

Formaldehyde and brain disorders: A meta-analysis and bioinformatics approach: Supplement

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A1. Search strategy and inclusion/exclusion criteria

We performed electronic searches of online databases (PubMed, Web of Science Core Collection, Biosis Previews, Embase, Google Scholar, Toxline/DART, Chinese National Knowledge Infrastructure (CNKI), Wanfang Data, and Chongqing VIP Information (CQVIP)) using search terms outlined below. Search terms were developed using the Medical Subject Headings (MeSH) database to compile synonyms for formaldehyde and outcomes related to NDD and brain cancer. Searches included all human (cohort and case-control) studies of formaldehyde and NDD or BT. Only data published in peer-reviewed journals or edited books were eligible for inclusion. No language restrictions were applied.

Studies were excluded if they did not include estimates of relative risk and variance or the data needed to calculate them, they had no cases of disease, lacked a clearly exposed group, reported data on the same cohort as another publication used in the meta-analysis (in which case the most recent analysis was selected), or were not published in a scientific journal/official reports. We analyzed population-based studies with no known high exposure source and studies that reported standardized proportionate incidence ratios (SPIR) only in sensitivity analyses, but not in the main meta-analysis. SPIR was excluded because formaldehyde is known to cause other leukemia and nasopharyngeal cancer, meaning the SPIR would bias the

relative risk estimates towards the null. The effect of these exclusions has been evaluated in the sensitivity analysis ([Section 3.2.3](#)).

A1.1 ALS search terms

("Formaldehyde"[Mesh] OR 50-00-0[RN] OR Formaldehyde[tiab] OR cadaver[tiab] OR embalm*[tiab] OR garment-workers[tiab] OR textile-workers[tiab] OR housing[tiab] OR "housing"[Mesh] OR Travel-trailer*[tiab] OR manufactured-home*[tiab] OR mobile-home*[tiab] OR manufactured-hous*[tiab] OR modular-home*[tiab]) OR "temporary housing unit"[tiab] OR "temporary housing units"[tiab] OR cadaver[tiab] OR embalm*[tiab] OR garment-workers[tiab] OR textile-workers[tiab] OR wood-workers[tiab] OR woodworkers[tiab] OR Construction workers[tiab]) AND Sclerosis, Amyotrophic Lateral OR Charcot Disease OR Motor Neuron Disease, Amyotrophic Lateral Sclerosis OR Lou Gehrig Disease OR Lou Gehrig's Disease OR Lou-Gehrigs Disease Disease, Lou-Gehrigs OR ALS (Amyotrophic Lateral Sclerosis) OR Gehrig's Disease OR Gehrig Disease OR Gehrings Disease OR Amyotrophic Lateral Sclerosis, Guam Form OR Amyotrophic Lateral Sclerosis, Parkinsonism-Dementia Complex of Guam OR Amyotrophic Lateral Sclerosis, Parkinsonism Dementia Complex of Guam OR Guam Form of Amyotrophic Lateral Sclerosis OR Amyotrophic Lateral Sclerosis-Parkinsonism-Dementia Complex 1 OR Amyotrophic Lateral Sclerosis Parkinsonism Dementia Complex 1 OR Guam Disease OR Disease, Guam OR Amyotrophic Lateral Sclerosis With Dementia OR Dementia With Amyotrophic Lateral Sclerosis

Performed on 7/23/2018 n = 39

Updated on 5/29/2019 n=2 (both excluded)

A1.2 PD search terms

Parkinsonian Syndrome OR Parkinsonism OR Parkinsonian Syndromes OR Parkinsonian Diseases OR Autosomal Dominant Parkinsonism OR Dominant Parkinsonism, Autosomal OR Parkinsonism, Autosomal Dominant OR Autosomal Recessive Juvenile Parkinson Disease OR Chromosome 6-Linked Autosomal Recessive Parkinsonism OR Chromosome 6 Linked Autosomal Recessive Parkinsonism OR Familial Parkinson Disease, Autosomal Recessive OR Juvenile Parkinson Disease, Autosomal Recessive OR Juvenile Parkinsonism, Autosomal Recessive OR Parkinsonism, Early Onset, with Diurnal Fluctuation OR Parkinsonism, Juvenile, Autosomal Recessive OR Parkinson Disease 2, Autosomal Recessive Juvenile OR Parkinsonism, Early-Onset, With Diurnal Fluctuation OR Parkinson Disease, Juvenile, Autosomal Recessive OR Parkinson Disease 2 OR Parkinson Disease Autosomal Recessive, Early Onset OR Autosomal Recessive Juvenile Parkinsonism OR Parkinson Disease, Familial, Autosomal Recessive OR Ramsay Hunt Paralysis Syndrome OR Familial Juvenile Parkinsonism OR Juvenile Parkinsonism, Familial OR Parkinsonism, Familial Juvenile OR Parkinsonism, Experimental OR Experimental Parkinsonisms OR Parkinsonisms, Experimental OR Parkinson Disease, Experimental OR Experimental Parkinsonism, MPTP-Induced OR Experimental Parkinsonism, MPTP Induced OR Parkinsonism, MPTP-Induced Experimental OR MPTP-Induced Experimental Parkinsonism OR MPTP Induced Experimental Parkinsonism OR Experimental Parkinson Disease OR Diseases, Experimental Parkinson OR Experimental Parkinson Diseases OR Parkinson Diseases, Experimental OR Experimental Parkinsonism OR Parkinsonism, Juvenile OR Juvenile Parkinsonism OR Juvenile Parkinsonisms OR Parkinsonisms, Juvenile OR Parkinson Disease, Juvenile OR Juvenile Parkinson Disease OR Autosomal Dominant Juvenile Parkinson Disease OR Juvenile Parkinson Disease, Autosomal Dominant OR Parkinsonism, Juvenile, Autosomal Dominant OR Parkinson Disease, Autosomal

Dominant. Juvenile OR Parkinson Disease, Juvenile, Autosomal Dominant OR Autosomal Dominant Juvenile Parkinsonism OR Juvenile Parkinsonism, Autosomal Dominant OR Autosomal Recessive Parkinsonism OR Parkinsonism, Autosomal Recessive OR Recessive Parkinsonism, Autosomal OR Parkinson Disease

Performed on 7/23/18 n = 66

Updated on 5/29/2019 n=2 (one excluded because it used mean differences, other one did not have FA)

A1.3 AD search terms

Alzheimer's Disease OR Dementia, Senile OR Senile Dementia OR Dementia, Alzheimer Type OR Alzheimer Type Dementia OR Alzheimer-Type Dementia (ATD) OR Alzheimer Type Dementia (ATD) OR Dementia, Alzheimer-Type (ATD) OR Alzheimer Type Senile Dementia OR Primary Senile Degenerative Dementia OR Dementia, Primary Senile Degenerative OR Alzheimer Sclerosis OR Sclerosis, Alzheimer OR Alzheimer Syndrome OR Alzheimer Dementia OR Alzheimer Dementias OR Dementia, Alzheimer OR Dementias, Alzheimer OR Senile Dementia, Alzheimer Type OR Acute Confusional Senile Dementia OR Senile Dementia, Acute Confusional OR Dementia, Presenile OR Presenile Dementia OR Alzheimer Disease, Late Onset OR Late Onset Alzheimer Disease OR Alzheimer's Disease, Focal Onset OR Focal Onset Alzheimer's Disease OR Familial Alzheimer Disease (FAD) OR Alzheimer Disease, Familial (FAD) OR Alzheimer Diseases, Familial (FAD) OR Familial Alzheimer Diseases (FAD) OR Alzheimer Disease, Early Onset OR Early Onset Alzheimer Disease OR Presenile Alzheimer Dementia

Performed on 7/23/18 n = 199

Updated on 5/29/2019 n=10

A1.4 MS search terms

Sclerosis, Multiple OR Sclerosis, Disseminated OR Disseminated Sclerosis OR MS (Multiple Sclerosis) OR Multiple Sclerosis, Acute Fulminating OR Demyelinating Autoimmune Disorders, CNS OR Demyelinating Disease, Autoimmune, CNS OR CNS Demyelinating Autoimmune Diseases OR Autoimmune Demyelinating Diseases, CNS OR Autoimmune Demyelinating Disorders, CNS OR CNS Autoimmune Demyelinating Disorders OR Demyelinating Autoimmune Diseases, Central Nervous System OR Autoimmune Demyelinating Diseases, Central Nervous System OR Autoimmune Diseases, Demyelinating, Brain OR Demyelinating Autoimmune Diseases, Brain OR Brain Autoimmune Demyelinating Diseases OR Spinal Cord Demyelinating Autoimmune Diseases OR Autoimmune Demyelinating Diseases, Spinal Cord OR Demyelinating Autoimmune Diseases, Spinal Cord OR Autoimmune Demyelinating Diseases, Cerebral OR Demyelinating Autoimmune Diseases, Cerebral OR Cerebral Demyelinating Diseases, Autoimmune

Performed on 7/23/18 n = 74

Updated on 5/29/2019 n=2

A1.5 Brain tumor search terms

((“Brain Neoplasms”[Mesh] OR “Nervous System Neoplasms”[Mesh] OR “Central Nervous System Neoplasms”[Mesh] OR Neoplasms, Brain[tiab] OR Neoplasm, Brain[tiab] OR Brain Tumors[tiab] OR Brain Tumor[tiab] OR Tumor, Brain[tiab] OR Tumors, Brain[tiab] OR Brain Cancer[tiab] OR Brain Cancers[tiab] OR Cancer, Brain[tiab] OR Cancers, Brain[tiab] OR Malignant Neoplasms, Brain[tiab] OR Brain Malignant Neoplasm[tiab] OR Brain Malignant Neoplasms[tiab] OR Malignant Neoplasm, Brain[tiab] OR Cancer of Brain[tiab] OR Cancer of the Brain[tiab] OR Neoplasms, Brain, Malignant[tiab] OR Brain Neoplasms, Malignant[tiab] OR Brain Neoplasm, Malignant[tiab] OR Malignant Brain Neoplasm[tiab] OR Malignant Brain Neoplasms[tiab] OR Neoplasms, Intracranial[tiab] OR Intracranial Neoplasm[tiab] OR Neoplasm, Intracranial[tiab] OR Intracranial Neoplasms[tiab] OR Brain Tumor, Recurrent[tiab] OR Brain Tumors, Recurrent[tiab] OR Recurrent Brain Tumor[tiab] OR Recurrent Brain Tumors[tiab] OR Malignant Primary Brain Tumors[tiab] OR Primary Malignant Brain Tumors[tiab] OR Malignant Primary Brain Neoplasms[tiab] OR Primary Malignant Brain Neoplasms[tiab] OR Brain Neoplasms, Malignant, Primary[tiab] OR Brain Neoplasms, Primary Malignant[tiab] OR Benign Neoplasms, Brain[tiab] OR Benign Neoplasm, Brain[tiab] OR Brain Benign Neoplasm[tiab] OR Brain Benign Neoplasms[tiab] OR Neoplasms, Brain, Benign[tiab] OR Brain Neoplasms, Benign[tiab] OR Benign Brain Neoplasm[tiab] OR Benign Brain Neoplasms[tiab] OR Brain Neoplasm, Benign[tiab] OR Brain Tumor, Primary[tiab] OR Brain Tumors, Primary[tiab] OR Primary Brain Tumor[tiab] OR Primary Brain Tumors[tiab] OR Neoplasms, Brain, Primary[tiab] OR Brain Neoplasm, Primary[tiab] OR Brain Neoplasms, Primary[tiab] OR Primary Brain Neoplasm[tiab] OR Primary Brain Neoplasms[tiab]))

Performed on 11/18/2017 n=1180

Updated on 5/29/2019 n=8

A2. Quality analysis results

Among the ALS studies, Pinkerton et al. (2013) and Roberts et al. (2016) were ranked as the highest quality cohort studies, and Fang et al. (2009) was the highest quality case-control study. Among the brain tumor studies, the highest quality cohort studies were Beane Freeman et al. (2013), Jiang et al. (1990), and Meyers et al. (2013); the highest quality case-control study of brain tumors was Coggon et al. (2014).

A3. Bioinformatics methods

A3.1 Gene-association data from CTD

The CTD is a large and publicly available resource that contains manually curated data for published chemical-gene and gene-disease interactions (it contained > 38 million relationships as of August 2018). We applied appropriate Medical Subject Heading (MeSH) search terms for [formaldehyde](#), [NDD](#), [ALS](#), [AD](#), [PD](#), [MS](#), and [brain tumor](#). To obtain the disease genes, only curated gene-association data were taken into account; curated implies that the gene of interest serves as a biomarker of the disease, is important in the etiology of the disease, or is used as a

therapeutic target for disease treatment. The gene association data that were obtained for the “Neurodegenerative Diseases” term (parent term NDD in MeSH tree) were corrected with what was already found in the results for AD, ALS and PD individually (the MeSH term “Neurodegenerative Diseases” includes a collection of different neuropathies, known as child terms). The other NDD (oNDD) group contains gene association data for the remaining NDD subtypes excluding ALS, AD, and PD. Within the MeSH tree, MS is not defined under the parent term “Neurodegenerative Diseases,” but instead is categorized under [“Demyelinating Autoimmune Diseases, CNS”](#).

A3.2 Inference of common biomarker genes

If chemical A interacts with gene B (via a curated chemical–gene interaction) and gene B is independently associated with disease C (via a curated gene–disease relationship), then it may be inferred that chemical A has a potential relationship with disease C (inferred via gene B). This integration provides possible chemical–gene–disease connections that may not otherwise be apparent and may form the basis for testable hypotheses about the mechanisms underlying the etiology of environmental disease, such as formaldehyde-induced NDDs and brain cancer.

A3.3 Gene set enrichment analysis (GSEA)

Each gene list obtained from CTD was copied and pasted into the ClueGO app and used for GSEA. We defined significant pathways as those with 1) a minimum of three formaldehyde genes or 2) four percent of total genes affected by formaldehyde in a pathway (see the [“ClueGO predefined selection criteria” document](#)). The resulting matrix files containing significant pathways on the rows and involved genes on the columns were used for further integration and visualization purposes.

Supplementary Table 1. Measures of association and International Classification of Disease (ICD) codes for brain tumor studies.

Study	ICD-8
Brain tumor: Professional workers (N=5)	
Hall, et al. ⁶⁶	191-2
Hauptmann, et al. ⁴⁴	191-2, 225, 238.1
Levine, et al. ⁶⁷	191-2
Stroup, et al. ⁶⁸	191-2
Wang, et al. ⁶⁹	NA (BC)
Brain tumor: Industrial workers (N=7)	
Andjelkovich, et al. ⁷⁰	191-2
Beane Freeman, et al. ⁴²	191-2
Coggon, et al. ⁴³	191-2
Fondelli, et al. ⁷¹	239
Jiang, et al. ⁷²	NA (BT)
Meyers, et al. ⁴⁵	C47, 70-72 ^a
Wong ⁷³	191

Abbreviations: BC, brain cancer; BT, brain tumor; N, number of studies; NA, not available; OR, odds ratio; SMR, standardized mortality ratio.

^a ICD-10 codes

Supplementary Table 2. Quality assessment of the cohort studies in the meta-analyses. ¹

Study	Selection				Comparability Controls for age	Outcome			Overall score ⁷
	Representativeness of exposed	Selection of non- exposed ²	Exposure assessment ³	Outcome absent at start		Assessment of outcome ⁴	Follow-up length ⁵	Adequacy of follow-up ⁶	
Amyotrophic lateral sclerosis									
Pinkerton, et al. ⁵²	1	2	0	0	1	1	2	1	8
Roberts, et al. ⁴⁹	1	1	1	0	1	1	2	1	8
Weisskopf, et al. ⁵¹	1	0	0	1	1	1	1	1	6
Brain tumor (N=10)									
Andjelkovich, et al. ⁶⁹	1	2	1	0	1	1	2	1	9
Beane Freeman, et al. ⁴²	1	2	2	0	1	1	2	1	10
Fondelli, et al. ⁷⁰	1	0	1	0	1	1	2	1	7
Hall, et al. ⁷³	1	0	1	0	1	1	1	1	6
Jiang, et al. ⁷¹	1	2	1	0	1	2	2	1	10
Levine, et al. ⁷⁴	1	1	1	0	1	1	2	1	8
Meyers, et al. ⁴⁵	1	2	2	0	1	1	2	1	10
Stroup, et al. ⁷⁵	1	0	1	0	1	1	2	1	7
Wang, et al. ⁷⁶	1	0	2	0	1	2	1	1	8
Wong ⁷²	1	0	0	0	1	1	2	1	6

¹ The study quality was assessed according to the Newcastle Ottawa Quality assessment scale for cohort studies ⁷⁷. One point was awarded for yes, and zero points were awarded for no, unable to determine, or inadequate, unless specified below.

² Two points were awarded if controls were selected from the same cohort, one point was awarded for controls specific to the county/province, and no points were awarded for using US standard population controls.

³ Two points were awarded for measured exposures, one point was awarded for secure record of job title, and no points were awarded for incomplete exposure assessment/self-report.

⁴ Two points were awarded for histological/medical verification, one point was awarded for death certificate, and no points were awarded for self-report.

⁵ Two points were awarded for a follow-up period of greater than 20 years, one point was awarded for a follow-up of greater than ten years, and no points were awarded for a follow-up period less than 10 years.

⁶ Less than 30% loss to follow-up was deemed adequate (one point awarded).

⁷ A maximum of 12 points could be earned.

Supplementary Table 3. Quality assessment of case-control studies in the meta-analyses. ¹

Study	Selection				Comparability	Outcome			Overall quality score ⁷
	Adequate case definition ²	Representativeness of cases	Control selection ³	Definition of controls ⁴	Controls for age	Exposure assessment ⁵	Method consistency	Non-response rate ⁶	
Amyotrophic lateral sclerosis									
Fang, et al. ⁴⁷	2	1	2	2	1	2	1	1	12
Peters, et al. ⁴⁸	2	1	2	2	1	1	1	1	11
Seals, et al. ⁵⁰	2	1	2	2	1	1	1	1	11
Brain tumor									
Hauptmann, et al. ⁴⁴	1	1	2	1	1	2	1	1	10
Coggon, et al. ⁴³	1	1	2	2	1	2	1	1	11

¹ The study quality was assessed according to the Newcastle Ottawa Quality assessment scale for case-control studies ⁷⁷. One point was awarded for yes, and zero points were awarded for no, unable to determine, or inadequate, unless specified below.

² Two points were awarded for histological/medical verification, one point was awarded for death certificate, and no points were awarded for self-report.

³ Two points were awarded if controls were selected from the same company/community, one point was awarded for controls specific to the county/province, and zero points were awarded for no description.

⁴ Two points were awarded for controls with no history of the disease, one point was awarded for a control with no disease at the time of death, and zero points were awarded for no description.

⁵ Two points were awarded for measured exposures/blinded interview, one point was awarded for secure record of job title, and no points were awarded for incomplete exposure assessment.

⁶ Less than 30% non-response rate was deemed adequate (one point awarded).

⁷ A maximum of 12 points could be earned.

Supplementary Table 4. Comparison of current and previous meta-analyses on brain cancer.

Studies	Blair <i>et al.</i> 1990			Bosetti <i>et al.</i> 2008			Current meta-analysis (2020)		
	Group	RR	N	Group	RR	N	Group	RR	N
Andjelkovich, et al. ⁶⁶	Not used			Same			Ever	0.62	2
Beane Freeman, et al. ⁴²	Not used			Not used			Peak ≥ 4.0 ppm	1.07	13
Coggon, et al. ¹⁰⁶	Not used			Not used			>2.0 ppm	0.56	8
Fondelli, et al. ⁶⁷	Not used			Not used			Ever	10.03	2
Hall, et al. ⁶⁸	Not used			Same			Ever	2.18	6
Hauptmann, et al. ⁴⁴	Not used			Not used			Peak ≥ 9.3 ppm	1.9	11
Jiang, et al. ⁶⁹	Not used			Not used			Duration 20+ years	3.90	1
Levine, et al. ⁷⁰	Same			Same			Ever	1.15	3
Meyers, et al. ⁴⁵	Not used			Not used			Duration 20+ years	1.72	11
Stroup, et al. ⁷¹	Ever, US standard control	2.7	10	Ever, US standard control	2.7	10	Gross anatomy	3.9	4
Wang, et al. ⁷²	Not used			Not used			Ever	8.27	2
Wong ⁷³	Not used			Not used			Hired before 1961	2.13	3
Blair, et al. ¹⁰⁷	Used	0.8	17	Not used			Not used, overlapping cohort		
Coggon, et al. ¹⁰⁶	Not used			Used	0.85	30	Not used, overlapping cohort		
Harrington and Oakes ¹⁰⁸	Used	3.3	4	Not used			Not used, overlapping cohort		
Hauptmann, et al. ^{109 110}	Not used			Used	0.92	43	Not used, overlapping cohort		
Hayes, et al. ¹¹¹	Not used			Used	1.19	24	Not used, overlapping cohort		
White	Used	1.2	24	Not used			Not used, overlapping cohort		
Nonwhite	Used	0.0	0	Not used			Not used, overlapping cohort		
Malker and Weiner ¹¹²	Used	0.9	89	Not used			Not used, low-exposure study		
Matanoski ¹¹³	Not used			Ever, US std. control	1.34	13	Not used, overlapping cohort		
Milham ¹¹⁴	Used	0.6	1	Not used			Not used, overlapping cohort		
Pinkerton, et al. ⁹⁸	Not used			Used	1.09	19	Not used, overlapping cohort		
Stayner, et al. ¹¹⁵	Used	0.7	5	Not used			Not used, overlapping cohort		
Walrath, et al. ¹¹⁶	Used	0.0	0	Not used			Not used, no brain tumor cases.		
Walrath and Fraumeni ¹¹⁷	Used	1.56	9	Used	1.56	9	Not used, overlapping cohort		
Walrath and Fraumeni ¹¹⁸	Used	1.94	9	Used	1.94	9	Not used, overlapping cohort		
Professionals meta-RR (95% CI)	1.5 (1.2-2.0) N=9^{a,b}			1.56 (1.24-1.96) N=7			2.42 (1.41-4.17) N=5		
Industry workers meta-RR (95% CI)	0.9 (0.7-1.1)^b N=3			0.92 (0.75-1.13) N=4			1.32 (0.72-2.44) N=7		
Overall meta-RR (95% CI)	1.29 (0.95-1.76)^c N=12			1.24 (0.99-1.55)^{c,d} N=11			1.71 (1.07-2.73) N=12		

Abbreviations: CI, confidence interval; n, subjects; N/A, not available; PMR, proportional mortality ratio; RR, relative risk; SMR, standard mortality ratio.

^a Hayes, et al.¹¹¹ reported white and nonwhite separately, so N = 2.

^b Confidence interval calculated by Authors.

^c Meta-RR calculated by Authors using random-effects model because heterogeneity was present ($\chi^2 >$ degrees of freedom). Degrees of freedom = number of studies minus one.

^d Risk estimates from original publications were used to calculate meta-RR because those reported in Bosetti, et al.⁴¹ were slightly different. When the numbers from Bosetti, et al.⁴¹ were used, the meta-RR was 1.26 (1.01-1.59).

Supplementary Table 5. Formaldehyde-gene association data from CTD related was compared with curated gene-disease associations for AD, ALS, PD, MS, brain tumor, and other types of NDD (oNDD).

Gene	AD	ALS	PD	MS	BT	oNDD	Gene	AD	ALS	PD	MS	BT	oNDD
SOD2	x	x	x		x	x	CALM1	x					
TNF	x	x	x			x	BAX	x					
SOD1		x	x			x	CRH	x					
HMOX1	x		x			x	NOS3	x					
IGF1R	x		x			x	FOS		x				
MAPT	x		x			x	SNAI1		x				
IL1B	x			x		x	JUND		x				
TP53		x			x		DBR1		x				
VEGFA	x				x		FUS		x				
DRD2			x		x		PLA2G4A		x				
CLU	x	x					CREBBP		x				
CST3	x	x					LDLR		x				
GSTP1		x	x				PENK		x				
CASP1		x		x			SIX2		x				
VAPB		x				x	OPTN		x				
TBK1		x				x	UNC13A		x				
SQSTM1		x				x	PTGS2		x				
CHCHD10		x				x	DNAJC6			x			
BDNF	x		x				GIGYF2			x			
BCHE	x			x			SLC18A2			x			
TFAM	x					x	GPX1			x			
GSK3B	x					x	BAG5			x			
PRNP	x					x	VPS13C			x			
TPP1	x					x	SYNJ1			x			
CASP3	x					x	NR4A2			x			
EDN1			x			x	DDIT4			x			
NGF			x			x	MAP3K5			x			
IL6			x			x	NOS1			x			
RAB39B			x			x	DRD1			x			
MAG			x			x	HSPA1A			x			
IFNG				x		x	IL7R				x		
KIF1B				x		x	VCAM1				x		
IL10				x		x	CBLB				x		
POMC				x		x	ICAM1				x		
PAXIP1	x						CD40				x		
DHCR24	x						NLRP3				x		
BCL2	x						TNFAIP3				x		
ARC	x						AGTR1					x	
MPO	x						GLI2					x	

HRAS	x	YAP1	x
CDK6	x	PPM1D	x
ITGB2	x	SOX2	x
APC	x	GH1	x
PTCH1	x	CCND1	x
FJX1	x	MSH6	x
TGM2	x	IL2	x
RELA	x	IQGAP2	x
CTC1	x	NRARP	x

Genes only associated with other NDD (N = 78) are not shown.

Supplementary Table 6. Significantly enriched pathways for formaldehyde and the NDD subgroups or brain tumor related genes.

Pathway name	Diseases	AD			ALS			PD			BT			MS			oNDD		
		#	%	p	#	%	p	#	%	p	#	%	p	#	%	p	#	%	p
Folate Metabolism	AD, ALS, BT, MS, PD, oNDD	4	5.71	1.10E-04	5	7.14	1.59E-06	6	8.57	1.04E-07	4	5.71	6.16E-05	3	4.29	3.58E-04	8	11.428572	3.97E-07
Photodynamic therapy-induced AP-1 survival signaling.	AD, ALS, BT, PD, oNDDs	3	5.88	8.14E-04	3	5.88	4.56E-04	3	5.88	7.12E-04	3	5.88	5.33E-04				3	5.882353	1.45E-02
Vitamin B12 Metabolism	AD, ALS, MS, PD, oNDD	4	7.55	3.66E-05	4	7.55	1.64E-05	4	7.55	3.04E-05				3	5.66	1.56E-04	6	11.320755	1.32E-05
Chromosomal and microsatellite instability in colorectal cancer	AD, ALS, BT, oNDD	4	5.41	1.36E-04	4	5.41	6.19E-05				4	5.41	7.67E-05						
Photodynamic therapy-induced NF-kB survival signaling	AD, BT, MS, oNDD	3	8.57	2.66E-04							4	11.43	3.78E-06	3	8.57	4.46E-05	5	14.285714	2.30E-05
Amyotrophic lateral sclerosis (ALS)	AD, ALS, PD, oNDD	5	13.16	1.99E-07	5	13.16	7.00E-08	5	13.16	1.56E-07							5	13.157895	3.48E-05
Selenium Micronutrient Network	AD, ALS, PD, oNDD	4	4.49	2.79E-04	5	5.62	5.26E-06	5	5.62	1.15E-05							7	7.8651686	2.75E-05
Oncostatin M Signaling Pathway	ALS, BT, oNDD				4	6.06	3.94E-05				4	6.06	4.89E-05				4	6.060606	4.27E-03
Copper homeostasis	AD, BT, oNDD	4	7.41	3.94E-05							3	5.56	6.31E-04				5	9.259259	1.94E-04
Oxidative Stress	ALS, PD, oNDD				3	10	9.25E-05	4	13.33	3.00E-06							4	13.333333	2.13E-04
Viral Acute Myocarditis	AD, PD, oNDD	5	5.88	1.16E-05				4	4.71	1.95E-04							13	15.294118	1.32E-12
Lung fibrosis	AD, PD, oNDD	3	4.76	1.51E-03				4	6.35	6.04E-05							8	12.698413	1.72E-07
Overview of nanoparticle effects	AD, PD, oNDD	4	21.05	5.26E-07				3	15.79	3.56E-05							4	21.052631	3.27E-05
Allograft Rejection	AD, MS, oNDD	4	4.44	2.91E-04										4	4.44	2.63E-05	8	8.888889	2.79E-06
Endochondral Ossification	AD, BT	3	4.62	1.65E-03							3	4.62	1.09E-03						
Hepatitis C and Hepatocellular Carcinoma	BT, oNDD										3	5.88	5.33E-04				6	11.764706	1.05E-05
Endometrial cancer	BT, oNDD										4	6.35	4.06E-05				3	4.7619047	2.54E-02
ErbB Signaling Pathway	BT, oNDD										3	5.56	6.31E-04				3	5.555553	1.69E-02
Pancreatic adenocarcinoma pathway	BT, oNDD										5	5.62	6.93E-06				5	5.6179776	1.94E-03

RAC1/PAK1/p38/MMP2 Pathway	BT, oNDD				4	5.8	5.82E-05		3	4.347826	3.21E-02
Non-small cell lung cancer	BT, oNDD				4	6.06	4.89E-05		3	4.5454545	2.87E-02
Apoptosis-related network due to altered Notch3 in ovarian cancer	ALS, oNDD		3	5.56			5.40E-04		6	11.111111	1.48E-05
TGF-beta Receptor Signaling	ALS, oNDD		3	5.17			6.66E-04		5	8.620689	2.72E-04
Aryl Hydrocarbon Receptor Pathway	AD, oNDD	3	6.25				6.81E-04		4	8.333333	1.32E-03
TNF related weak inducer of apoptosis (TWEAK) Signaling Pathway	AD, oNDD	3	7.14				4.58E-04		6	14.285714	3.30E-06
Alzheimers Disease	AD, oNDD	6	4.03				1.22E-05		11	7.3825502	2.12E-07
Cardiac Hypertrophic Response	AD, oNDD	3	5.26				1.13E-03		6	10.526316	2.03E-05
T-Cell antigen Receptor (TCR) pathway during Staphylococcus aureus infection	AD, oNDD	3	4.84				1.44E-03		5	8.064516	3.73E-04
Leptin signaling pathway	AD, oNDD	4	5.26				1.51E-04		6	7.894737	1.05E-04
IL-5 Signaling Pathway	AD, oNDD	3	7.5				3.96E-04		6	15	2.45E-06
Fas Ligand (FasL) pathway and Stress induction of Heat Shock Proteins (HSP) regulation	AD, oNDD	3	6.82				5.26E-04		6	13.636364	4.37E-06
NO/cGMP/PKG mediated Neuroprotection	AD, oNDD	5	10.42				6.62E-07		3	6.25	1.23E-02
Prion disease pathway	AD, oNDD	3	8.11				3.14E-04		5	13.513514	3.05E-05
Corticotropin-releasing hormone signaling pathway	AD, oNDD	5	5.38				1.80E-05		8	8.602151	3.57E-06
Spinal Cord Injury	PD, oNDD		5	4.17			4.92E-05		12	10	1.73E-09
Association Between Physico-Chemical Features and Toxicity Associated Pathways	PD, oNDD		3	4.41			1.65E-03		3	4.4117646	3.09E-02

One carbon metabolism and related pathways	PD, oNDD		3	5.56	8.42E-04				3	5.555553	1.69E-02
IL1 and megakaryocytes in obesity	MS, oNDD								4	16	1.40E-07
Cytokines and Inflammatory Response	MS, oNDD								3	11.11	2.01E-05
Aryl Hydrocarbon Receptor	BT								3	6.25	4.45E-04
G1 to S cell cycle control	BT								3	4.69	1.04E-03
Tumor suppressor activity of SMARCB1	BT								3	9.09	1.45E-04
Bladder Cancer	BT								4	9.76	7.23E-06
DNA Damage Response	BT								3	4.35	1.29E-03
Hedgehog Signaling Pathway	BT								3	6.82	3.44E-04
miRNAs involved in DNA damage response	BT								3	6	5.03E-04
DNA Damage Response (only ATM dependent)	BT								5	4.35	2.43E-05
Retinoblastoma Gene in Cancer	BT								4	4.55	1.51E-04
Wnt Signaling Pathway	BT								3	5.66	5.97E-04
Signaling Pathways in Glioblastoma	BT								5	6.02	4.91E-06
Integrated Cancer Pathway	AD		3	6.52	6.00E-04						
Oxidative Damage	AD		3	7.32	4.27E-04						
Regulation of Apoptosis by Parathyroid Hormone-related Protein	AD		3	13.64	6.45E-05						
Nanomaterial induced apoptosis	AD		3	15	4.80E-05						
Apoptosis	AD		5	5.81	1.23E-05						
Sleep regulation	PD								3	7.89	2.97E-04
Phosphodiesterases in neuronal function	PD								3	5.45	8.88E-04

Type II interferon signaling (IFNG)	MS	3	8.11	5.28E-05
Nucleotide-binding Oligomerization Domain (NOD) pathway	MS	3	7.32	7.21E-05

Pathways only associated with other NDD (N = 50) are not shown.

Supplementary Table 7. Connection between genes and pathways associated with formaldehyde.

Gene name	Pathway name
AHCY	Folate Metabolism
APC	Chromosomal and microsatellite instability in colorectal cancer DNA Damage Response (only ATM dependent) Copper homeostasis Wnt Signaling Pathway Endometrial cancer
BAX	Apoptosis Chromosomal and microsatellite instability in colorectal cancer Integrated Cancer Pathway Viral Acute Myocarditis Regulation of Apoptosis by Parathyroid Hormone-related Protein Photodynamic therapy-induced AP-1 survival signaling. Leptin signaling pathway Overview of nanoparticle effects Aryl Hydrocarbon Receptor Pathway Nanomaterial induced apoptosis Amyotrophic lateral sclerosis (ALS)
BCL2	Oxidative Damage Fas Ligand (FasL) pathway and Stress induction of Heat Shock Proteins (HSP) regulation Corticotropin-releasing hormone signaling pathway Integrated Cancer Pathway Photodynamic therapy-induced AP-1 survival signaling. Prion disease pathway Viral Acute Myocarditis Overview of nanoparticle effects Regulation of Apoptosis by Parathyroid Hormone-related Protein Chromosomal and microsatellite instability in colorectal cancer Apoptosis NO/cGMP/PKG mediated Neuroprotection IL-5 Signaling Pathway Amyotrophic lateral sclerosis (ALS) Nanomaterial induced apoptosis
BDNF	Spinal Cord Injury
CALM1	Cardiac Hypertrophic Response Alzheimers Disease T-Cell antigen Receptor (TCR) pathway during Staphylococcus aureus infection NO/cGMP/PKG mediated Neuroprotection Endochondral Ossification
CASP1	Amyotrophic lateral sclerosis (ALS) Nucleotide-binding Oligomerization Domain (NOD) pathway
CASP3	Corticotropin-releasing hormone signaling pathway Alzheimers Disease Fas Ligand (FasL) pathway and Stress induction of Heat Shock Proteins (HSP) regulation Chromosomal and microsatellite instability in colorectal cancer Copper homeostasis Prion disease pathway TNF related weak inducer of apoptosis (TWEAK) Signaling Pathway Viral Acute Myocarditis Allograft Rejection Amyotrophic lateral sclerosis (ALS) Integrated Cancer Pathway Oxidative Damage Apoptosis Nanomaterial induced apoptosis Brain-Derived Neurotrophic Factor (BDNF) signaling pathway MAPK Signaling Pathway

	<p>AGE/RAGE pathway Oncostatin M Signaling Pathway Spinal Cord Injury Hepatitis C and Hepatocellular Carcinoma TNF alpha Signaling Pathway Prolactin Signaling Pathway Sudden Infant Death Syndrome (SIDS) Susceptibility Pathways</p>
CAV1	<p>Non-genomic actions of 1,25 dihydroxyvitamin D3 VEGFA-VEGFR2 Signaling Pathway Viral Acute Myocarditis</p>
CCND1	<p>miRNAs involved in DNA damage response Chromosomal and microsatellite instability in colorectal cancer Endometrial cancer Retinoblastoma Gene in Cancer Photodynamic therapy-induced AP-1 survival signaling. Photodynamic therapy-induced NF-kB survival signaling Wnt Signaling Pathway Copper homeostasis G1 to S cell cycle control ErbB Signaling Pathway Hedgehog Signaling Pathway Hepatitis C and Hepatocellular Carcinoma Pancreatic adenocarcinoma pathway DNA Damage Response (only ATM dependent) DNA Damage Response Bladder Cancer Non-small cell lung cancer Signaling Pathways in Glioblastoma</p>
CD40	<p>Allograft Rejection</p>
CDK6	<p>DNA Damage Response Pancreatic adenocarcinoma pathway Tumor suppressor activity of SMARCB1 Wnt Signaling Pathway G1 to S cell cycle control Signaling Pathways in Glioblastoma Retinoblastoma Gene in Cancer Non-small cell lung cancer miRNAs involved in DNA damage response</p>
CREBBP	<p>TGF-beta Receptor Signaling</p>
CRH	<p>Corticotropin-releasing hormone signaling pathway</p>
CST3	<p>Amyotrophic lateral sclerosis (ALS)</p>
CXCL8	<p>miRNAs in the signaling pathway of the immune response in sepsis Allograft Rejection TLR4 Signaling and Tolerance EBV LMP1 signaling IL-3 Signaling Pathway Corticotropin-releasing hormone signaling pathway Non-genomic actions of 1,25 dihydroxyvitamin D3 Lung fibrosis Toll-like Receptor Signaling Pathway Photodynamic therapy-induced NF-kB survival signaling Senescence and Autophagy in Cancer Sudden Infant Death Syndrome (SIDS) Susceptibility Pathways Hepatitis C and Hepatocellular Carcinoma Overview of nanoparticle effects Thymic Stromal Lymphopoietin (TSLP) Signaling Pathway RIG-I-like Receptor Signaling Spinal Cord Injury</p>

	Regulation of toll-like receptor signaling pathway VEGFA-VEGFR2 Signaling Pathway
DRD1	Sleep regulation Phosphodiesterases in neuronal function Phosphodiesterases in neuronal function Sleep regulation
EDN1	Lung fibrosis Viral Acute Myocarditis MicroRNAs in cardiomyocyte hypertrophy Physiological and Pathological Hypertrophy of the Heart
EGR2	Brain-Derived Neurotrophic Factor (BDNF) signaling pathway Adipogenesis
EIF2AK3	VEGFA-VEGFR2 Signaling Pathway Alzheimers Disease
EPO	EPO Receptor Signaling Hematopoietic Stem Cell Differentiation Differentiation Pathway
FOS	Chromosomal and microsatellite instability in colorectal cancer TGF-beta Receptor Signaling Oncostatin M Signaling Pathway Photodynamic therapy-induced AP-1 survival signaling. Oxidative Stress
GH1	Endochondral Ossification
GLI2	Tumor suppressor activity of SMARCB1 Hedgehog Signaling Pathway
GPX1	Oxidative Stress Amyotrophic lateral sclerosis (ALS) One carbon metabolism and related pathways Selenium Micronutrient Network Association Between Physico-Chemical Features and Toxicity Associated Pathways Folate Metabolism
GPX3	One carbon metabolism and related pathways Folate Metabolism Oxidative Stress Selenium Micronutrient Network
GSK3B	Chromosomal and microsatellite instability in colorectal cancer IL-5 Signaling Pathway Cardiac Hypertrophic Response Leptin signaling pathway Copper homeostasis Corticotropin-releasing hormone signaling pathway Viral Acute Myocarditis Alzheimers Disease TNF related weak inducer of apoptosis (TWEAK) Signaling Pathway T-Cell antigen Receptor (TCR) pathway during Staphylococcus aureus infection Regulation of Apoptosis by Parathyroid Hormone-related Protein Association Between Physico-Chemical Features and Toxicity Associated Pathways IL-7 Signaling Pathway Prolactin Signaling Pathway VEGFA-VEGFR2 Signaling Pathway Factors and pathways affecting insulin-like growth factor (IGF1)-Akt signaling Notch Signaling Pathway Endometrial cancer Brain-Derived Neurotrophic Factor (BDNF) signaling pathway IL17 signaling pathway

	<ul style="list-style-type: none"> ErbB Signaling Pathway IL-6 signaling pathway Regulation of Microtubule Cytoskeleton Energy Metabolism MicroRNAs in cardiomyocyte hypertrophy Senescence and Autophagy in Cancer
HMOX1	<ul style="list-style-type: none"> Lung fibrosis Overview of nanoparticle effects Oxidative Stress
HRAS	<ul style="list-style-type: none"> Oncostatin M Signaling Pathway Bladder Cancer DNA Damage Response (only ATM dependent) Aryl Hydrocarbon Receptor RAC1/PAK1/p38/MMP2 Pathway Signaling Pathways in Glioblastoma Endometrial cancer ErbB Signaling Pathway Non-small cell lung cancer
HSPA8	
	MAPK Signaling Pathway
HSPB1	
	<ul style="list-style-type: none"> MAPK Signaling Pathway Extracellular vesicles in the crosstalk of cardiac cells Apoptosis-related network due to altered Notch3 in ovarian cancer VEGFA-VEGFR2 Signaling Pathway Fas Ligand (FasL) pathway and Stress induction of Heat Shock Proteins (HSP) regulation
HSPD1	
	<ul style="list-style-type: none"> Sudden Infant Death Syndrome (SIDS) Susceptibility Pathways Apoptosis-related network due to altered Notch3 in ovarian cancer
ICAM1	
	<ul style="list-style-type: none"> IL1 and megakaryocytes in obesity Photodynamic therapy-induced NF-kB survival signaling Vitamin B12 Metabolism Type II interferon signaling (IFNG) Folate Metabolism
IFNG	
	<ul style="list-style-type: none"> Cytokines and Inflammatory Response Vitamin B12 Metabolism Allograft Rejection Folate Metabolism IL1 and megakaryocytes in obesity Type II interferon signaling (IFNG) Senescence and Autophagy in Cancer Non-genomic actions of 1,25 dihydroxyvitamin D3 T-Cell antigen Receptor (TCR) pathway during Staphylococcus aureus infection Aryl Hydrocarbon Receptor Pathway NO/cGMP/PKG mediated Neuroprotection Spinal Cord Injury Photodynamic therapy-induced AP-1 survival signaling. TGF-beta Receptor Signaling RIG-I-like Receptor Signaling Viral Acute Myocarditis Development and heterogeneity of the ILC family Selenium Micronutrient Network
IGF1R	
	<ul style="list-style-type: none"> Apoptosis Endochondral Ossification Factors and pathways affecting insulin-like growth factor (IGF1)-Akt signaling Human Thyroid Stimulating Hormone (TSH) signaling pathway MicroRNAs in cardiomyocyte hypertrophy Senescence and Autophagy in Cancer
IL10	
	<ul style="list-style-type: none"> Allograft Rejection Cytokines and Inflammatory Response

T-Cell antigen Receptor (TCR) pathway during Staphylococcus aureus infection
Sudden Infant Death Syndrome (SIDS) Susceptibility Pathways
Viral Acute Myocarditis

IL1A

Sudden Infant Death Syndrome (SIDS) Susceptibility Pathways
Structural Pathway of Interleukin 1 (IL-1)
Fas Ligand (FasL) pathway and Stress induction of Heat Shock Proteins (HSP) regulation
Photodynamic therapy-induced NF-kB survival signaling
Allograft Rejection
Spinal Cord Injury
T-Cell antigen Receptor (TCR) Signaling Pathway
MAPK Signaling Pathway
Hematopoietic Stem Cell Differentiation
miRNAs in the signaling pathway of the immune response in sepsis
Cytokines and Inflammatory Response
IL-1 signaling pathway
Senescence and Autophagy in Cancer

IL1B

Vitamin B12 Metabolism
Allograft Rejection
Folate Metabolism
Photodynamic therapy-induced NF-kB survival signaling
Leptin signaling pathway
Aryl Hydrocarbon Receptor Pathway
Selenium Micronutrient Network
NO/cGMP/PKG mediated Neuroprotection
Alzheimers Disease
Lung fibrosis
Cytokines and Inflammatory Response
IL1 and megakaryocytes in obesity
Nucleotide-binding Oligomerization Domain (NOD) pathway
Type II interferon signaling (IFNG)
Sudden Infant Death Syndrome (SIDS) Susceptibility Pathways
Oligodendrocyte Specification and differentiation(including remyelination), leading to Myelin Components for CNS
MAPK Signaling Pathway
Senescence and Autophagy in Cancer
T-Cell antigen Receptor (TCR) Signaling Pathway
Spinal Cord Injury
Hematopoietic Stem Cell Differentiation
Development and heterogeneity of the ILC family
Toll-like Receptor Signaling Pathway
Regulation of toll-like receptor signaling pathway
IL-1 signaling pathway

IL2

Photodynamic therapy-induced AP-1 survival signaling.
Folate Metabolism
Photodynamic therapy-induced NF-kB survival signaling

IL6

Vitamin B12 Metabolism
Folate Metabolism
Overview of nanoparticle effects
Photodynamic therapy-induced AP-1 survival signaling.
Viral Acute Myocarditis
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Lung fibrosis
Spinal Cord Injury
Sleep regulation
Sudden Infant Death Syndrome (SIDS) Susceptibility Pathways
Non-genomic actions of 1,25 dihydroxyvitamin D3
Photodynamic therapy-induced NF-kB survival signaling
T-Cell antigen Receptor (TCR) Signaling Pathway
IL-6 signaling pathway
Senescence and Autophagy in Cancer
Differentiation Pathway
Extracellular vesicles in the crosstalk of cardiac cells
Development and heterogeneity of the ILC family

	Hematopoietic Stem Cell Differentiation Adipogenesis TNF related weak inducer of apoptosis (TWEAK) Signaling Pathway TLR4 Signaling and Tolerance TNF alpha Signaling Pathway Thymic Stromal LymphoPoietin (TSLP) Signaling Pathway Cytokines and Inflammatory Response Hepatitis C and Hepatocellular Carcinoma Regulation of toll-like receptor signaling pathway Toll-like Receptor Signaling Pathway
ITPR1	Serotonin Receptor 2 and ELK-SRF/GATA4 signaling T-Cell antigen Receptor (TCR) Signaling Pathway Alzheimers Disease
JUND	Oncostatin M Signaling Pathway Apoptosis-related network due to altered Notch3 in ovarian cancer
LDLR	Selenium Micronutrient Network Folate Metabolism Vitamin B12 Metabolism Oncostatin M Signaling Pathway
LMNA	Fas Ligand (FasL) pathway and Stress induction of Heat Shock Proteins (HSP) regulation Adipogenesis
MAG	Spinal Cord Injury Oligodendrocyte Specification and differentiation leading to Myelin Components for CNS
MAP3K5	Amyotrophic lateral sclerosis (ALS) Photodynamic therapy-induced AP-1 survival signaling.
MAPK1	Pancreatic adenocarcinoma pathway Prion disease pathway TNF related weak inducer of apoptosis (TWEAK) Signaling Pathway AGE/RAGE pathway IL-2 Signaling Pathway Physiological and Pathological Hypertrophy of the Heart PDGF Pathway IL-7 Signaling Pathway TGF-B Signaling in Thyroid Cells for Epithelial-Mesenchymal Transition RAC1/PAK1/p38/MMP2 Pathway IL17 signaling pathway Cardiac Hypertrophic Response Thymic Stromal LymphoPoietin (TSLP) Signaling Pathway IL-6 signaling pathway Chromosomal and microsatellite instability in colorectal cancer Senescence and Autophagy in Cancer EBV LMP1 signaling Association Between Physico-Chemical Features and Toxicity Associated Pathways Corticotropin-releasing hormone signaling pathway TCA Cycle Nutrient Utilization and Invasiveness of Ovarian Cancer Spinal Cord Injury Alzheimers Disease Interleukin-11 Signaling Pathway IL-5 Signaling Pathway IL-3 Signaling Pathway Non-small cell lung cancer MET in type 1 papillary renal cell carcinoma IL-1 signaling pathway Toll-like Receptor Signaling Pathway Apoptosis-related network due to altered Notch3 in ovarian cancer Regulation of toll-like receptor signaling pathway Kit receptor signaling pathway TNF alpha Signaling Pathway RANKL/RANK (Receptor activator of NFKB (ligand)) Signaling Pathway

VEGFA-VEGFR2 Signaling Pathway
 Viral Acute Myocarditis
 Leptin signaling pathway
 Brain-Derived Neurotrophic Factor (BDNF) signaling pathway
 Oncostatin M Signaling Pathway
 IL-9 Signaling Pathway
 Signaling of Hepatocyte Growth Factor Receptor
 IL-4 Signaling Pathway
 Endometrial cancer
 Structural Pathway of Interleukin 1 (IL-1)
 Serotonin Receptor 2 and ELK-SRF/GATA4 signaling
 Prolactin Signaling Pathway
 EPO Receptor Signaling
 Non-genomic actions of 1,25 dihydroxyvitamin D3
 MAPK Signaling Pathway
 MicroRNAs in cardiomyocyte hypertrophy
 T-Cell antigen Receptor (TCR) Signaling Pathway
 Follicle Stimulating Hormone (FSH) signaling pathway
 Human Thyroid Stimulating Hormone (TSH) signaling pathway
 ErbB Signaling Pathway

MAPK3

AGE/RAGE pathway
 MET in type 1 papillary renal cell carcinoma
 Follicle Stimulating Hormone (FSH) signaling pathway
 IL-3 Signaling Pathway
 Viral Acute Myocarditis
 Prion disease pathway
 RAC1/PAK1/p38/MMP2 Pathway
 Corticotropin-releasing hormone signaling pathway
 IL-2 Signaling Pathway
 Serotonin Receptor 2 and ELK-SRF/GATA4 signaling
 Non-genomic actions of 1,25 dihydroxyvitamin D3
 MAPK Signaling Pathway
 Regulation of toll-like receptor signaling pathway
 EPO Receptor Signaling
 T-Cell antigen Receptor (TCR) pathway during Staphylococcus aureus infection
 Non-small cell lung cancer
 TNF alpha Signaling Pathway
 Alzheimers Disease
 Signaling of Hepatocyte Growth Factor Receptor
 IL-1 signaling pathway
 TGF-beta Receptor Signaling
 Pancreatic adenocarcinoma pathway
 Structural Pathway of Interleukin 1 (IL-1)
 Toll-like Receptor Signaling Pathway
 Thymic Stromal LymphoPoietin (TSLP) Signaling Pathway
 PDGF Pathway
 VEGFA-VEGFR2 Signaling Pathway
 IL-5 Signaling Pathway
 IL17 signaling pathway
 T-Cell antigen Receptor (TCR) Signaling Pathway
 Endometrial cancer
 IL-7 Signaling Pathway
 Spinal Cord Injury
 Kit receptor signaling pathway
 IL-6 signaling pathway
 Human Thyroid Stimulating Hormone (TSH) signaling pathway
 Hepatitis C and Hepatocellular Carcinoma
 Interleukin-11 Signaling Pathway
 TGF-B Signaling in Thyroid Cells for Epithelial-Mesenchymal Transition
 Oncostatin M Signaling Pathway
 IL-9 Signaling Pathway
 Chromosomal and microsatellite instability in colorectal cancer
 TCA Cycle Nutrient Utilization and Invasiveness of Ovarian Cancer
 Prolactin Signaling Pathway
 IL-4 Signaling Pathway

	<p>Leptin signaling pathway RANKL/RANK (Receptor activator of NFkB (ligand)) Signaling Pathway TNF related weak inducer of apoptosis (TWEAK) Signaling Pathway Cardiac Hypertrophic Response Brain-Derived Neurotrophic Factor (BDNF) signaling pathway MicroRNAs in cardiomyocyte hypertrophy</p>
MAPT	<p>Copper homeostasis Alzheimers Disease IL-5 Signaling Pathway Regulation of Microtubule Cytoskeleton Kit receptor signaling pathway IL-2 Signaling Pathway MAPK Signaling Pathway Brain-Derived Neurotrophic Factor (BDNF) signaling pathway Notch Signaling Pathway</p>
MPO	<p>Selenium Micronutrient Network Folate Metabolism Vitamin B12 Metabolism</p>
MSH6	<p>Retinoblastoma Gene in Cancer Signaling Pathways in Glioblastoma Chromosomal and microsatellite instability in colorectal cancer</p>
NGF	<p>Brain-Derived Neurotrophic Factor (BDNF) signaling pathway MAPK Signaling Pathway Sudden Infant Death Syndrome (SIDS) Susceptibility Pathways</p>
NLRP3	<p>IL1 and megakaryocytes in obesity Nucleotide-binding Oligomerization Domain (NOD) pathway</p>
NOS1	<p>Folate Metabolism Amyotrophic lateral sclerosis (ALS) Viral Acute Myocarditis Phosphodiesterases in neuronal function Spinal Cord Injury Association Between Physico-Chemical Features and Toxicity Associated Pathways</p>
NOS3	<p>Leptin signaling pathway Corticotropin-releasing hormone signaling pathway NO/cGMP/PKG mediated Neuroprotection</p>
PARP1	<p>Fas Ligand (FasL) pathway and Stress induction of Heat Shock Proteins (HSP) regulation Corticotropin-releasing hormone signaling pathway Viral Acute Myocarditis</p>
POMC	<p>Corticotropin-releasing hormone signaling pathway</p>
PPP3CA	<p>MAPK Signaling Pathway Amyotrophic lateral sclerosis (ALS) Alzheimers Disease Spinal Cord Injury Physiological and Pathological Hypertrophy of the Heart MicroRNAs in cardiomyocyte hypertrophy Cardiac Hypertrophic Response Energy Metabolism VEGFA-VEGFR2 Signaling Pathway</p>
PPP3CB	<p>MicroRNAs in cardiomyocyte hypertrophy Alzheimers Disease Energy Metabolism Physiological and Pathological Hypertrophy of the Heart MAPK Signaling Pathway Amyotrophic lateral sclerosis (ALS)</p>
PRNP	<p>Copper homeostasis</p>

	Prion disease pathway
PTCH1	Tumor suppressor activity of SMARCB1 Hedgehog Signaling Pathway Endochondral Ossification
PTGS2	Selenium Micronutrient Network Chromosomal and microsatellite instability in colorectal cancer
RELA	Photodynamic therapy-induced NF-kB survival signaling Aryl Hydrocarbon Receptor Pancreatic adenocarcinoma pathway RAC1/PAK1/p38/MMP2 Pathway Folate Metabolism Oncostatin M Signaling Pathway
RPS6KB1	Apoptosis-related network due to altered Notch3 in ovarian cancer Follicle Stimulating Hormone (FSH) signaling pathway IL-4 Signaling Pathway IL-5 Signaling Pathway ErbB Signaling Pathway Interleukin-11 Signaling Pathway Brain-Derived Neurotrophic Factor (BDNF) signaling pathway IL-6 signaling pathway IL-2 Signaling Pathway VEGFA-VEGFR2 Signaling Pathway Pancreatic adenocarcinoma pathway Prolactin Signaling Pathway Factors and pathways affecting insulin-like growth factor (IGF1)-Akt signaling Leptin signaling pathway Human Thyroid Stimulating Hormone (TSH) signaling pathway Kit receptor signaling pathway
SOD1	Selenium Micronutrient Network Oxidative Stress Folate Metabolism Amyotrophic lateral sclerosis (ALS) Vitamin B12 Metabolism One carbon metabolism and related pathways Association Between Physico-Chemical Features and Toxicity Associated Pathways Extracellular vesicles in the crosstalk of cardiac cells Copper homeostasis AGE/RAGE pathway Folate Metabolism Vitamin B12 Metabolism Selenium Micronutrient Network Oxidative Stress One carbon metabolism and related pathways DNA Damage Response (only ATM dependent) VEGFA-VEGFR2 Signaling Pathway
SQSTM1	Apoptosis-related network due to altered Notch3 in ovarian cancer Senescence and Autophagy in Cancer Brain-Derived Neurotrophic Factor (BDNF) signaling pathway Regulation of toll-like receptor signaling pathway IL-1 signaling pathway RANKL/RANK (Receptor activator of NFkB (ligand)) Signaling Pathway
STAT3	IL-2 Signaling Pathway Leptin signaling pathway AGE/RAGE pathway Notch Signaling Pathway Physiological and Pathological Hypertrophy of the Heart IL-5 Signaling Pathway Prion disease pathway IL17 signaling pathway

TCA Cycle Nutrient Utilization and Invasiveness of Ovarian Cancer
 EPO Receptor Signaling
 IL-9 Signaling Pathway
 Regulation of Microtubule Cytoskeleton
 IL-6 signaling pathway
 PDGF Pathway
 TGF-beta Receptor Signaling
 Prolactin Signaling Pathway
 Hepatitis C and Hepatocellular Carcinoma
 IL-3 Signaling Pathway
 Adipogenesis
 Extracellular vesicles in the crosstalk of cardiac cells
 VEGFA-VEGFR2 Signaling Pathway
 Thymic Stromal LymphoPoietin (TSLP) Signaling Pathway
 Pancreatic adenocarcinoma pathway
 IL-7 Signaling Pathway
 Brain-Derived Neurotrophic Factor (BDNF) signaling pathway
 Non-small cell lung cancer
 Oncostatin M Signaling Pathway
 Interleukin-11 Signaling Pathway
 IL-4 Signaling Pathway
 MET in type 1 papillary renal cell carcinoma
 Signaling of Hepatocyte Growth Factor Receptor
 Kit receptor signaling pathway
 Viral Acute Myocarditis
 MicroRNAs in cardiomyocyte hypertrophy
 RAC1/PAK1/p38/MMP2 Pathway
 Human Thyroid Stimulating Hormone (TSH) signaling pathway

TBK1

Chromosomal and microsatellite instability in colorectal cancer
 TLR4 Signaling and Tolerance
 TNF alpha Signaling Pathway
 Regulation of toll-like receptor signaling pathway
 Toll-like Receptor Signaling Pathway
 RIG-I-like Receptor Signaling

TFAM

Energy Metabolism

TGFB1

Adipogenesis
 Lung fibrosis
 Allograft Rejection
 TGF-B Signaling in Thyroid Cells for Epithelial-Mesenchymal Transition
 Chromosomal and microsatellite instability in colorectal cancer
 Differentiation Pathway
 T-Cell antigen Receptor (TCR) Signaling Pathway
 MicroRNAs in cardiomyocyte hypertrophy
 TGF-beta Receptor Signaling
 MAPK Signaling Pathway
 Viral Acute Myocarditis
 Cardiac Hypertrophic Response
 Aryl Hydrocarbon Receptor Pathway
 IL-3 Signaling Pathway
 Spinal Cord Injury
 Pancreatic adenocarcinoma pathway
 Hepatitis C and Hepatocellular Carcinoma
 Corticotropin-releasing hormone signaling pathway
 Senescence and Autophagy in Cancer
 Cytokines and Inflammatory Response
 Interleukin-11 Signaling Pathway

TIMP1

Lung fibrosis
 IL-6 signaling pathway
 IL1 and megakaryocytes in obesity

TNF

Vitamin B12 Metabolism
 Amyotrophic lateral sclerosis (ALS)

Photodynamic therapy-induced AP-1 survival signaling.
 Folate Metabolism
 Selenium Micronutrient Network
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 NO/cGMP/PKG mediated Neuroprotection
 Fas Ligand (FasL) pathway and Stress induction of Heat Shock Proteins (HSP) regulation
 Cardiac Hypertrophic Response
 Photodynamic therapy-induced NF-kB survival signaling
 Aryl Hydrocarbon Receptor Pathway
 Alzheimers Disease
 Spinal Cord Injury
 Oxidative Damage
 Apoptosis
 MicroRNAs in cardiomyocyte hypertrophy
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 Toll-like Receptor Signaling Pathway
 TLR4 Signaling and Tolerance
 miRNAs in the signaling pathway of the immune response in sepsis
 EBV LMP1 signaling
 MAPK Signaling Pathway
 Regulation of toll-like receptor signaling pathway

TP53

Folate Metabolism
 Photodynamic therapy-induced AP-1 survival signaling.
 Oncostatin M Signaling Pathway
 Chromosomal and microsatellite instability in colorectal cancer
 Endometrial cancer
 Bladder Cancer
 miRNAs involved in DNA damage response
 Signaling Pathways in Glioblastoma
 DNA Damage Response (only ATM dependent)
 Pancreatic adenocarcinoma pathway
 ErbB Signaling Pathway
 G1 to S cell cycle control
 DNA Damage Response
 Retinoblastoma Gene in Cancer
 RAC1/PAK1/p38/MMP2 Pathway
 Copper homeostasis
 Hepatitis C and Hepatocellular Carcinoma
 Non-small cell lung cancer
 Amyotrophic lateral sclerosis (ALS)

VCAM1

Photodynamic therapy-induced NF-kB survival signaling

VEGFA

Endochondral Ossification
 Photodynamic therapy-induced NF-kB survival signaling
 Hepatitis C and Hepatocellular Carcinoma
 Oncostatin M Signaling Pathway
 Aryl Hydrocarbon Receptor
 Pancreatic adenocarcinoma pathway
 Bladder Cancer
 Allograft Rejection

Supplementary Table 8. Ratio of genes affected by formaldehyde (FA) to total genes among all pathways overlapping three or more diseases.

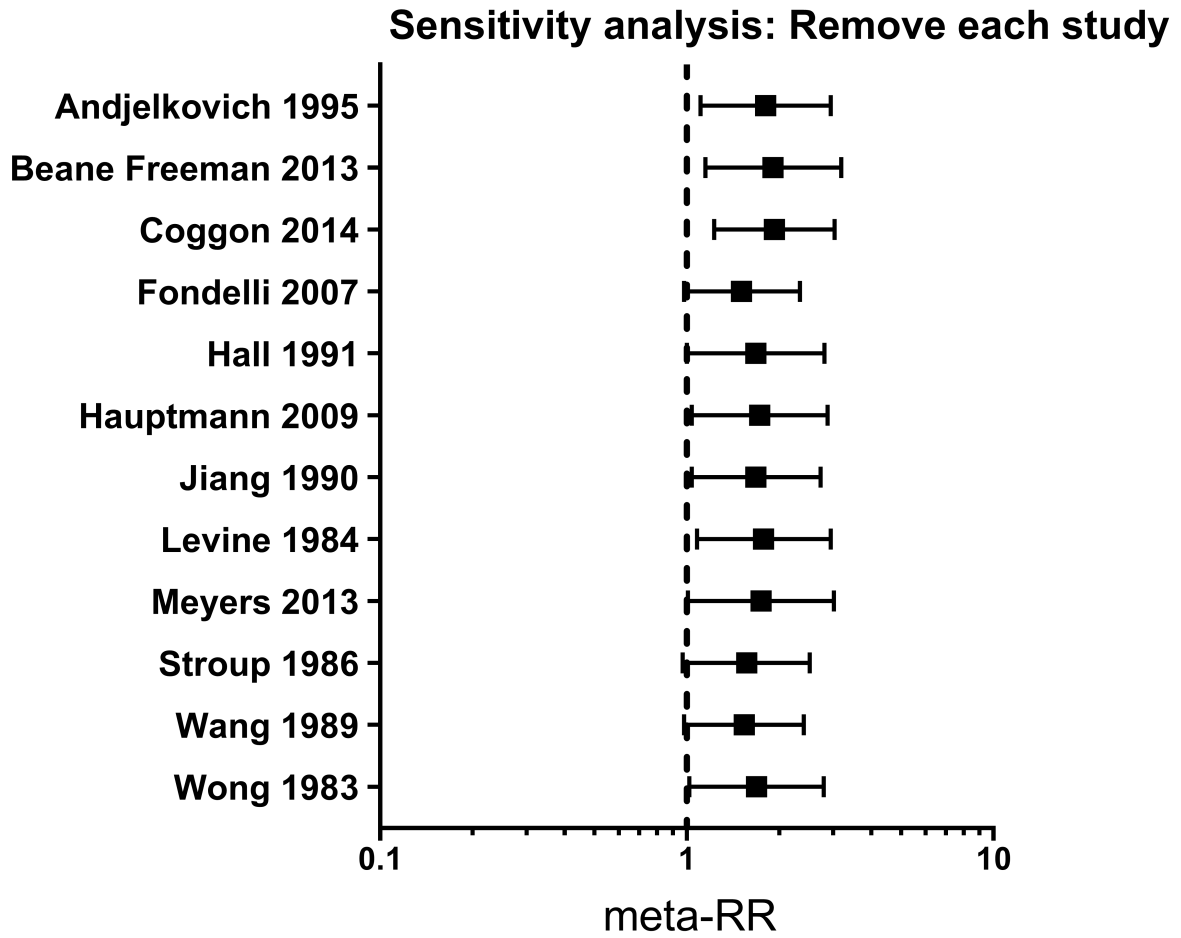
Pathways	Formaldehyde Genes ^a		#	Pathway Genes ^b	FA/Pathway (%)
	Name				
Amyotrophic lateral sclerosis (ALS)	BAX, BCL2, CASP1, CASP3, CST3, GPX1, MAP3K5, NOS1, PPP3CA, PPP3CB, SOD1, TNF, TP53		13	38	34%
Overview of nanoparticle effects	BAX, BCL2, CXCL8, HMOX1, IL6, TNF		6	19	32%
Photodynamic therapy-induced NF-κB survival signaling	CCND1, CXCL8, ICAM1, IL1A, IL1B, IL2, IL6, RELA, TNF, VCAM1, VEGFA		11	35	31%
Folate Metabolism	AHCY, GPX1, GPX3, ICAM1, IFNG, IL1B, IL2, IL6, LDLR, MPO, NOS1, RELA, SOD1, SOD2, TNF, TP53		16	70	23%
Oxidative Stress	FOS, GPX1, GPX3, HMOX1, SOD1, SOD2		6	30	20%
Photodynamic therapy-induced AP-1 survival signaling.	BAX, BCL2, CCND1, FOS, IFNG, IL2, IL6, MAP3K5, TNF, TP53		10	51	20%
Viral Acute Myocarditis	BAX, BCL2, CASP3, CAV1, EDN1, GSK3B, IFNG, IL10, IL6, MAPK1, MAPK3, NOS1, PARP1, STAT3, TGFB1, TNF		16	85	19%
Chromosomal and microsatellite instability in colorectal cancer	APC, BAX, BCL2, CASP3, CCND1, FOS, GSK3B, MAPK1, MAPK3, MSH6, PTGS2, TBK1, TGFB1, TP53		14	74	19%
Oncostatin M (OSM) Signaling Pathway (OSM)	CASP3, FOS, HRAS, JUND, LDLR, MAPK1, MAPK3, RELA, STAT3, TP53, VEGFA		11	66	17%
Vitamin B12 Metabolism	ICAM1, IFNG, IL1B, IL6, LDLR, MPO, SOD1, SOD2, TNF		9	53	17%
Copper homeostasis	APC, CASP3, CCND1, GSK3B, MAPT, PRNP, SOD1, TP53		8	54	15%
Lung fibrosis	CXCL8, EDN1, HMOX1, IL1B, IL6, TGFB1, TIMP1, TNF		8	63	13%
Selenium Micronutrient Network	GPX1, GPX3, IFNG, IL1B, IL6, LDLR, MPO, PTGS2, SOD1, SOD2, TNF		11	89	12%
Allograft rejection	CASP3, CD40, CXCL8, IFNG, IL10, IL1A, IL1B, TGFB1, TNF, VEGFA		10	90	11%

Abbreviations: FA; formaldehyde

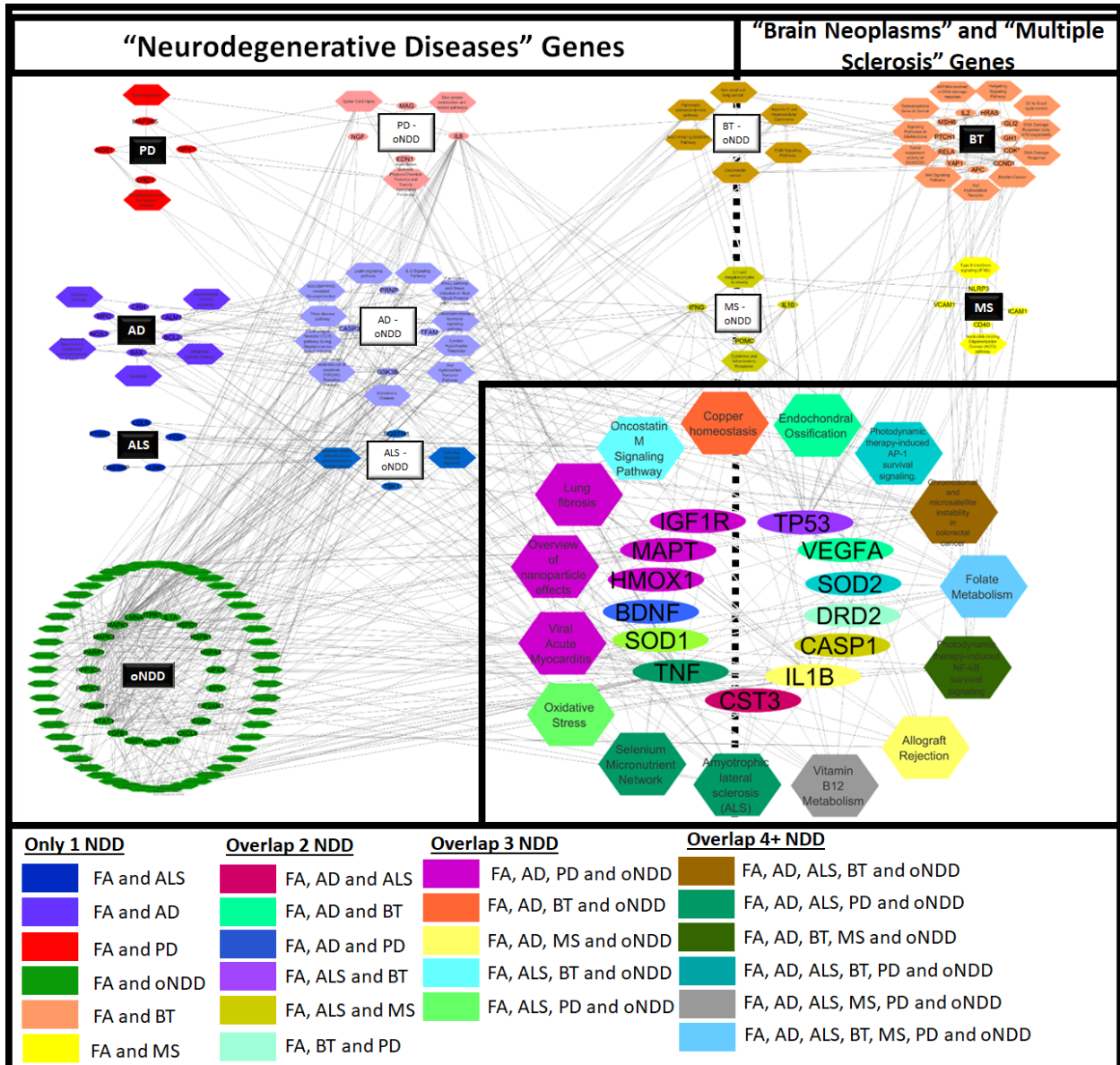
^a Derived from Supplementary Table 7.

^b Derived from Supplementary Table 6.

Supplementary Figure 1. Brain cancer sensitivity analysis: one study excluded at a time using random effects model.



Supplementary Figure 2. An integrative network that visualizes the unique and overlapping genes and pathways affected by **AD** (purple nodes), **ALS** (blue nodes), **brain tumor** (orange nodes), **MS** (yellow nodes), **PD** (red nodes). The pathways and genes that were only found when analyzing the other Neurodegenerative Diseases (oNDD) (excluding AD, ALS and PD) are also represented in the network (green nodes). In the middle of the network, the overlapping pathways and genes are visualized between two or more neurodegenerative diseases



Supplementary Figure 3. Representation of formaldehyde-affected genes within the Amyotrophic Lateral Sclerosis Pathway.

Title: Amyotrophic lateral sclerosis (ALS)
 Organism: Homo sapiens

