A - RESPIRATORY ALLERGIC REACTIONS Allergy (M); asthma (M); respiratory (M; 8-M); IgE (M); anaphylaxis (M); Th2 (M; 4-H); mast cells (M); respiratory symptoms (M); histamine; rhinitis; analgesic (19-H); bronchial; hypersensitivity.
FACTOR 26B - BRAIN DAMAGE FROM NANOPARTICLES cortex (H; 3-M); silica (M; 8-H; 28-M); nanoparticles (M; 5-M; 8-M; 28-M); striatum (M); Silica nanoparticles (M; 5-M; 28-M); frontal cortex (M); MCP-1 (M); brain (M; 3-H; 24-M); monocyte (M); Iron (M; 15-M; 16-M; 21-H); mRNA (M; 13-M; 22-H); IL-1beta (4-M; 22-M); cerebral cortex; prefrontal cortex.
FACTOR 27A - OVARIECTOMY-INDUCED ADIPOSITY weight (H; 2-M); body weight (H; 2-M); weight gain (M; 2-M); ovariectomy (M); ovary (M); Bax (M; 1-H); adipose tissue (M; 2-H); uterus; Bcl-2; fat (2-H).
FACTOR 27B - NEURODEGENERATIVE DISEASES sclerosis (M; 28-M); Multiple sclerosis (M; 28-H); neurodegenerative diseases (M; 3-H); neuronal cell (1-H); autoimmune (28-M); central nervous system (24-M); Parkinson's disease; nervous system (24-H); neurological (24-H); Alzheimer's disease (3–H); methylprednisolone (28-M); diabetes (2-H).
FACTOR 28 - LIVER DAMAGE BIOMARKERS alanine aminotransferase (H; 12-M); aminotransferase (H; 12-M); hepatotoxicity (H); aspartate aminotransferase (H); liver injury (H; 12-M); Multiple sclerosis (H; 27-M); liver (M; 12-H); sclerosis (M; 27-M); hepatic (M; 12-H); Silica nanoparticles (M; 5-M; 26-M); nanoparticles (M; 5-M; 8-M; 26-M); methylprednisolone (M); liver function (M); hepatocytes (M; 12-M); necrosis (M; 4-M); autoimmune (M); silica (M; 8-H; 26-M).
FACTOR 29 - SUBSTANCE ABUSE, EMPHASIZING SMOKING smoking (H); tobacco (H); alcohol (H); maternal smoking (H); birth weight (H); maternal smoking during pregnancy (H); substance abuse (H); nicotine (H); tobacco smoke; low birth weight (M); cocaine (M); alcohol intake (M); cannabis (M); gestational age (M); drug abuse (M); cigarette smoke (M).
FACTOR 30 - DNA DAMAGE DNA (H; 10-M; 13-M); genotoxic (H); DNA damage (H; 10-M); carcinogenic (M; 15-M); lymphocytes (M; 4-H); micronuclei (M); micronucleus (M); carcinogenesis (M; 15-M); DNA adducts (M; 15-M); Polycyclic aromatic hydrocarbons (M; 13-H); DNA strand breaks (M); metabolites; hydrocarbons (13-H); mutagenic; peripheral blood lymphocytes; amines; thymus (4-M); DNA repair.
FACTOR 31 - IMMUNE RESPONSE IgM (H); IgG (H); B-cell (H; 14-M); C3 (H); Heat shock (H; 22-H); immunoglobulin (H); complement (H); IgA (H); shock (M; 22-M); HSP70 (M; 22-H); phosphatase (M; 16-M); rituximab (M); B-cell lymphoma (M); immune response (M; 4-M; 23-M); immune function (M); antibodies (M; 25-M); immune organs; immunoglobulin G; IL-12 (4-M); spleen (4-M); lymphoma (14-M); thymus (4-M).
FACTOR 32 - NITRITE TOXICITY, ESPECIALLY PROTEIN OXIDATION Sodium nitrite (H); nitrite (H); NaNO2 (H); sodium (H); methemoglobin (H); erythrocytes (H); hemoglobin (M); protein oxidation (M; 10-M); nitrate (M); antioxidant defense (M; 10-M); membrane (M; 1-H); metabolic alterations (M); amino acid; membrane damage; blood cells; cysteine; meat intake (15-H); red blood cells; lipid peroxidation (10-H); cell membrane.

Code: Format is phrase followed by factor loading in parentheses. H is high factor loading (absval >0.3) and M is medium factor loading (0.2<absval<0.3). If phrase occurs in multiple factors with significant factor loadings, the first factor loading in parentheses is for the factor being discussed followed by the factor loading (s) and the number(s) of the additional factors. As an example, in Factor 1 the word "membrane" occurs with high factor loading and also occurs in Factor 32 with medium factor loading. Thus, it is denoted by "membrane (H; 32-M)".

Table 4
Hierarchical taxonomy of eighty CF impact records

LEVEL 2	LEVEL 4	LEVEL 6
CL 60 (1729) Impact of exposure to toxic substances on risks of chronic diseases primarily and infectious diseases secondarily	CL8 (125) Impact of air pollutants on health	CL8 (125) Impact of air pollutants on health
	CL53 (663) Impact of toxic personal habits and exposure to toxic substances on development of disease	CL25 (180) Impacts of maternal smoking and smoke exposure on children CL30 (241) Health impacts of malnutrition and sedentary lifestyle CL3 (54) Risk of red meat consumption, especially cancer CL20 (88) Impacts of polycyclic aromatic hydrocarbons on cancer CL22 (100) DNA damage, especially from ionizing radiation and polycyclic aromatic hydrocarbons
	CL18 (204) T-cell responses to viral infections	CL18 (204) T-cell responses to viral infections
	CL56 (737) Impacts of medical treatments and substance abuse on development and exacerbation of chronic and infectious disease in humans	CL17 (118) Infections and chronic diseases following kidney transplants CL24 (146) Adverse effects of drugs (especially nitrofurantoin, methyl prednisolone, rituximab), with emphasis on inducing liver disease in autoimmune patients CL26 (153) Toxicity of cancer treatments, especially radiotherapy, immunotherapy, chemotherapy CL12 (68) Role of substance abuse (especially alcohol) in developing chronic and infectious diseases CL14 (56) Opioid-induced chronic and infectious diseases CL15 (66) Role of antipsychotics (especially clozapine) and antidepressants in developing chronic and infectious diseases CL6 (63) Adverse events after pneumococcal vaccination CL0 (30) Toxicity of PFOS and PFOA CL4 (37) Increased risk of infectious and chronic diseases from proton pump inhibitors
CL61 (1804) Effects of vitamin and mineral deficiencies, and exposures to toxic substances, mainly to test animals in lab experiments	CL48 (164) Association of vitamin and mineral deficiencies with development and exacerbation of chronic and infectious diseases	CL1 (50) Adverse effects of Vitamin B12 deficiency on chronic diseases CL2 (55) Adverse effects of Vitamin D deficiency on chronic and infectious diseases CL7 (59) Primary emphasis on adverse effects of Vitamin K deficiency in chronic and infectious diseases, and secondary emphasis on adverse effects of Iron deficiency on chronic diseases
	CL49 (237) Impact of vitamin (mainly C) and mineral (mainly Se, Zn,Fe, Mg) on biomarkers (mainly inflammation, oxidative stress) of organ and tissue damage	CL5 (64) Adverse effects of selenium deficiency on organs and tissues, especially inflammation and oxidative stress CL9 (79) Adverse effects of Vitamin C deficiency primarily, and Zinc deficiency secondarily, on chronic and infectious diseases CL16 (94) Adverse effects of Zinc deficiency on chronic and infectious diseases, and secondarily adverse effects of Iron deficiency on chronic diseases
	CL28 (262)	CL28 (262) Adverse effects of high-fat/Western diet on chronic diseases
	CL55 (1141) Impact of toxic substance exposures (especially heavy metals, BPA, myotoxins, dioxins, benzene, chlorinated drinking water, air pollutants, and nanoparticles) on tissue and organ biomarkers (emphasizing oxidative stress, inflammation)	CL31 (292) Contributing factors to increases in oxidative stress CL23 (146) Adverse effects of heavy metals on tissue and organ biomarkers CL13 (54) Adverse effects of BPA primarily and Mercury secondarily on tissue and organ biomarkers CL29 (127) Toxic effects of lead primarily and myotoxins secondarily on tissues and organs CL10 (72) Mechanisms of TCDD toxicity effects on organs, tissues, and cells primarily and benzene toxicity effects on organs, tissues, and cells secondarily CL21 (123) Toxicity of chloroform in drinking water and exposure to nitrites and nitrates CL27 (176) Damage to lungs from air pollutants CL11 (62) Association of circadian disruption with diseases CL19 (89) health risks of Methyl Bromide primarily and nanoparticle exposure secondarily

APPENDIX 4SUMMARY BIOMARKER DATA FOR EACH IMPACT

Direct Impact of CFs on COVID-19.

Table 5 contains the key biomarkers whose abnormal values reflect adverse impacts from the eighty CFs on COVID-19.

Table 5
Biomarkers Abnormally Impacted by COVID-19

GENERAL AND SPECIFIC BIOMARKERS
ACE2
adaptive immunity
age
airway inflammation
angiotensin-converting enzyme (ACE)2
apoptosis
Body mass index
bronchitis
cardiovascular disease
chronic diseases
COPD
cytokine storm
diabetes
endothelial cell
fibromyalgia
hyperinflammation
hypertension
immune function
immune response
Immune system
immunotoxicity
impaired mucociliary clearance
infection
infectious disease
inflammation
influenza
innate immune system
interleukin (IL)-6 hypersecretion
kidney cells
lower education
methylprednisolone
neurodegeneration
neuroinflammatory
non-inflammatory rheumatic conditions
not being married
obesity
osteoarthritis
osteoporosis
oxidative stress
pre-existing medical conditions
recent receipt of chemotherapy
reduced barrier function
respiratory diseases
respiratory dysfunction
respiratory syncytial virus
respiratory viral infections
severe acute respiratory syndrome coronavirus 2
viral diseases
viral infection
vitamin D
zinc

Impact of CFs on Weakening Immune System.

Table 6 contains the key biomarkers whose abnormal values reflect weakening of the host immune system by the eighty CFs.

Table 6
Biomarkers reflecting Weakened Immune System

GENERAL AND SPECIFIC BIOMARKERS
adaptive immune system
adipocytes
antibodies
antiviral immune response
Apoptosis
asthma
B cells
body mass index
Bone marrow
cancer
cardiac failure
CD4
CD8 T cell
cell-mediated immunity
cellular immune response
chemokines
C-reactive protein
cytokines
cytotoxicity
depression
epithelial cells
Foxp3
humoral immune functions
hypertension
IgA
IgE
IgG
IgM
IL-10
IL-1β
IL-4
IL-6
immune cells
immune defense
immune function
immune response
immune system
immunity
immunoglobulin
immunosuppression
immunotoxic
infection
inflammation
inflammatory cytokines
influenza
Influenza viruses
innate immunity
interferon-γ
interleukin 6
leukocyte counts
lung injuries
lymphocyte
lymphoid structures
macrophages
Monocytes
naive T-cells
natural killer T cells
neutrophils
NK cells
oxidative stress
PBMCs
peripheral blood mononuclear cells
phagocytes
phagocytosis
platelets
pneumonia
pro-inflammatory cytokines
pulmonary infections

(*continued on next page*)

Table 6 (*continued*)

GENERAL AND SPECIFIC BIOMARKERS
reactive oxygen species
regulatory T cells
respiratory infections
spleen
splenocytes
T cell
Th1/Th2
THP-1-derived macrophages
thymocytes
thymus
tissue damage
TLRs
TNF-α
toxicity
Tregs
tumor necrosis factor-α

Impact of CFs on Increasing Inflammation and Coagulation.
Table 7 contains the key biomarkers whose abnormal values reflect increased levels of inflammation and coagulation due to the eighty CFs.

Table 7
Increased Inflammation and Coagulation Biomarkers

GENERAL AND SPECIFIC BIOMARKERS
age
antithrombin III
APTT
arterial endothelial cells
atherosclerosis
AT-III
autoimmune diseases
bleeding
blood coagulation
blood flow
Blood samples
blood velocity
body mass index
cardiovascular disease
CD3+T lymphocytes
CD4+T lymphocytes
cell proliferation
chronic inflammation
coagulation
coagulation factors
coagulopathy
complement activation
C-reactive protein
cytokine storm
cytokines
D-dimer
diabetes
Disseminated intravascular coagulation
endothelial cell injury
endothelial dysfunction
erythrocyte aggregation
Factor X
fever
fibrin formation
fibrinogen
fibrinolysis
fibrinolytic factors
glutathione
hepatic fibrin deposition
homocysteine
hs-CRP
hypercoagulability
hyperhomocysteinemia
hypertension
IFN-γ

(*continued on next page*)

Table 7 (*continued*)

GENERAL AND SPECIFIC BIOMARKERS
IL-10
IL-6
IL-8
impairing immunological mechanisms
inflammation
inflammatory cytokines
intercellular adhesion molecule-1
interleukin-1β
JAK1/TF signaling pathway
kidney failure
leukocytes
lipids
liver
liver damage
low-density lipoproteins
macrophages
MCP-1
metabolic stress
miR-155
Monocyte chemoattractant protein-1
monocytes
mRNA
multi-organ failure
myocardial dysfunction
neutrophils
NF-kappa B signaling pathway
nitric oxide
NO
non-alcoholic fatty liver disease
oxidative stress
PAI-1
peripheral nervous system
plasminogen activator inhibitor type 1
platelet aggregation
PPAR
procoagulant cytokines
procoagulation
pro-inflammatory
pro-inflammatory cytokines
prothrombin time
renal failure
Retinoids
sepsis
SIRS
sodium
spleen
systemic inflammation
T cells
TF
thrombocytopenia
thrombosis
tissue factor
TNF-α
tPA
tumor necrosis factor-alpha
vascular cell adhesion molecule-1
vascular diseases
vascular endothelial cells
vascular endothelial growth factor
vascular permeability
vitamin D
von Willebrand factor
white blood cells
zinc

Impact of CFs on Increasing Neural Damage.

Table 8 contains the key biomarkers whose abnormal values reflect increased levels of neural damage due to the eighty CFs.

Table 8
Increased Neural Damage Biomarkers

GENERAL AND SPECIFIC BIOMARKERS
[Ca2+]i
5-HT
8-OhdG
Abca1
AChE
Akt
AMPA
amyloid β peptide
apolipoprotein E
apoptosis
APP
ATP
autophagy
BACE1
Bax
Bcl2
BDNF
Beclin-1
CaMKII
caspase 3
caspase 8
caspase 9
CAT
Cdk-5
choline
CNS inflammation
cognitive decline
cognitive impairment
COX-2
CREB
cytochrome C
cytochrome *c* oxidase
Dementia
DNA damage
dopamine
encephalopathy
endolysosome pH
ERK
GABA
GFAP
glutamate
GPx
GSH
GSK-3β
GSSG
hippocampal atrophy
HO-1
hyperphosphorylated Tau
Iba-1
IFN-γ
IL-1
IL-10
IL-1β
IL-6
IL-8
inflammation
iNOS
MAO
MAP2
MAPK
MDA
memory decline
memory impairment
microglia responses
mitochondrial cytochrome *c* oxidase
mitochondrial dysfunction
MMP9
NADPH oxidase
NeuN
neurodegeneration
neuroinflammation
neuronal apoptosis
neuropsychiatric disorders

(*continued on next page*)

Table 8 (*continued*)

GENERAL AND SPECIFIC BIOMARKERS
neurotoxicity
NF-κB
NMDA
NMDA receptor
NO
NOS
Nrf2
Oxidative stress
p53
PARP
PGE-2
PKA
P-Tau
RAGE
RNS
ROS
SOD
stroke
synaptic dysfunction
Tau
TLRs
TNF-α
α-synuclein

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