

Appendix S1. Literature queries

1. Gastrointestinal cancer (GIC) core literature: PubMed

The PubMed MeSH Tree for Gastrointestinal Neoplasms was used as the starting point for developing this GIC core literature query. The myriad neoplasms subsumed under Gastrointestinal Neoplasms in the MeSH Tree were converted into text terms, and added to the basic Gastrointestinal Neoplasms building block. Thus, if, for example, Esophageal Neoplasms was one of the branches in the Gastrointestinal Neoplasms tree, Esophageal Carcinoma and Esophageal Carcinogenesis and Esophageal Tumor and Esophageal Cancer were added to the initial query. They were added as title terms to ensure that the articles retrieved had them as focal points. The full query (applied to the time period 1990-early 2021) follows.

(‘Gastrointestinal Carcinoma*’ [ti] OR ‘Esophageal Carcinoma*’ [ti] OR ‘Intestinal Carcinoma*’ [ti] OR ‘Cecal Carcinoma*’ [ti] OR ‘Colorectal Carcinoma*’ [ti] OR ‘Colonic Carcinoma*’ [ti] OR ‘Rectal Carcinoma*’ [ti] OR ‘Duodenal Carcinoma*’ [ti] OR ‘Ileal Carcinoma*’ [ti] OR ‘Jejunal Carcinoma*’ [ti] OR ‘Stomach Carcinoma*’ [ti] OR ‘Colon Carcinoma*’ [ti]) OR (‘Gastrointestinal Carcinogenesis’ [ti] OR ‘Esophageal Carcinogenesis’ [ti] OR ‘Intestinal Carcinogenesis’ [ti] OR ‘Cecal Carcinogenesis’ [ti] OR ‘Colorectal Carcinogenesis’ [ti] OR ‘Colonic Carcinogenesis’ [ti] OR ‘Rectal Carcinogenesis’ [ti] OR ‘Duodenal Carcinogenesis’ [ti] OR ‘Ileal Carcinogenesis’ [ti] OR ‘Jejunal Carcinogenesis’ [ti] OR ‘Stomach Carcinogenesis’ [ti] OR ‘Colon Carcinogenesis’ [ti]) OR (‘Gastrointestinal Tumor*’ [ti] OR ‘Esophageal Tumor*’ [ti] OR ‘Intestinal Tumor*’ [ti] OR ‘Cecal Tumor*’ [ti] OR ‘Colorectal Tumor*’ [ti] OR ‘Colonic Tumor*’ [ti] OR ‘Rectal Tumor*’ [ti] OR ‘Duodenal Tumor*’ [ti] OR ‘Ileal Tumor*’ [ti] OR ‘Jejunal Tumor*’ [ti] OR ‘Stomach Tumor*’ [ti] OR ‘Colon Tumor*’ [ti]) OR (Gastrointestinal Neoplasms [mh] OR ‘Gastrointestinal Cancer*’ [ti] OR ‘Esophageal Cancer*’ [ti] OR ‘intestinal Cancer*’ [ti] OR ‘Cecal Cancer*’ [ti] OR ‘Colorectal Cancer*’ [ti] OR ‘Colonic Cancer*’ [ti] OR ‘Colon Cancer*’ [ti] OR ‘Rectal Cancer*’ [ti] OR ‘Duodenal Cancer*’ [ti] OR ‘Ileal Cancer*’ [ti] OR ‘Jejunal Cancer*’ [ti] OR ‘Stomach Cancer*’ [ti]).

2. COVID core literature: PubMed

The COVID-19 core literature consisted of articles focused solely on COVID-19 augmented by other coronavirus articles. The bulk of the total retrieval was focused on COVID-19 due to the volume of pandemic-related articles published in 2020-early 2021. The full query follows.

(2019-nCoV OR 2019nCoV OR COVID-19 OR COVID* OR SARSCOV* OR SARS-COV* OR SARS-CoV-2 OR coronavirus OR coronaviruses OR coronaviridae OR coronavirinae OR 'corona virus' OR 'SARS-CoV' OR 'MERS-CoV' OR 'severe acute respiratory syndrome' OR 'Middle East respiratory syndrome').

3. LRDI-based discovery query: Web of Science Medline

This query was developed to augment the dot-product approach [which provided only direct impact contributing factors (CFs)] with an LRDI-based discovery approach (which could provide indirect impact CFs). The basic concept for LRDI-based discovery is outlined in the Introduction section of the manuscript. For the discovery of COVID-19 indirect impact CFs, patterns of abnormalities associated with COVID-19 were identified. These patterns were used as a query for the non-COVID-19 literature to identify substances or behaviors associated with these patterns of abnormalities that were assumed to have contributed to the abnormalities, and the substances/behaviors identified then became candidate indirect impact CFs for COVID-19.

To identify these patterns of abnormalities, the strictly COVID-19 core literature (covering mainly 2020 and early 2021) was imported into VantagePoint (VP) text analysis software (www.theVantagePoint.com; V12 Pro/64), and a number of thousands of phrases were examined, mainly but not exclusively those with the highest record frequencies of occurrence. Various aggregation processes were used to arrive at five major themes related to COVID-19 abnormalities. These themes were inflammation, coagulation, viral entry, lung damage, and pre-existing conditions or treatments or exposures. A query consisting of i) patterns comprised of sub-groups of these themes; and ii) a direct impact GIC CF of interest (which was one of the 2150 GIC direct impact CFs that did not overlap with the direct impact COVID-19 CFs) was applied to the non-COVID-19 Medline literature. The two patterns examined were i) all groups of three of the five themes; and ii) all groups of four of the five themes. The pattern consisting of all groups of

three sub-group themes seemed to provide an appropriate balance of volume of retrieval and relevance, and was used to obtain the data in this part of the study.

Typically, numerous articles were retrieved for each CF intersected with the three-theme query, and the more relevant articles were selected for the present study. The full discovery query follows.

Theme 1: Inflammation. {**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 'TNF α ' 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)-1 β ' OR 'IL-1 β ' 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 'leucocyte*' 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')]}.

Theme 2: Coagulation. {**coagula** OR **thrombo** OR **thrombi** OR 'emboli*' OR **fibrin** OR 'fibros*' OR 'endotheli*' 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')]}.

Theme 3: Viral entry. {[‘spike’ near/5 (*protein* OR ‘receptor*’ OR ‘neutralizing’ OR ‘ACE2’)] OR ‘virus entry’ OR ‘viral entry’ OR ‘neutralizing antibody*’ OR ‘cell receptor Angiotensin-converting enzyme’ OR ‘cross-neutralizing’ OR ‘neutralizing activity’}.

Theme 4: Lung damage. {[[(‘Pulmonary’ OR ‘lung’ OR ‘respiratory’) near/5 (‘injury’ OR ‘distress’ OR ‘disease’ OR ‘dysfunction’ OR ‘infection*’ OR ‘disorder*’ OR ‘damage’ OR ‘hypox*’ OR ‘lesion*’ OR ‘edema’ OR ‘impair*’ OR ‘deteriorat*’ OR ‘insufficiency’)] OR ‘acute respiratory syndrome’ OR ‘viral pneumonia’ OR ‘hypoxi*’ OR ‘hypoxe*’ OR ‘Ground-glass opacit*’ OR ‘pneumocyte hyperplasia’ OR ‘lung parenchyma’ OR ‘pulmonary infiltrate*’ OR ‘MUC1’ OR ‘MUC5AC’}.

Theme 5: Pre-existing conditions or treatments or exposures. {[(*vitamin’ OR ‘25OHD’) near/5 (‘deficien*’ OR ‘low*’)] OR ‘hyperglycemi*’ OR ‘hyperglycaem*’ OR ‘hyperinsulinaemia’ OR ‘hyperinsulinemia’ OR ‘hyperandrogenism’ OR ‘hypertension’ OR ‘hypokalemia’ OR [(‘increas*’ OR ‘elevat*’ OR ‘high*’) NEAR/5 (‘body mass index’ OR ‘BMI’ OR ‘blood pressure’ OR ‘fasting plasma glucose’ OR ‘FPG’ OR ‘fasting blood glucose’ OR ‘FBG’ OR ‘FiO(2)’ OR ‘fraction of inspired oxygen’)] OR ‘obesity’ OR ‘diabetes’ OR ‘insulin resistance’ OR ‘heart disease’ OR ‘liver disease’ OR ‘blood cancer*’ OR ‘leukaemia’ OR ‘leukemia’ OR ‘myeloma’ OR ‘lymphoma’ OR ‘lung cancer’ OR ‘breast cancer’ OR ‘prostate cancer’ OR ‘immunotherapy’ OR ‘antibody treatment*’ OR ‘protein kinase inhibitors’ OR ‘PARP inhibitors’ OR ‘chemotherapy’ OR ‘radical radiotherapy’ OR ‘bone marrow transplant*’ OR ‘stem cell transplant*’ OR [(‘immunosuppress*’ OR ‘immunotoxic*’) NEAR/5 (‘treatment*’ OR ‘drug*’ OR ‘agent*’ OR ‘substance*’ OR ‘exposure*’)]}.

Combinations of three terms. [(#1 AND #2 AND (#3 OR #4 OR #5)] OR [#1 AND #3 AND (#4 OR #5)] OR (#1 AND #4 AND #5) OR [#2 AND #3 AND (#4 OR #5)] OR (#2 AND #4 AND #5) OR (#3 AND #4 AND #5) NOT (COVID Query).

Combinations of four terms. [(#1 AND #2 AND #3 AND #4) OR (#1 AND #2 AND #3 AND #5) OR (#1 AND #2 AND #4 AND #5) OR (#1 AND #3 AND #4 AND #5) OR (#2 AND #3 AND #4 AND #5)] NOT (COVID Query).

The aforementioned combinations of three and four terms were then intersected with the CFs of interest to arrive at the final query.

Appendix S2. Limitations of the dot-product approach

There were a number of limitations to the dot-product approach that resulted in substantial underestimation of the number of common CFs between GIC and COVID-19, and necessitated the augmentation of the dot-product approach with the literature-related discovery and innovation (LRDI)-based CF discovery approach for a more complete account of the CF commonality between the two superficially different diseases. These limitations are summarized herein, and a more detailed description can be found in a previous study by the authors (2).

First, only CFs that occurred within the GIC and COVID-19 core literatures (direct impact CFs) were used for the dot-product component. Second, all the matching and dot-product operations required exact phrase matching. Third, there are myriad substances and radiation forms that, at specified dosages, exhibit toxic effects only when combined with other toxic substances and radiation forms. Fourth, in order for a toxic substance or behavior to have been included in the core literature for GIC or COVID-19, it had to have been researched and reported in Medline. Finally, there are many types of documentation (containing credible research results) other than journals indexed in Medline (or the Science Citation Index), such as books, Web documents, less-well-known indexing services, more obscure journals, etc.

Appendix S3. Commonality of contributing factors between GIC and COVID-19
(descriptions of links between CFs and diseases)

Category 1: Lifestyle

Advanced glycation end products (AGEs)

GIC: ‘C2BBel adenocarcinoma enterocytes were exposed to 200 µg/mL glycated casein (AGEs-Csn) for up to 24 h. AGEs-Csn exposure resulted in increased cell proliferation, maladaptive changes in SOD and CAT activity and moderate levels of hydrogen peroxide (H₂O₂) intracellular accumulation. AGEs-Csn activated pro-survival and proliferation signalling, such as the phosphorylation of mTOR (Ser2448) and Akt (Ser473). GSK-3β phosphorylation also increased, potentially inducing extracellular matrix remodelling and thus enabling metastasis. Moreover, AGEs-Csn induced MMP-1, -3, -7, -9 and -10 expression and activated MMP-2 and MMP-9, which are regulators of the extracellular matrix and cytokine functions. AGEs-Csn induced inflammatory responses that included extracellular IL-1β at 6 h; time-dependent increases in IL-8; RAGE and NF-κB p65 upregulation; and IκB inhibition. Co-treatment with anti-RAGE or anti-TNF-α blocking antibodies and AGEs-Csn partially counteracted these changes; however, IL-8, MMP-1 and -10 expression and MMP-9 activation were difficult to prevent. AGEs-Csn perpetuated signalling that led to cell proliferation and matrix remodelling, strengthening the link between AGEs and colorectal cancer aggressiveness’ (53).

COV: ‘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’ (74).

DISC: ‘The role of dietary advanced glycation end-products (AGEs) in the modulation of immune responses (innate and adaptive responses) and chronic oxidative stress has been established. But less is known about AGE implication in naturally acquired immunity and susceptibility to malaria..... In populations with AGE-rich cooked foods as their main food source, chronic activation of RAGE by AGE may induce and maintain pro-inflammatory cytokine

production, oxidative stress, reactive oxygen species (ROS), and AOPP production, and result in innate immune tolerance, inadequate adaptive immune response, cellular dysfunction, and depletion of antioxidative mechanisms. The disturbance of host defense systems may increase susceptibility to malaria in these populations' (75).

Alcohol consumption

GIC: 'Alcohol also generates reactive oxygen species (ROS) by suppressing the expression of antioxidant and cytoprotective enzymes and inducing expression of CYP2E1 which contribute to the metabolic activation of chemical carcinogens' (76).

COV: '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' (77).

DISC: 'Acute alcohol exposure stimulates the beating of the cilia of mucociliary epithelium cells but the effects of chronic ethanol over-exposure are different, with a progressive desensitization of ciliary response: ethanol exposure reduces airway mucociliary clearance. As a result this important innate primary defense mechanism, which protects the lungs from the deleterious effects of different pollutants, allergens and pathogens, is weakened. Chronic alcohol exposure alters the adaptative immune response to pathogens (decreasing the phagocytic function of macrophages) and leads to an inflammatory response (pro-inflammatory cytokines). Respiratory function is impaired by alcohol misuse: asthma, chronic obstructive pulmonary disease, lung infections, and the acute respiratory distress syndrome are more frequent and severe' (78).

Circadian disruption/poor sleep

GIC: 'The risk of colorectal cancer in patients with sleep disorders was found to be significantly higher by case-control study and particularly pronounced among those with sleep disorders with depression, exhibiting a joint effect on colorectal cancer risk' (79).

COV: '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' (80).

DISC: ‘Jet lag, or circadian disruption, perturbs these rhythms to produce gut dysbiosis. When mice are orally infected with *Salmonella typhimurium* in the morning (the beginning of their rest period) they show higher levels of colonization and gut inflammation vs. infection at other times of day. At the cellular level, recent studies highlight circadian regulation of innate and adaptive gut immunity in coordination with the microbiome, as well as intestinal stem cell growth and regeneration.....Taken together, these reports support a key role for circadian rhythms in regulating the gut microbiome and host responses to gastrointestinal pathogens’ (81).

High temperature cooking (indirect impact on COVID)

GIC: ‘In a colorectal adenoma study, we found an elevated risk for red meat consumption that was mainly due to an association with well-done/very well-done red meat. High-temperature cooking methods (i.e. grilling) were also associated with increased risk’ (82).

COV: None.

DISC: ‘trials using palm and soy oils that were repeatedly heated showed an increase in blood pressure, enhanced phenylephrine-induced contractions, reduced acetylcholine- and sodium nitroprusside-induced relaxations relative to the control and rats that were fed fresh vegetable oils.....The blood pressure-raising effect of the heated vegetable cooking oils is associated with increased vascular reactivity and a reduction in nitric oxide levels. The chronic consumption of heated vegetable oils leads to disturbances in endogenous vascular regulatory substances, such as nitric oxide. The thermal oxidation of the cooking oils promotes the generation of free radicals and may play an important contributory role in the pathogenesis of hypertension in rats’ (83).

High-fat diet

GIC: ‘A high-fat diet promotes CRC risk through stimulated bile acid metabolism, facilitating bile acid conversion by the gut microbiota to tumor-promoting deoxycholic acid’ (84).

COV: ‘mice with comorbid diabetes (aging, high-fat diet, and streptozotocin-induced diabetes) had heightened lung ACE2 and TMPRSS2 protein levels and increased lung ACE2 activity. ... Upregulation of lung ACE2 activity in comorbid diabetes may contribute to an increased risk of severe COVID-19’ (85).

DISC: ‘we investigated the influence of a high-fat (HF) diet upon parameters that influence *Listeria monocytogenes* infection in mice.....We determined that short-term administration of a HF diet increases the number of goblet cells, a known binding site for the pathogen, in the gut and also induces profound changes to the microbiota and promotes a pro-inflammatory gene expression profile in the host. Host physiological changes were concordant with significantly increased susceptibility to oral *L. monocytogenes* infection in mice fed a HF diet relative to low fat (LF)- or chow-fed animals. Prior to *Listeria* infection, short-term consumption of HF diet elevated levels of *Firmicutes* including *Coprococcus*, *Butyricoccus*, *Turicibacter* and *Clostridium XIVa* species. During active infection with *L. monocytogenes*, microbiota changes were further exaggerated but host inflammatory responses were significantly downregulated relative to *Listeria*-infected LF- or chow-fed groups, suggestive of a profound tempering of the host response influenced by infection in the context of a HF diet. The effects of diet were seen beyond the gut, as a HF diet also increased the sensitivity of mice to systemic infection and altered gene expression profiles in the liver’ (86).

Malnutrition

GIC: ‘Nutrition and health are closely connected and malnutrition can seriously endanger health. The consequences are higher risks of developing diseases. Of these, cancers are of special importance. The most frequent nutrition-associated type of cancer is colon cancer’ (87).

COV: ‘We demonstrate the existence of a high prevalence of malnutrition in a general cohort of COVID-19 inpatients according to GLIM criteria. Nutritional support in COVID-19 care seems an essential element’ (88).

DISC: ‘We found that mice maintained on the VLP diet, when compared to mice fed with the AP diet, exhibited more severe disease following influenza infection based on virus persistence, trafficking of inflammatory cell types to the lung tissue, and virus-induced mortality. Furthermore, groups of mice maintained on the VLP diet showed significantly lower virus-specific antibody response and a reduction in influenza nuclear protein-specific CD8(+) T cells compared with mice fed on the AP diet. Importantly, switching diets for the group maintained on the VLP diet to the AP diet improved virus clearance, as well as protective immunity to viral challenge.....Our results highlight the impact of protein energy on

immunity to influenza infection and suggest that balanced protein energy replenishment may be one strategy to boost immunity against influenza viral infections' (89).

Nitrosamines (indirect impact on COVID)

GIC: 'Carcinogenic N-nitrosamines were identified in all six samples of traditional beer examined (N=18 analyses), and docking studies confirmed a high affinity of the nitrosamine N-nitrosopyrrolidone with the S100A2 protein. This may result in the altered expression of the S100A2 protein, leading to tumour progression and prognosis' (90).

COV: None.

DISC: 'Adult female B6C3F1 mice were injected ip with 0.2 ml phosphate-buffered saline (PBS) only or PBS containing 1.5, 3, or 5 mg dimethylnitrosamine (DMN)/kg body wt daily for 14 days. On Day 16, mice were evaluated for changes in immune status.....DMN-exposed animals exhibited reduced humoral antibody responses, T-cell mitogenesis, and AM bactericidal activity. B-cell mitogenesis, NK cell activity, and delayed hypersensitivity were increased. Resistance to challenge with *Listeria monocytogenes*, *Trichinella spiralis*, or Herpes simplex types 1 or 2 virus (HSV-1, HSV-2) was not significantly impaired, while that to *Streptococcus zooepidemicus* and influenza virus was significantly reduced' (91).

Red meat

GIC: 'Mechanism of colorectal carcinogenesis triggered by heme iron from red meat' (92).

COV: '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' (93).

DISC: 'Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases' (94).

Sedentary/physical inactivity

GIC: ‘Physical activity is inversely associated with and sedentary behaviour is positively (and independently) associated with an increased risk of more than ten types of cancer, including colorectal cancer (and advanced adenomas)’ (95).

COV: ‘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’ (96).

DISC: ‘AE (Aerobic Exercise] inhibited PS [Pseudomonas aeruginosa] colonization ($p < 0.001$) and lung inflammation (total cells, neutrophils, lymphocytes [$p < 0.01$] in bronchoalveolar lavage [BAL]), with significant differences in BAL levels of IL-1beta ($p < 0.001$), IL-6 ($p < 0.01$), CXCL1 ($p < 0.001$), and TNF-alpha ($p < 0.001$), as well as parenchymal neutrophils ($p < 0.001$). AE increased BAL levels of IL-10 and parenchymal ($p < 0.001$) and epithelial ($p < 0.001$) IL-10 expression, while epithelial ($p < 0.001$) and parenchymal ($p < 0.001$) NF-kappaB expression was decreased. AE diminished pulmonary lipid peroxidation ($p < 0.001$) and increased glutathione peroxidase ($p < 0.01$). Pre-incubation of BEAS-2B with IL-10 inhibited PS-induced epithelial cell expression of TNF-alpha ($p < 0.05$), CD40 ($p < 0.01$), and dichlorodihydrofluorescein diacetate ($p < 0.05$)....AE inhibits PS-induced lung inflammation and bacterial colonization in elderly mice, involving IL-10/NF-kappaB, and redox signaling’ (97).

Smoking

GIC ‘smoking increase the risk of colorectal cancer’ (98).

COV: ‘and smoking history (RR = 1.71, 95% CI 1.25 to 2.35) are potential risk factors for the severity of COVID-19’ (99).

DISC: ‘Cigarette smoke exposure is a risk factor for many pulmonary diseases, including Chronic Obstructive Pulmonary Disease (COPD). Cigarette smokers are more prone to respiratory infections with more severe symptoms. In those with COPD, viral infections can lead to acute exacerbations resulting in lung function decline and death. Epithelial cells in the lung are the first line of defense against inhaled insults such as tobacco smoke and are the target for many respiratory pathogens. Endocytosis is an essential cell function involved in nutrient uptake, cell signaling, and sensing of the extracellular environment....Here, we

report for the first time that cigarette smoke alters the function of several important endocytic pathways in primary human small airway epithelial cells. Cigarette smoke exposure impairs clathrin-mediated endocytosis and fluid phase macropinocytosis while increasing caveolin mediated endocytosis. We also show that influenza virus uptake is enhanced by cigarette smoke exposure. These results support the concept that cigarette smoke-induced dysregulation of endocytosis contributes to lung infection in smokers' (100).

Sodium intake

GIC: 'Salt taste preference test could be a simple way to evaluate an inherited characteristic of sodium intake, and our study confirms the gastric cancer is associated with sodium intake and H.pylori' (101).

COV: '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' (102).

DISC: '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).....Hypertension treatment by induced sodium removal or reduced sodium intake should reduce endothelial glycocalyx dysfunction, inflammation, NETosis, and coagulation disorders, leading to improved vascular health and cardiac diastolic function' (103).

Substance abuse/morphine/cocaine/opioids/heroin/methamphetamine

GIC: 'Epidemiological and experimental data suggest that some chemicals and lifestyle factors, including polycyclic aromatic hydrocarbons (PAHs), cigarette smoking, opium use, and hot tea drinking are associated with the development of ESCC in Golestan' (104).

COV: 'The findings suggest that COVID-19 patients with substance use disorders are at increased risk for adverse outcomes' (105).

DISC: ‘Abuse of psychostimulants, such as cocaine, has been shown to be closely associated with complications of the lung, such as pulmonary hypertension, edema, increased inflammation, and infection...we demonstrated cocaine-mediated disruption of the alveolar epithelial barrier, as evidenced by increased epithelial monolayer permeability with a concomitant loss of the tight junction protein zonula occludens-1 (Zo-1) in both mouse primary alveolar epithelial cells and the alveolar epithelial cell line, L2 cells....we demonstrated that cocaine-mediated induction of permeability factors, platelet-derived growth factor (PDGF-BB) and vascular endothelial growth factor, involved reactive oxygen species (ROS)-dependent induction of hypoxia-inducible factor (HIF)-1alpha.....this study identifies, for the first time, that ROS/HIF-1alpha/PDGF-BB autocrine loop contributes to cocaine-mediated barrier disruption via amplification of oxidative stress and downstream signaling. Corroboration of these cell culture findings in vivo demonstrated increased permeability of the alveolar epithelial barrier, loss of expression of Zo-1, and a concomitantly increased expression of both HIF-1alpha and PDGF-BB’ (106).

Vitamin D deficiency

GIC: ‘recent epidemiological and experimental studies support the association of vitamin D deficiency with a large variety of human diseases, and particularly with the high risk of colorectal cancer’ (107).

COV: ‘In this single-center, retrospective cohort study, likely deficient vitamin D status was associated with increased COVID-19 risk, a finding that suggests that randomized trials may be needed to determine whether vitamin D affects COVID-19 risk’ (108).

DISC: ‘VDD offspring had decreased alveolar and vascular growth and abnormal airway reactivity and lung function. Impaired lung structure and function in VDD offspring were similar to those observed in control rats exposed to postnatal hyperoxia alone. Maternal VDD causes sustained abnormalities of distal lung growth, increases in airway hyperreactivity, and abnormal lung mechanics during infancy. These changes in VDD pups were as severe as those measured after exposure to postnatal hyperoxia alone. We speculate that antenatal disruption of vitamin D signaling increases the risk for late-childhood respiratory disease’ (109).

Western diet

GIC: ‘Together, our data reveal a previously unsuspected link between the Western diet, microbiota, and necroptosis and identify the mTOR/RIPK3/necroptosis axis as a driving force for intestinal inflammation and cancer’ (110).

COV: ‘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’ (111).

DISC: ‘Western diet-fed female rats exhibited dysregulation of metabolism, revealing increased body weight and abdominal fat, decreased expression of adiponectin in white adipose tissue, glucose intolerance, and impaired insulin sensitivity. Western diet exposure increased hepatic triglycerides and cholesterol alongside hepatic steatosis, categorizing nonalcoholic fatty liver disease. Moreover, a Western diet negatively affected vascular function, revealing hypertension, impaired endothelium-dependent vasorelaxation, aortic remodeling, and increased reactive oxygen species (ROS) production. Aortic protein expression of TLR4 and its downstream proteins were markedly increased in the Western diet-fed group in association with elevated serum levels of free fatty acids. In vitro experiments were conducted to test whether free fatty acids contribute to vascular ROS overproduction via the TLR4 signaling pathway. Cultured endothelial cells were stimulated with palmitate in the presence of TAK-242, a TLR4 signaling inhibitor. Palmitate-induced overgeneration of ROS in endothelial cells was abolished in the presence of TAK-242. Our data show that a Western diet induced endothelial dysfunction in female rats and suggest that endothelial TLR4 signaling may play a key role in abolishing female cardiovascular protection’ (112).

Category 2: Iatrogenic

Bone marrow transplantation

GIC: ‘Human gastrointestinal neoplasia-associated myofibroblasts can develop from bone marrow-derived cells following allogeneic stem cell transplantation’ (113).

COV: ‘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’ (114).

DISC: ‘Bone marrow transplant (BMT) recipients experience frequent and severe respiratory viral infections (RVIs).....we hypothesized that antiviral T cell immunity is impaired as a consequence of allogeneic BMT, independent of pharmacologic immunosuppression, and is responsible for increased susceptibility to RVI.....Severe and persistent airway inflammation, epithelial injury, and enhanced mortality are found after viral infection in Allo mice but not in control Syn and non-transplanted mice. In addition, viral clearance is delayed in Allo mice as evidenced by prolonged detection of viral transcripts at Day 15 post-inoculation (p.i.) but not in control mice. In concert with these events, we also detected decreased levels of total and virus-specific CD8(+) T cells, as well as increased T cell expression of inhibitory receptor programmed death-1 (PD-1), in the lungs of Allo mice at Day 8 p.i. Adoptive transfer of CD8(+) T cells from non-transplanted mice recovered from SeV infection into Allo mice at Day 8 p.i. restored normal levels of viral clearance, epithelial repair, and lung inflammation.....Taken together these results indicate that allogeneic BMT results in more severe RVI based on the failure to develop an appropriate pulmonary CD8(+) T cell response, providing an important potential mechanism to target in improving outcomes of RVI after BMT’ (115).

Liver transplantation

GIC: ‘the most common de novo malignancy associated with liver transplantation is gastric cancer’ (116).

COV: ‘those with cirrhosis, hepatocellular carcinoma, non-alcoholic fatty liver disease, autoimmune liver diseases or liver transplant may have a greater risk for severe COVID-19’ (117).

DISC: ‘Infectious complications represent one of the main causes of perioperative morbidity and mortality of liver transplant recipients....Global incidence of postoperative infections was 21%. Pneumonia was the most frequent infection and, globally, gram-negative bacteria were the most common agents. Septic shock was present in 22% of infection cases and hospital mortality was higher in patients with postoperative infection. Preoperative chronic obstructive pulmonary disease, malnutrition, preoperative ascites, encephalopathy, and early re-transplantation were significantly associated to post orthotopic LT infections.....Infections represent a major cause of early postoperative morbidity and mortality’ (118).

Omeprazole/proton pump inhibitors

GIC: ‘Long-term use of PPIs was still associated with an increased GC risk in subjects even after HP eradication therapy’ (119).

COV: ‘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’ (120).

DISC: ‘use of GA inhibitors was associated with an increased risk of acute gastroenteritis and community-acquired pneumonia in GERD-affected children....we observed an increased incidence of intestinal and respiratory infection in otherwise healthy children taking GA inhibitors for GERD treatment. On the contrary, the majority of the previous data showed that the patients most at risk for pneumonia were those with significant comorbid illnesses such as diabetes or immunodeficiency, and this points to the importance of GA suppression as a major risk factor for infections. In addition, this effect seems to be sustained even after the end of therapy. The results of our study are attributable to many factors, including direct inhibitory effect of GA inhibitors on leukocyte functions and qualitative and quantitative gastrointestinal microflora modification’ (121).

Ovariectomy

- GIC: ‘Studies on rats with mutated Apc tumour-suppressor gene subjected to either ovariectomy or orchidectomy exhibit different risks of CRC. Female rats subjected to ovariectomy are at higher risk of CRC, whereas orchidectomised male rats exhibit a lower risk of developing CRC’ (122).
- COV: ‘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 oedema’ (123).
- DISC: ‘Physiological hormones modulate immune responses and implicate in associated susceptibilities to infections. To clarify these endocrinological effects, the influence of estrogen and thyroid deficiency, due to ovariectomy and thyroidectomy, respectively, on course and outcome of *Trichinella spiralis* infection in rats was studied. While in ovariectomized rats there was significant increase in both adult and muscle larval counts as compared to intact infected rats, in thyroidectomized rats there was a significant increase in larval but not in adult count’ (124).

Radiotherapy

- GIC: ‘Our findings show radiotherapy causes DSBs at significantly higher levels in normal colonic mucosa of patients post neo-adjuvant treatment which may represent RIBE. If this damage remains unrepaired, increased levels of genomic instability may contribute to the higher occurrence of second cancers in patients treated post neo-adjuvant radiotherapy’ (125).
- COV: ‘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’ (126).
- DISC: ‘the side effects of RT are pneumonitis and pulmonary fibrosis. RT-induced lung injury causes damage to alveolar-epithelial cells and vascular endothelial cells. Macrophages play an important role in the development of pulmonary fibrosis despite its role in immune response. These injury activated macrophages develop into classically activated M1

macrophage or alternative activated M2 macrophage. It secretes cytokines, interleukins, interferons, and nitric oxide. Several pro-inflammatory lipids and pro-apoptotic proteins cause lipotoxicity such as LDL, FC, DAG, and FFA. The overall findings in this review conclude the importance of macrophages in inducing toxic/inflammatory effects during RT of lung cancer, which is clinically vital to treat the radiation-induced fibrosis' (127).

Renal transplantation

GIC: 'Renal transplantation is associated with an increased risk of neoplasia, including colorectal cancer (CRC)' (128).

COV: 'KTR had a higher COVID-19-related mortality compared to nontransplant hospitalized patients' (129).

DISC: 'Infections are the most common noncardiovascular causes of death after kidney transplantation..... Altogether, 953 patients (29%) died during the follow-up, with 204 infection-related deaths.....The main causes of infectious deaths were common bacterial infections: septicemia in 38% and pulmonary infections in 45.....Older recipient age, higher plasma creatinine concentration at the end of the first post-transplant year, diabetes as a cause of ESKD, longer pretransplant dialysis duration, acute rejection, low albumin level, and earlier era of transplantation were associated with increased risk of infectious death in multivariable analysis' (130).

Category 3: Biotoxins

Cytomegalovirus

GIC: 'Human cytomegalovirus-encoded US28 may act as a tumor promoter in colorectal cancer' (131).

COV: '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' (132).

DISC: 'MicroRNAs (miRNAs) play an important role in the development of vascular remodeling in essential hypertension (EH) by mediating the effects of human cytomegalovirus (HCMV) on the vascular system. Therefore, the aim of the present study was to investigate the effects

of murine cytomegalovirus (MCMV) infection on blood pressure and vascular function in mice, in order to elucidate the role of miR-1929-3p in this process.....The results revealed that MCMV infection increased the blood pressure, promoted vascular remodeling, caused endothelial cell injury, and downregulated miR-1929-3p' (133).

Herpes simplex virus

GIC: 'Viruses such as human papillomavirus, ebstein-barr virus and herpes simplex virus have been implicated in the pathogenesis of esophageal cancer' (134).

COV: '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' (135).

DISC: 'Here we show that infection of human primary macrophages (MDMs) by HSV-2 results in an increase of CCR5 expression levels on cell surface and allows higher efficiency of MDMs to support entry of R5 HIV-1 strains. This finding could strengthen, at the molecular level, the evidence linking HSV-2 infection to an increased susceptibility to HIV-1 acquisition' (136).

Mycotoxins

GIC: 'Fumonisin exposure may be a risk factor for EC in humans. This association was first posited in South African populations at unusually high risk for EC who consumed relatively large amounts of fumonisin-contaminated maize (Marasas 2006). Since then, the results of studies in other nations have supported this association' (137).

COV: 'Our findings suggest that mycotoxin could influence the prevalence of coronavirus and provide new ideas for the prevention and control of coronavirus' (138).

DISC: 'mycotoxin T-2 toxin (T-2), a frequent food contaminant, alters host resistance to lung infection by reovirus, a model respiratory virus.....Taken together, T-2 increased lung viral burden, bronchopneumonia and pulmonary cellular infiltration in reovirus-infected mice. These effects might be attributable to reduced alveolar macrophage levels as well as modulated cytokine and mucosal Ig responses' (139).

Category 4: Occupational/environmental

Aluminum (indirect impact on COVID)

GIC: ‘AlCl₃ can promote the metastatic proclivity of colorectal cancer cells through MMP-7, -9, and TGF- β /Smad2/3 pathway’ (140).

COV: None.

DISC: ‘The results revealed a significant relative increase in splenic weights mostly observed in the highest AS dose treated group. Reduction in the total leukocytic count was noticed in the three AS treated groups with relative lymphocytosis. Additionally, a significant decline in RBCs counts and hemoglobin concentrations were recorded. Tumor necrosis factor- was significantly elevated in the three Al treated groups, while, interferon- showed a non-significant reduction compared to the control group. A significant increment in IgG and decline in IgE concentrations with no change in IgM level among groups were observed..... Perinatal AS exposure caused mostly non-linear dose-dependent hematotoxicity and immunological impairment especially for the acquired immunity either cellular or humoral’ (141).

Arsenic/As

GIC: ‘we studied the effects of arsenic trioxide (ATO) administration on a 1,2-dimethylhydrazine (DMH)-induced preneoplastic colon carcinogenesis model.....Our study has shown that ATO administration accelerated colon cancer development suggesting the heaviness of such treatments and the need to explore combinations and cycle type formulas’ (142).

COV: ‘Compared to the non-severe COVID-19 patients, severe cases showed significant higher levels of whole blood calcium, chromium, and copper, but lower levels of magnesium, manganese, iron, zinc, arsenic, thallium, and lead. These differences were further found consistently across the clinical course since the disease onset by longitudinal analysis. Among the severe patients, chromium and cadmium were higher in the deceased group compared to the recovered group, while arsenic was lower’ (143).

DISC: ‘Elevated Arsenic Exposure Is Associated with an Increased Risk of Chronic Hepatitis B Virus Infection: NHANES (2003-2014) in US Adults’ (144).

Asbestos (indirect impact on COVID)

GIC: ‘Experimental evidence suggested a role for timing and extent of exposure, and showed that ingested AFs induce toxic effects on the stomach, ileum and colon, histological alterations and negative effects at a molecular level, cross the placenta and enter foetal organs (including the liver), and seem able to act as a co-carcinogen agent’ (145).

COV: None.

DISC: ‘Deposition in the lung parenchyma results in an inflammatory/progressively fibrotic response, with impaired gas exchange and reduced lung compliance ('asbestosis'), causing progressive dyspnoea and respiratory failure for which only palliation is indicated, although anti-fibrotic agents used for idiopathic usual interstitial pneumonitis remain to be evaluated. Benign pleural effusion, diffuse pleural fibrosis (occasionally with associated rolled atelectasis) and pleural plaques are the non-malignant pleural diseases that result from fibres reaching the pleura. But the main issues that led to the ban on asbestos in industry are those of malignancy: lung cancer, malignant mesothelioma (MM) of the pleura and MM of the peritoneum. Bronchogenic carcinoma risk from asbestos exposure is dose-dependent and multiplies the risk attributable to tobacco smoking’ (146).

Benzene

GIC: ‘Increased risk was observed for all colorectal cancer (OR = 1.12, 95% CI 1.05-1.18) for the high decile of cumulative benzene exposure, indicating a statistically significant dose-response relationship.....This study showed an association between workplace benzene exposure and colorectal cancer. The risk was restricted to ascending and transversal colon, and was the strongest among women’ (147).

COV: ‘The result of GW-RF (geographically weighted random forest] showed that the risk factors (i.e. going to work by walking, airborne benzene concentration, householder with a mortgage, unemployment, airborne PM2.5 concentration and per cent of the black or African American) have a high correlation with the spatial distribution of the COVID-19 death rate’ (148).

DISC: ‘To further examine if genetic variation contributes to benzene haematotoxicity, we analysed 1023 tagSNPs in 121 gene regions important for benzene metabolism,

haematopoiesis, leukaemia and lymphoma among 250 workers exposed to benzene and 140 unexposed controls in a cross-sectional study carried out in China....VEGF (minp = 0.0030) and ERCC3 (minp = 0.0042) were the most significantly associated gene regions with altered WBC counts among benzene-exposed workers.....genetic variation in VEGF, which plays an important role in blood vessel growth, and ERCC3, which is a member of the DNA repair pathway and is responsible for repairing bulky DNA adducts formed by chemicals, may contribute to individual susceptibility to benzene-induced haematotoxicity at relatively low levels of benzene exposure' (149).

Benzidine

GIC: 'These findings appear to confirm previous clinical data suggesting an increased occurrence of multiple primary cancers in workers exposed to benzidine/beta-naphthylamine, pointing to a pluripotential action of these carcinogens' (150).

COV: 'COVID-19 mortality and individual factors were examined.....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' (151).

DISC: 'Benzidine (4,4'-diaminobiphenyl).....was immunosuppressive in mice after subchronic exposure. Suppression, particularly of cell-mediated immunity, occurred at dose levels previously found to be subtumorigenic in mice, as evidenced by suppressed lymphoproliferative and delayed hypersensitivity responses. In addition, benzidine exposure was found to decrease host resistance, including resistance to the growth of transplantable tumor cells and infection with *Listeria*. These data suggest that the development of neoplastic disease may be facilitated by the ability of benzidine to alter the immune response.....These data are consistent with the hypothesis that alterations in lymphocyte functions may occur as a result of quantitative changes or depletion of conversion products in the arachidonate/lipoxygenase pathway induced by the addition of compounds that serve as co-oxidative substrates for hydroperoxidases, the prototype being benzidine' (152).

Bisphenol A

GIC: ‘BPA impairs the E2-induced activation of the apoptotic cascade which is at the root of the protective role played by the hormone against colon cancer growth. Thus, women may be considered a highly susceptible population with an increased risk of colon cancers after BPA exposure’ (153).

COV: ‘... potential BPA-induced effects on key SARS-CoV-2 infection mediators, such as angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) ... suggesting that BPA exposure may impact on the local expression of these SARS-CoV-2 infection mediators’ (154).

DISC: ‘Chronic exposure to BPA resulted in prominent inflammation and oxidative stress responses as evidenced by an increase in levels of malondialdehyde (MDA), reduced concentrations of superoxide dismutase (SOD), and upregulation of Interleukin-18 (IL-18) expression in lung tissue. In addition, chronic exposure led to modulation of the fibrosis-related gene expression, as we observed augmented follistatin-like1 (FSTL1) expression and diminished a disintegrin and metalloproteinase with thrombospondin motif 5 (ADAMTS5) expression.....Taken together, the results from the study reveal that chronic exposure to BPA may promote the development of pulmonary inflammatory diseases with possible induction of lung fibrosis’ (155).

Cadmium/Cd

GIC: ‘results suggest that exposure to low levels of Cd promotes a more migratory cancer phenotype in a ROS-p38-COX-2-PGE2 pathway as well as ROS-Akt pathway’ (156).

COV: ‘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 abnormalities in urinary levels of the trace metals were tightly associated with the severe illness and fatal outcome of COVID-19’ (157).

DISC: ‘an elevated blood cadmium level above the median was significantly associated with HBV (AOR=1.5; 95 % CI=1.2-2.0) and H. pylori (AOR=1.5; 95 % CI=1.2-1.7) seropositivity.....The results of this cross-sectional human health survey suggest that the immunological effects of lead and cadmium toxicity may be associated with an increased susceptibility to chronic infections’ (158).

Carbon dioxide/CO₂/CO(2) (indirect impact on COVID)

GIC: ‘The insufflation of carbon dioxide promotes tumor growth compared with helium and control in a rat model’ (159).

COV: None.

DISC: ‘we hypothesize that chronic exposure to elevated $p\text{CO}_2$ with increasing atmospheric CO_2 (>400 ppm), and extended time spent in confined, crowded indoor atmospheres ($p\text{CO}_2$ up to 5,000 ppm) with urban lifestyles, may be an important, largely overlooked driver of change in human proteome performance. The reduced pH (downregulated from 0.1 to 0.4 units below the optimum pH) of extant humans chronically exposed to elevated CO_2 is likely to lead to proteome malfunction. This malfunction is due to protein misfolding, aggregation, charge distribution, and altered interaction with other molecules (e.g., nucleic acids, metals, proteins, and drugs). Such alterations would have systemic effects that help explain the prevalence of syndromes (obesity, diabetes, respiratory diseases, osteoporosis, cancer, and neurological disorders) characteristic of the modern lifestyle’ (160).

Carbon tetrachloride (indirect impact on COVID)

GIC: ‘Pretreatment with CCl_4 caused not only early death from chemical toxicity of MAM but also an increase in small-bowel tumors’ (161).

COV: None.

DISC: ‘ CCl_4 is strong toxic in the kidney, testicle, brain, heart, lung, other tissues, and particularly in the liver. CCl_4 is a powerful hepatotoxic, nephrotoxic and prooxidant agent which is widely used to induce hepatotoxicity in experimental animals and to create hepatocellular carcinoma, hepatic fibrosis/cirrhosis and liver injury, chemical hepatitis model, renal failure model, and nephrotoxicity model in recent years. The damage-causing mechanism of CCl_4 in tissues can be explained as oxidative damage caused by lipid peroxidation which starts after the conversion of CCl_4 to free radicals of highly toxic trichloromethyl radicals (CCl_3) and trichloromethyl peroxy radical (CCl_3O_2) via cytochrome P450 enzyme. Complete disruption of lipids (i.e., peroxidation) is the hallmark of oxidative damage.....These toxic free radicals induce a chain reaction and lipid peroxidation in membrane-like structures rich in phospholipids, such as mitochondria and endoplasmic reticulum. CCl_4 -induced lipid

peroxidation is the cause of oxidative stress, mitochondrial stress, endoplasmic reticulum stress' (162).

Chlordane (indirect impact on COVID)

GIC: 'Working in areas with high use of the phenoxyacetic acid herbicide 2,4-D was associated with gastric cancer (OR=1.85; 95% CI=1.05-3.25); use of the organochlorine insecticide chlordane was also associated with the disease (OR=2.96; 95% CI=1.48-5.94)' (163).

COV: None.

DISC: 'The immunotoxicity of cis- and trans-nonachlor and chlordane were investigated in adult male and female Sprague-Dawley rats following a 28-day oral (gavage) treatment.....The present data indicated that the chlordane compounds tested in this study had significant effects on a number of immunologic endpoints. In comparison to technical chlordane, cis- and trans-nonachlors were more immunotoxic' (164).

Chlorinated drinking water

GIC: 'Published reports have revealed increased risk of colorectal cancers in people exposed to chlorinated drinking water or chemical derivatives of chlorination' (165).

COV: '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' (166).

DISC: 'Dibromoacetic acid (DBA) is a haloacetic acid that is present in drinking water as a by-product of chlorinated disinfection. To evaluate its potential adverse health effects, the immunotoxicological effects of DBA on the thymus and spleen of BALB/c mice were investigated.....The mice orally administered DBA exhibited obvious immunotoxicity, as indicated by changes in the thymus and spleen.....In conclusion, DBA induces obvious

immunotoxicity in the thymus and spleen, and immune-cell apoptosis mediated by the Fas/FasL pathway may be the potential mechanism underlying this immunotoxicity' (167).

Chloroform (indirect impact on COVID)

GIC: 'Male and female Eker rats were treated via drinking water with low and high concentrations of potassium bromate, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), chloroform, or bromodichloromethane individually or in a mixture for 10 months.....Treatment with 4 individual DBPs, as well as a mixture of them, caused the development of ACF (Aberrant crypt foci], the putative preneoplastic lesion of colon cancer' (168).

COV: None.

DISC: 'Chloroform (CHCl₃) and bromodichloromethane (BDCM) are generally the two most prevalent disinfection by-products formed during chlorination of drinking water, and both have been shown to be hepatotoxic, nephrotoxic, and carcinogenic in rodents.....Ninety-day-old male Fischer 344 rats were gavaged with either 0.125, 0.1875, 0.25, 0.5, 0.75, 1.0, or 1.5 mmol CHCl₃ or BDCM/kg body weight in 10% Alkamuls EL-620 (5 ml/kg body weight).....Both CHCl₃ and BDCM induced dose-dependent hepatotoxicity; serum alanine aminotransferase, aspartate aminotransferase, and sorbitol dehydrogenase were elevated significantly over control at 1.5, 1.0, and 0.5 mmol/kg. At these dose levels after 24 h, the two THMs appeared to be equipotent hepatotoxicants' (169).

Chlorpyrifos (indirect impact on COVID)

GIC: 'Chlorpyrifos promotes colorectal adenocarcinoma H508 cell growth through the activation of EGFR/ERK1/2 signaling pathway but not cholinergic pathway' (170).

COV: None.

DISC: 'The aim of the study was to investigate the effects of dietary exposure to chlorpyrifos (CPF) on systemic and hepatic immune-cell phenotypes in C57BL/6 mice with streptozotocin (STZ)-induced diabetes.....Both blood and hepatic neutrophil populations were enhanced by CPF exposure. CPF-exposed groups had lower percentages of blood T cells without altering the proportions of CD4⁺ and CD8⁺ T-cell subsets, and lower expression levels of the Bcl-2 antiapoptotic gene in the spleen. CPF exposure reduced the percentage of blood

regulatory T cells (Tregs); however, the Treg population was upregulated in the liver even when hepatic T cells were not affected by CPF in diabetic mice....These findings suggest that dietary exposure to CPF affects the distribution of both myeloid and lymphoid immune cells in the blood and liver under hyperglycemic conditions, which may lead to hyperinflammation when encountering immune stimuli' (171).

Chromium/Cr

GIC: 'Oral exposure to hexavalent chromium (Cr(VI)) induces intestinal tumors in mice' (172).

COV: '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 abnormalities in urinary levels of the trace metals were tightly associated with the severe illness and fatal outcome of COVID-19' (157).

DISC: 'Exposure to MMA-SS, soluble Cr, or the mixture of all three metals before infection significantly increased bacterial lung burden and tissue damage when compared to control....Animals pre-treated with soluble Cr had alterations in inflammation and in the production of different cytokines (TNFalpha, IL-6, IL-2, and IL-12) involved in lung immune responses. This study indicates that soluble Cr present in MMA-SS is likely the primary component responsible for the suppression of lung defense responses associated with stainless steel welding fumes' (173).

Crude oil (indirect impact on COVID)

GIC: 'We found a fourfold excess risk of oesophageal adenocarcinoma among male workers assumed to have had the most extensive contact with crude oil' (174).

COV: None.

DISC: 'In animals, the effect of exposure to crude oil on the immune system depends on the species, dose, exposure route, and type of oil. Important observations included; hematological changes resulting in anemia and alterations in white blood cell numbers, lymph node and splenic atrophy, genotoxicity in immune cells, modulation of cytokine gene expression and increased susceptibility to infectious diseases. In humans, there are reports

that exposure to crude oil can increase the risk of developing certain types of cancer and cause immunomodulation' (175).

Di(2-ethylhexyl) phthalate (indirect impact on COVID)

GIC: 'this study indicates that exposure to DEHP may exacerbate DMH-induced colon tumorigenesis' (176).

COV: None.

DISC: 'male and female zebrafish were fed DEHP (3 ppm) daily for two months. At the transcriptome level, DEHP significantly upregulated gene networks in the intestine associated with helper T cells' (Th1, Th2, and Th17) specific pathways. The activation of gene networks associated with adaptive immunity was linked to the suppression of networks for tight junction, gap junctional intercellular communication, and transmembrane transporters, all of which are precursors for impaired gut integrity and performance.....This finding suggests that the gut microbiota may contribute to the adverse effects of DEHP on the host by altering metabolites sensed by both intestinal and immune Th cells. Our results suggest that the microbiome-gut-immune axis can be modified by DEHP and emphasize the value of multiomics approaches to study microbiome-host interactions following chemical perturbations' (177).

Heterocyclic amine (indirect impact on COVID)

GIC: 'This meta-analysis suggests that there is a positive association of HCAs, BaP, mutagenicity index with risk of CRA' (178).

COV: None.

DISC: 'Treatment of the thymocytes with PhIP [2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine] moderately inhibited T-cell mitogen-induced cell proliferation and interleukin (IL)-2 secretion. Reverse transcription-polymerase chain reaction (RT-PCR) analysis demonstrated that PhIP attenuated IL-2 mRNA expression in the thymocytes and EL4 cells stimulated with phytohemagglutinin (PHA) plus phorbol 12-myristate 13-acetate (PMA).....These results suggest that PhIP has potential immunosuppressive effects by inhibiting T-cell proliferation and IL-2 expression through down regulation of ROS generation and thereby inhibiting NF-kappaB, AP-1 and NF-AT activation' (179).

Ionizing radiation

GIC: ‘In conclusion, intestinal and colonic tumor frequency and size was similar irrespective of energetic heavy ion radiation dose rate suggesting that carcinogenic potential of energetic heavy ions is independent of dose rate’ (180).

COV: ‘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’ (29).

DISC: ‘The endothelium.....contributes to key aspects of vascular homeostasis and is also involved in pathophysiological processes, such as thrombosis, inflammation, and hypertension. Epidemiological data show that high doses of ionizing radiation lead to cardiovascular disease over time. The aim of this review is to summarize the current knowledge on endothelial cell activation and dysfunction after ionizing radiation exposure as a central feature preceding the development of cardiovascular diseases’ (181).

Mercury/Hg

GIC: ‘A high intake of dietary mercury was associated with an increased risk of CRC’ (182).

COV: ‘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 abnormalities in urinary levels of the trace metals were tightly associated with the severe illness and fatal outcome of COVID-19’ (157).

DISC: ‘We report here that Hg impairs host resistance to malaria infection at exo-erythrocytic stages. Hg exposed mice have higher parasitemia following infection with sporozoites, but not after transfusion of infected red cells.....These results have potential implications for the incidence and prevalence of malaria among populations exposed to mercury from artisanal goldmining and consumption of contaminated fish regions with high rates of malaria and other infectious diseases’ (183).

Microplastics (indirect impact on COVID)

GIC: ‘The adsorption of PS to tetracycline (TC) was studied and their toxicity to gastric cancer cells (AGS) was researched. The adsorption experimental results show that PS absorbing capacity increased with increasing TC concentrations. The defense mechanism results show that 60 nm PS-NPs, 500 nm PS-MPs and their complex induce different damage to AGS cells. Furthermore, 600 mg/L PS-NPs and PS-MPs decline cell viability, induce oxidation stress and cause apoptosis. There is more serious damage of 60 nm PS-NPs than 500 nm PS-MPs in cell viability and intracellular reactive oxygen species (ROS). DNA are also damaged by 60 nm PS-NPs and PS-TC NPs, 500 nm PS-MPs and PS-TC MPs, and 60 nm PS-NPs damage DNA more serious than 500 nm PS-MPs. Moreover, 60 nm PS-NPs and PS-TC NPs seem to promote bcl-2 associated X protein (Bax) overexpression. All treatments provided us with evidence on how PS-NPs, PS-MPs and their compounds damaged AGS cells’ (184).

COV: None.

DISC: ‘Numerous animal studies have shown that exposure to nano- and microplastics leads to impairments in oxidative and inflammatory intestinal balance, and disruption of the gut's epithelial permeability. Other notable effects of nano- and microplastic exposure include dysbiosis (changes in the gut microbiota) and immune cell toxicity. Moreover, microplastics contain additives, adsorb contaminants, and may promote the growth of bacterial pathogens on their surfaces: they are potential carriers of intestinal toxicants and pathogens that can potentially lead to further adverse effects....Despite the scarcity of reports directly relevant to human, this review brings together a growing body of evidence showing that nano- and microplastic exposure disturbs the gut microbiota and critical intestinal functions. Such effects may promote the development of chronic immune disorders. Further investigation of this threat to human health is warranted’ (185).

Nanoparticles

GIC ‘Different mechanisms are involved in oxidative DNA damage and genotoxicity induction by ZnO and TiO₂ nanoparticles in human colon carcinoma cells’ (186).

COV: ‘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' (187).

DISC: 'Human primary bronchial epithelial cells were exposed to TiO₂-NP for 24h prior to infection with recombinant red RSV (rrRSV)....rrRSV infection efficiency more than doubled in human bronchial cells pre-exposed to TiO₂-NP compared to controls. NGF and its TrkA receptor were upregulated in RSV-infected bronchial cells pre-exposed to TiO₂-NP compared to controls exposed to either rrRSV or TiO₂-NP alone. Silencing NGF gene expression with siRNA significantly inhibited rrRSV infection. rrRSV-infected cells pre-exposed to TiO₂-NP also showed increase in necrotic cell death and reduction in apoptosis, together with 4.3-fold increase in expression of the early autophagosomal gene beclin-1. Pharmacological inhibition of beclin-1 by wortmannin resulted in increased apoptotic rate along with lower viral load. This study shows that TiO₂-NP exposure enhances the infectivity of RSV in human bronchial epithelial cells by upregulating the NGF/TrkA axis. The mechanism of this interaction involves induction of autophagy promoting viral replication and necrotic cell death' (188).

Nickel (indirect impact on COVID)

GIC: 'Mortality and cancer incidence were examined for an updated cohort of nonsinter nickel workers in Sudbury and Port Colborne, Ontario, Canada. ... Significant elevations in colorectal cancer incidence were observed in Sudbury underground mining, mining maintenance, and maintenance work areas' (189).

COV: None.

DISC: 'Nickel (Ni) is a widely distributed metal in the environment and an important pollutant because of its many industrial applications. With increasing incidences of Ni contamination, Ni toxicity has become a global public health concern and recent evidence suggests that Ni adversely affects the immune system. Hence, this paper reviews the literature on immune-related effects of Ni exposure, the immunotoxicological effects of Ni, and the underlying mechanism of Ni immunotoxicity. The main focus was on the effect of Ni on the development of organs of immune system, lymphocyte subpopulations, cytokines, immunoglobulins, natural killer (NK) cells, and macrophages. Moreover, Ni toxicity also induces inflammation and several studies demonstrated that Ni could induce

immunotoxicity. Excessive Ni exposure can inhibit the development of immune organs by excessively inducing apoptosis and inhibiting proliferation. Furthermore, Ni can decrease T and B lymphocytes, the specific mechanism of which requires further research....Cytokine levels increased in Ni-induced inflammation responses, and Ni activates inflammation through toll like (TL)4-mediated nuclear factor-kappaB (NF-kappaB) and signal transduction cascades mitogen-activated protein kinase (MAPK) pathways. Ni has been indicated to inactivate NK cells and macrophages both in vitro and in vivo. Identifying the mechanisms underlying the Ni-induced immunotoxicity may help to explain the growing risk of infections and cancers in human populations that have been exposed to Ni for a long time' (190).

Nitrate

GIC: 'We found statistically significant increased risks at drinking water levels above 3.87 mg/L, well below the current drinking water standard of 50 mg/L. Our results add to the existing evidence suggesting increased CRC risk at drinking water nitrate concentrations below the current drinking water standard' (191).

COV: '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' (192).

DISC: 'In order to evaluate the effects of nitrates on birds, we have exposed captive red-legged partridges to nitrates concentrations of 0 (control), 100 (dwell water in farming areas) or 500 mg/l (fertirrigation level).....Several blood parameters such as aspartate aminotransferase, creatinine phosphokinase and lactate dehydrogenase activities and magnesium level decreased with nitrate exposure, whereas alkaline phosphatase activity and creatinine level increased. The oxidant effect of nitrates was evidenced by the increase in blood metHb, accompanied by the lipid peroxidation of red blood cells, the increased levels of oxidized glutathione (GSH) in liver, and the generation of oxidative DNA damage in plasma lymphocytes. GSH in erythrocytes was negatively correlated with blood metHb. The cellular immune function was slightly lower at partridges exposed to nitrates. These results

suggest that adverse effects of nitrates on birds occur at concentrations potentially present in the field' (193).

Nitrite

GIC: 'The available evidence supports a positive association between nitrite and nitrosamine intake and GC' (194).

COV: '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' (192).

DISC: 'Nitrite is a major environmental pollutant in aquatic environments that negatively affects aquatic species. In this study, we investigated the impact of nitrite exposure on plasma biochemical parameters and immune responses in *Takifugu rubripes*.....Levels of GOT, ALT, C3, and C4 were significantly enhanced in the high nitrite concentration group (3 and 6 mM), whereas those of TP, Alb, LZM, and IgM decreased significantly with the same treatments. Nitrite significantly upregulated *hsp70*, *hsp90*, *tnf-alpha*, *il-6*, *il-12*, and *baff* mRNA levels after 96 h of exposure. These results indicated that nitrite exposure altered the blood physiological status and immune system response, resulting in dysfunction and immunotoxicity in *T. rubripes*' (195).

Nitrogen dioxide/NO₂/NO(2)

GIC: 'PM_{2.5} combinations with NO₂ were significantly associated with both stomach and colorectal cancer mortality RR (95%CI): 1.0103 (1.009, 1.021) and 1.054 (1.0324, 1.0667), respectively' (196).

COV: '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' (197).

DISC: 'Repeated daily exposure of healthy human subjects to NO₂ induces an acute airway inflammatory response characterised by neutrophil influx in the bronchial

mucosa.....Expression of IL-5, IL-10, IL-13, and ICAM-1 increased following NO₂ exposure.....Upregulation of the Th2 cytokines suggests that repeated exposure to NO₂ has the potential to exert a "pro-allergic" effect on the bronchial epithelium. Upregulation of ICAM-1 highlights an underlying mechanism for leucocyte influx, and could also explain the predisposition to respiratory tract viral infections following NO₂ exposure since ICAM-1 is a major receptor for rhino and respiratory syncytial viruses' (198).

Organochlorines (indirect impact on COVID)

GIC: 'An elevated risk of colorectal cancer was associated with higher serum concentrations of mono-ortho polychlorinated biphenyl (PCB) congeners 28 and 118' (199).

COV: None.

DISC: 'This study was undertaken to assess if high levels of organochlorines (OCs) are associated with decreased ability to produce antibodies in free-ranging polar bears.....The OCs alone contributed with up to 7% to the variations in the immunological parameters.....The present study demonstrated that high OC levels may impair the polar bears ability to produce antibodies and thus may produce impaired resistance to infections' (200).

Organophosphates

GIC: 'Positive correlation between human exposure to organophosphate esters and gastrointestinal cancer in patients from Wuhan, China' (201).

COV: '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' (202).

DISC: 'we analyzed the course of *T. cruzi* infection, MPhi profiles from peritoneal exudate cells (PECs), inflammatory cell infiltration and fibrosis in the heart of BALB/c mice exposed to diethyldithiophosphate (DEDTP), diethylthiophosphate (DETP) or diethylphosphate (DEP, 0.01g/kg), common DAPs produced by OP pesticides, 24h before infection with *T. cruzi*. We found that DEDTP increased the parasite burden in blood by 99% at the peak of the

infection and enhanced the myocardial damage due to an increase in infiltrated inflammatory cells (induced by DEDTP or DETP) and fibrosis (induced by EtDAPs). In the PECs, exposure to EtDAPs increased the proportion of the MPhi subpopulations of M2a, M2b and M2d, which are associated with tissue repair. These results indicate that exposure to EtDAPs can exacerbate the acute phase of a parasitic infection and increase the long-term damage to the heart' (203).

Ozone (indirect impact on COVID)

GIC: 'PM_{2.5} combination with O₃ was significantly associated with colorectal cancer mortality, RR (95%CI): 1.0151 (1.0091, 1.0172)' (196).

COV: None.

DISC: 'We observed increased risk of.....unspecified acute upper respiratory infections related to O₃ within 2-6h' (204).

Pb

GIC: 'Divalent lead (Pb²⁺) is a common industrial pollutant epidemiologically associated with gastric cancers. Pb²⁺ was found to promote tumorigenesis, which may include interleukin (IL)-8, a pro-inflammatory chemokine that promotes angiogenesis and tumor metastasis' (205).

COV: 'The existing data demonstrate that As, Cd, Hg, and Pb exposure is associated with respiratory dysfunction and respiratory diseases (COPD, bronchitis). These observations corroborate laboratory findings on the role of heavy metal exposure in impaired mucociliary clearance, reduced barrier function, airway inflammation, oxidative stress, and apoptosis. The association between heavy metal exposure and severity of viral diseases, including influenza and respiratory syncytial virus has been also demonstrated. The latter may be considered a consequence of adverse effects of metal exposure on adaptive immunity. Therefore, 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' (32).

DISC: 'Persistent exposure to inorganic lead (Pb) is known to adversely affect the immune system. In the present study, we assessed the effect of chronic Pb exposure on susceptibility to

infection by the facultative intracellular pathogen *Salmonella enterica* serovar Typhimurium.....Pb exposure rendered mice susceptible to *Salmonella* infection, manifested by increased bacterial burden in target organs and heightened mortality.....Analysis of the ability of ex vivo-cultured splenocytes to secrete cytokines demonstrated a marked reduction in IFN-gamma and IL-12p40 production associated with Pb exposure. In contrast, secretion of IL-4 by splenocytes of Pb-treated mice was 3- to 3.6-fold higher than in normal mice.....We conclude that chronic exposure to high levels of Pb results in a state of immunodeficiency which is.....largely caused by a shift in immune responsiveness to Th2-type reactions' (206).

Perfluorooctanoic acid (indirect impact on COVID)

GIC: 'Our study confirmed that PFOA could induce colorectal cancer cell DLD-1 invasive ability and MMP-2/-9 expression through activating NF- κ B' (207).

COV: None.

DISC: 'Experimental studies reported that exposure to PFAS results in immunotoxicity. We have previously reported that prenatal exposure to PFAS decreased the risk of allergies, while it increased the risk of infectious diseases at ages 2 and 4years.....This study aimed at investigating the effects of prenatal exposure to PFAS on the prevalence of allergies and infectious diseases in children up to age 7..... For infectious diseases, PFDA and PFDoDA were associated with increased risk of pneumonia and PFOA was associated with increased risk of RSV infection among children not having any siblings (only-one-child). Our results corroborate the hypothesis on immunosuppressive and immunomodulating effects of PFAS on allergies and infectious diseases in children' (208).

PM(10)/PM10

GIC: 'PM₁₀ (p=0.046) and NO₂ (p=0.03) both had significant linear correlations with esophageal cancer mortality rates. After introducing smoking as a risk factor in models of multiple linear regression analyses, PM₁₀ was still an independent risk factor that increased esophageal cancer mortality rates' (209).

COV: '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)' (210).

DISC: ‘Recent studies have suggested a link between particulate matter (PM) exposure and increased mortality and morbidity associated with pulmonary and cardiovascular diseases.....Inflammation in the respiratory tract of PM10sum-treated mice has been confirmed in BALf and lung parenchyma by increased PMNs percentage, increased ET-1, MPO and cytokines levels. A systemic spreading of lung inflammation in PM10sum-treated mice has been related to the increased blood total cell count and neutrophils percentage, as well as to increased blood MPO. The blood-endothelium interface activation has been confirmed by significant increases of plasma ET-1 and sP-selectin.....PM10sum induced heart endothelial activation and PAHs metabolism, proved by increased ET-1 and Cyp1B1 levels. Moreover, PM10sum causes an increase in brain HO-1 and ET-1. These results state the translocation of inflammation mediators, ultrafine particles, LPS, metals associated to PM10sum, from lungs to bloodstream, thus triggering a systemic reaction, mainly involving heart and brain’ (211).

PM(2.5)/PM_{2.5}

GIC: ‘As a single pollutant, PM_{2.5} was significantly associated with stomach cancer mortality only RR (95%CI): 1.0003 (1.0001, 1.002). For the multi-pollutant analysis, PM_{2.5} combinations with NO₂ were significantly associated with both stomach and colorectal cancer mortality RR (95% CI): 1.0103 (1.009, 1.021) and 1.054 (1.0324, 1.0667), respectively’ (196).

COV: ‘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’ (212).

DISC: ‘Ambient fine particulate matter (PM_{2.5}) pollution poses a great threat on global health. Previous studies have reported that PM_{2.5} regulates circulating fibrinogen and IL-6 levels in the development of cardiovascular and respiratory disease.....Each 10µg/m³ increase in PM_{2.5} concentration was significantly correlated with a 1.76% increase in circulating fibrinogen level (95% CI: 0.38%-3.14%, P=0.013) and a 4.66% increase in IL-6 level (95% CI: 1.14%-8.18%, P=0.010). Subgroup analysis revealed that high-level PM_{2.5} exposure had a more significant association with circulating IL-6 level (11.67%, 95% CI: 0.66%-

22.69%, P=0.038) than low-level exposure, but this association was not observed in fibrinogen (2.50%, 95% CI: -0.78%-5.77%, P=0.135).....Circulating fibrinogen and IL-6 significantly increased with exposure to PM_{2.5}' (213).

Polychlorinated biphenyls/PCBs (indirect impact on COVID)

GIC: 'An elevated risk of colorectal cancer was associated with higher serum concentrations of mono-ortho polychlorinated biphenyl (PCB) congeners 28 and 118' (199).

COV: None.

DISC: 'We investigated whether prenatal exposure from the maternal diet to the toxicants polychlorinated biphenyls (PCBs) and dioxins is associated with the development of immune-related diseases in childhood.....Maternal exposure to PCBs and dioxins was found to be associated with an increased risk of wheeze and more frequent upper respiratory tract infections. Furthermore, maternal exposure to PCBs and dioxins was found to be associated with reduced antibody response to a measles vaccine.....Our results suggest that prenatal dietary exposure to PCBs and dioxins may increase the risk of wheeze and the susceptibility to infectious diseases in early childhood' (214).

Polycyclic aromatic hydrocarbons

GIC: 'Esophageal squamous cell carcinoma (ESCC)..... polycyclic aromatic hydrocarbons (PAHs) ... Studies in humans have shown an association between PAH exposure and development of ESCC in many populations. The results of a recent case-control study in a high risk population in northeastern Iran showed a dramatic dose-response relationship between PAH content in non-tumor esophageal tissue (the target tissue for esophageal carcinogenesis) and ESCC case status, consistent with a causal role for PAH exposure in the pathogenesis of ESCC' (215).

COV: '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' (216).

DISC: 'Experimental studies show that PAHs may trigger various processes linked to non-malignant respiratory diseases. Physiological- and pathological responses include redox imbalance, oxidative stress, inflammation both from the innate and adaptive immune systems, smooth muscle constriction, epithelial- and endothelial dysfunction and dysregulated lung development. Such biological responses may at the molecular level be initiated by PAH-binding to the aryl hydrocarbon receptor (AhR), but possibly also through interactions with beta-adrenergic receptors. In addition, reactive PAH metabolites or reactive oxygen species (ROS) may interfere directly with ion transporters and enzymes involved in signal transduction. Overall, the reviewed literature shows that respiratory effects of PAH-exposure in ambient air may extend beyond lung cancer' (217).

Silica

GIC: 'We found a significant relationship between occupational crystalline silica exposure and gastric cancer' (218).

COV: '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' (219).

DISC: 'Lung inflammation induced by silica impairs host control of tuberculosis, yet the underlying mechanism remains unclear. Here, we show that silica-driven exacerbation of *M. tuberculosis* infection associates with raised type 2 immunity. Silica increases pulmonary Th2 cell and M2 macrophage responses, while reducing type 1 immunity after *M. tuberculosis* infection. Silica induces lung damage that prompts extracellular self-DNA release and activates STING. This STING priming potentiates *M. tuberculosis* DNA sensing by and activation of cGAS/STING, which triggers enhanced type I interferon (IFN1) response and type 2 immunity. cGAS-, STING-, and IFNAR-deficient mice are resistant to silica-induced exacerbation of *M. tuberculosis* infection. Thus, silica-induced self-DNA primes the host response to *M. tuberculosis*-derived nucleic acids, which increases type 2 immunity while reducing type 1 immunity, crucial for controlling *M. tuberculosis* infection.

These data show how cGAS/STING pathway activation, at the crossroads of sterile inflammation and infection, may affect the host response to pathogens such as *M. tuberculosis*' (220).

Talc (indirect impact on COVID)

GIC: 'Workers exposed to all forms of talc had a significantly increased mRR of 1.21 (95% CI: 1.03-1.42, $p = 0.02$) for stomach cancer' (221).

COV: None.

DISC: 'Granulomatosis caused by four subcutaneous talc powder-suspension injections induced strong immunosuppression in rats. The disturbance included reduction of mononuclear white blood cell count in the peripheral blood, atrophy of the thymic cortex, spleen enlargement with predominance of red over the white pulp, increase in the number of lymph node germinal centres and a significant delay of the first-set and second-set allograft rejection' (222).

TCDD [2,3,7,8-tetrachlorodibenzodioxin (TCDD)]

GIC: 'In colon cancer cells, 5-day incubation with TCDD stimulated a twofold dose-dependent increase in cell proliferation that was detectable with 1 nM and maximal with 30 nM TCDD. TCDD induced dose- and time-dependent phosphorylation of EGFR (Tyr845) and ERK1/2; maximal phosphorylation was observed 5 to 10 min after addition of 30 nM TCDD' (223).

COV: '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' (166).

DISC: 'Exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a widespread highly toxic environmental contaminant, suppresses immune response and leads to an increased susceptibility to infectious agents. In particular, several studies have provided evidence that

TCDD decreases resistance to numerous viruses. Indeed, in vivo and in vitro investigations showed that the presence of TCDD is able to interfere with the replication of both human and animal viruses, such as influenza A viruses, coxsackie virus B3, immunodeficiency virus type-1 (HIV-1), cytomegalovirus (CMV), herpes simplex II, and bovine herpesvirus 1. Moreover, TCDD could induce an exacerbation of latent infection produced by HIV-1, CMV or Epstein-Barr virus' (224).

Trichloroethylene (indirect impact on COVID)

GIC: 'A case-control study on colon cancer was conducted encompassing 329 cases and 658 controls.....Regarding exposure to trichloroethylene in general, a slightly increased risk was found whereas such exposure among dry cleaners gave a seven-fold increase of the risk' (225).

COV: None.

DISC: 'we assessed the potential effects of TCE and chloroform on resistance to pulmonary bacterial infection and related alveolar macrophage (AM) function. CD-1 mice were exposed by inhalation to filtered air (control) or concentrations of TCE ranging from 5 to 200 ppm, or concentrations of chloroform ranging from 100 to 2000 ppm. Immediately following exposure, mice were challenged with an aerosol of *Streptococcus zooepidemicus* and monitored for clearance of bacteria from the lung and mortality. In separate experiments, exposed mice were injected intratracheally with viable bacteria and phagocytic function was evaluated in macrophages obtained from lung washes 30 min later. The NOEL for enhanced mortality to infection was 25 ppm for TCE and 500 ppm for chloroform. Relative to the air controls, differences in clearance of bacteria from the lung were noted in mice exposed to TCE (NOEL = 50 ppm) and to chloroform (NOEL 100 ppm), and differences in AM phagocytic index were noted for TCE (NOEL=100ppm) and for chloroform (NOEL < 100 ppm)' (226).

Category 5: Psychosocial/socioeconomic

Chronic stress

GIC: 'Chronic stress contributes to colon cancer progression and induces a Th1/Th2 imbalance in the mouse immune system, which is considered critical during cancer progression' (227).

COV: ‘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’ (228).

DISC: ‘Our study indicated that high levels of psychological stress are associated with increased risk of HZ [herpes zoster]’ (229).

Restraint stress (indirect impact on COVID)

GIC: ‘colorectal carcinoma (CRC) ... chronic restraint stress (CRS) ... We conclude that CRS promotes CRC xenograft tumor growth in nude mice by stimulating CRC cell proliferation through the AR signaling-dependent activation of ERK1/2’ (230).

COV: None.

DISC: ‘restraint stress significantly increased the mortality and the severity of pneumonia in mice caused by A/FM/1/47(H1N1) virus infection’ (231).

References: For all reference citations, please see the References in the main manuscript.