

## Supplementary materials

### DNA methylation in the association between pesticide exposures and type 2 diabetes

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<b>Supplementary Table 1 Characteristics of 115 studies of pesticide exposure and DNA methylation.</b>					
<b>Ref.</b>	<b>Year</b>	<b>Type of pesticide</b>	<b>Type of study</b>	<b>Genes</b>	<b>Main conclusion</b>
M. J. Mass <sup>1</sup>	1997	Arsenic	Human	p53	Exposure of human lung adenocarcinoma A549 cells to sodium arsenite or sodium arsenat, produced significant dose-responsive hypermethylation within a 341-base pair fragment of the promoter of p53.
H. Jin <sup>2</sup>	2001	Arsenic	Human	p15	p15 gene failed to express in molt4 after methylation.
H. Tong <sup>3</sup>	2002	Arsenic trioxide	Human	p15	As <sub>2</sub> O <sub>3</sub> could activate the expression of p15 gene by demethylation or/and by inhibiting DNMT3A and DNMT3B gene.
J. Q. Li <sup>4</sup>	2004	Arsenic trioxide	Human	p16	As <sub>2</sub> O <sub>3</sub> could induce p16 gene re-expression in human myeloma cell line U266 through DNA demethylation.
W. Y. Au <sup>5</sup>	2005	Arsenical	Human	<i>CDKN2B</i>	Both acquisition and loss of CDKN2B methylation happened at relapse, with acquisition more frequent.
H. Y. Fu <sup>6</sup>	2005	Arsenical	Human	p16	Hypermethylation of CpG island of p16 gene was observed in 54.8% of the MM patients in our group.
H. Y. Fu <sup>7</sup>	2007	Arsenical	Human	<i>DNMT 1, DNMT3A, 3B</i>	As <sub>2</sub> O <sub>3</sub> can activate and up-regulate the expression of p16 gene which inhibits the proliferation of U266 cell through inducing the G(0) - G(1) arrest by demethylation or/and by inhibiting DNMT 1, DNMT3A and 3B gene.
J. A. Rusiecki <sup>8</sup>	2008	Organochlorine	Human	<i>Alu, LINE-1</i>	Statistically significant inverse linear relationships mainly for the Alu assay for p,p'-DDT (1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane; $\beta = -0.26$ ), p,p'-DDE [1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene; $\beta = -0.38$ ], $\beta$ -hexachlorocyclohexane ( $\beta = -0.48$ ), oxychlordan ( $\beta = -0.32$ ), $\alpha$ -chlordan ( $\beta = -0.75$ ), mirex ( $\beta = -0.27$ ).

M. M. Wang <sup>9</sup>	2008	Arsenical	Human	U266, RPMI8226, socs-1	The results indicated that hypermethylation of CpG island of socs-1 gene was observed without expression of socs-1 in myeloma cell lines U266, RPMI8226.
D. Desaulniers <sup>10</sup>	2009	organochlorine	Animal (female Sprague-Dawley rats)	p16	The high-dose groups (except OCP) generally decreased the methylation of CpG sites (position -63 to -29) in the promoter of the tumor suppressor gene p16(INK4a).
J. L. Hu <sup>11</sup>	2009	Arsenical	Human	RASSF1A	After the effect of As <sub>2</sub> O <sub>3</sub> , the methylation of RASSF1A gene became weaker by increasing the concentration of As <sub>2</sub> O <sub>3</sub> .
Y. Shutoh <sup>12</sup>	2009	Organochlorine	Animal (male young rats)	Global DNA methylation	There was no significant difference in methylation in the 0.06 and 60 mg/kg/day groups, compared with controls.
Y. Wang <sup>13</sup>	2009	Tributyltin	Animal (Sebastiscus marmoratus)	DNMT1	TBT, TPT, and a mixture of the two significantly induced DNA hypomethylation in the fish livers in a dose-dependent manner.
L. Yang <sup>14</sup>	2009	Arsenical	Human	SHP-1	As <sub>2</sub> O <sub>3</sub> can effectively cause demethylation and inhibit the growth of tumor by reactivating the SHP-1 gene transcription.
L. Yang <sup>15</sup>	2009	Arsenical	Human	SHP-1	As <sub>2</sub> O <sub>3</sub> led to progressive demethylation and re-expression of SHP-1 in T2 cells, as well as down-regulation of phosphorylated c-kit.
A. M. Zama <sup>16</sup>	2009	Methoxychlor	Animal (Rats)	ERβ	Developmental exposure to MXC led to significant hypermethylation in the ERβ promoter regions.
H. Y. Fu <sup>17</sup>	2010	Arsenical	Human	CDKN2B, CDKN2A	The CDKN2B promoter was hypermethylated in Molt4 and MUTZ-1 cells, while the CDKN2A promoter was hypermethylated in U937, U266 and CA46 cells.

K. Y. Kim <sup>18</sup>	2010	Organochlorine	Human	Global DNA methylation	Low-dose exposure to POPs, in particular OC pesticides, was associated with global DNA hypomethylation in apparently healthy Koreans.
T. Y. Yang <sup>19</sup>	2010	Organochlorine	Human	p16	Only p16 gene methylated in the liver treated with hexachlorobenzene (HCB) and tetrachlorodibenzo-p-dioxin (TCDD) by using methylation specific PCR (MSP).
R. Ruiz-Ramos <sup>20</sup>	2010	Organochlorine	Human	Global DNA methylation	Only among MTHFR677 TT carriers, non-significant negative associations were observed between DDE and DDT with global DNA methylation, respectively.
S. F. Shen <sup>21</sup>	2010	Arsenical	Human	hdpr1	As <sub>2</sub> O <sub>3</sub> could reverse hypermethylation of hdpr1 gene.
H. R. Zhou <sup>22</sup>	2010	Arsenical	Human	p16	The As <sub>2</sub> O <sub>3</sub> may up-regulate the expression of p16 gene, recover the activity of p16 gene.
A. C. Gore <sup>23</sup>	2011	Organochlorine	Animal (Fischer rats)	Esr1	EB-treated rats had significantly higher percentage of methylation at three CpG sites in the Esr1 promoter compared with control rats.
N. Holland <sup>24</sup>	2011	Pesticide	Human	Alu, LINE-1	Over 2,500 CpG sites that were differentially methylated by age and >70 CpG sites displaying sex-specific differences.
S. Özden <sup>25</sup>	2011	Organochlorine	Animal (male rat)	p16	Only p16 gene was found to be partially methylated in the liver treated with HCB and TCDD by using methylation-specific PCR (MSP).
C. Stouder <sup>26</sup>	2011	Organochlorine	Animal (male mice)	Meg3, Mest, Snrpn, Peg3	MXC treatment of adult mice decreased the percentages of methylated CpGs of Meg3 and increased those of Mest, Snrpn, and Peg3 in the sperm DNA.
X. Zhang <sup>27</sup>	2011	Organophosphorus	Human	Global DNA methylation	Significant differences in genomewide DNA methylation patterns in relation to exposure to three pesticides (i.e., fonofos, parathion, and terbufos).

M. B. Hossain <sup>28</sup>	2012	Arsenical	Human (202 women)	p16, MLH1	Log-transformed urinary arsenic concentrations were positively associated with methylation of p16 and MLH1, but not with LINE1.
L. Hou <sup>29</sup>	2012	Dicarboximide	Animal (mice)	Global DNA methylation	VCZ-induced genome-wide epigenetic changes on F1 mice sperm DNA by global methylation profiling
L. Lind <sup>30</sup>	2012	Organochlorine	Human	Global DNA methylation	High levels of pp-DDE were related to DNA hypermethylation.
M. Manikkam <sup>31</sup>	2012	Pyrethroid, Insect repellents	Animal (rats)	Global DNA methylation	Analysis of the pesticide lineage F3 generation sperm epigenome identified 363 differential DNA methylation regions (DMR) termed epimutations.
V. Tsang <sup>32</sup>	2012	Arsenical	Animal (male mouse)	2,931 genes	The combined folate-iAs exposure changed the CpG island methylation in 2,931 genes.
P. Yousefi <sup>33</sup>	2012	Arsenical	Human	Alu and LINE-1	Weak yet consistent inverse relationships between prenatal DDT/E exposure and Alu and LINE-1 methylation in cord blood DNA, however these associations did not reach statistical significance
X. Zhang <sup>34</sup>	2012	Organophosphate	Human	712 genes	These three pesticides induced similar methylation changes in the promoter regions of 712 genes, while also exhibiting their own OP-specific methylation alterations.
X. Zhang <sup>35</sup>	2012	Diazinon	Human	984 genes	1069 CpG sites in 984 genes with significant methylation changes in diazinon-treated cells.
L. Bastos Sales <sup>36</sup>	2013	Tributyltin	Animal (Murine) and human	Global DNA methylation	A further decrease in global methylation status was found for cells treated with TRO and TBT.
K. Huen Northcote <sup>37</sup>	2013	Organochlorine	Human	Global DNA methylation	Prenatal exposures to organochlorines and PBDEs were related to global hypomethylation.

L. Lind <sup>38</sup>	2013	Organochlorine	Human (524 subjects)	Global DNA methylation	High levels of the PCB126 congener, the OCDD, and the pesticide metabolite p,p'-DDE were related to DNA hypermethylation.
K. Huen <sup>39</sup>	2014	Organochlorine	Human (358 newborns and children)	Alu	Associations of POPs with LINE-1 methylation were only identified after examining the co-exposure of DDT/E with PBDEs simultaneously.
H. Itoh <sup>40</sup>	2014	Organochlorine	Human (399 women)	Global DNA methylation	Global methylation level was significantly decreased by 0.33-0.83% per quartile category for serum o,p'-dichlorodiphenyltrichloroethane (o,p'-DDT), p,p'-DDT, p,p'-dichlorodiphenyldichloroethylene, trans-nonachlor, oxychlorodane, hexachlorobenzene, $\beta$ -hexachlorocyclohexane.
M. Tellez-Plaza <sup>41</sup>	2014	Arsenical	Human	Global DNA methylation	Arsenic exposure and metabolism were consistently associated with both epigenetic markers in cross-sectional and prospective analyses.
S. Y. Park <sup>42</sup>	2015	Organochlorine	Human	Global DNA methylation	Hypermethylation decreased as OCPs increased (Ptrend=0.02).
H. S. Shin <sup>43</sup>	2015	Organophosphorus	Animal (mice)	H19	H19 methylation level of liver and thymus showed decreased pattern in a dose-dependent manner in males.
H. Xing <sup>44</sup>	2015	Organophosphorus, Triazine	Animal (carp)	Global DNA methylation	A significant global DNA hypomethylation in the common carp exposed to atrazine (ATR), chlorpyrifos (CPF) and their mixture was observed compared to the control fish.
C. Consales <sup>45</sup>	2016	Organochlorine	Human	Sat $\alpha$	The only significant effect in the adjusted results was a sporadic negative association between the methylation level of Sat $\alpha$ and p, p'-DDE serum levels in Warsaw, where for each unitary increase of the (ln) p,p'-DDE concentration, Sat $\alpha$ methylation level decreased by 6.3%.

H. Eyvani <sup>46</sup>	2016	Arsenical	Human	RBL1 (p107), CHFR and p16	Only promoters of RBL1 (p107), CHFR and p16 genes were aberrantly methylated in three cell lines.
B. B. Green <sup>47</sup>	2016	Arsenical	Human (343 individuals)	LYRM2	Placenta arsenic levels were associated with 163 differentially methylated loci, with 11 probes within the LYRM2 gene reaching genome-wide significance.
N. Holland <sup>48</sup>	2016	Organophosphate	Human	PON1-108	The PON1-108 that affects birth outcomes and neurodevelopment was strongly associated with PON methylation.
G. Kostka <sup>49</sup>	2016	Organochlorine	Animal (rat)	p53, p16	DDT induced alternations in methylation of the promoter region in both p53 and p16 genes.
D. Van Der Plaat <sup>50</sup>	2016	Pesticides	Human (1561 participants)	Global DNA methylation	The top CpG (cg02286193 near ESRRB) was hypomethylated in highly exposed subjects and the other CpGs were hypermethylated.
K. Declerck <sup>51</sup>	2017	pesticides	Human (48 children)	PON1 192R-allele	A specific methylation profile was observed in prenatally pesticide exposed children carrying the PON1 192R-allele.
M. Kajta <sup>52</sup>	2017	Organochlorine	Animal (mice)	Global DNA methylation	Prenatally administered DDT accumulated in mouse brain as determined with gas chromatography and tandem mass spectrometry, led to global DNA hypomethylation, and altered the levels of methylated DNA in specific genes.
M. Kwiatkowska <sup>53</sup>	2017	Organophosphorus	Human	Global DNA methylation and p53	We also observed a decrease in global DNA methylation level at 0.25 mM of glyphosate. Glyphosate at 0.25 mM and 0.5 mM increased p53 promoter methylation.
M. H. Lee <sup>54</sup>	2017	organochlorine	Human (444 Koreans)	Alu, LINE-1	Significant inverse associations between p,p'-DDE, cis-Heptachlor epoxide and Alu assay in men, p,p'-DDE was positively associated with LINE-1 assay in women

F. Moghaddaskho <sup>55</sup>	2017	Arsenical	Human	RBL1 (p107), RASSF1A, and cyclin D2	Only promoters of RBL1 (p107), RASSF1A, and cyclin D2 were aberrantly methylated in studied breast cancer cell lines.
P. Phookphan <sup>56</sup>	2017	Arsenical	Human	COX2, EGR1, and SOCS3	When compared to unexposed children, arsenic-exposed children had hypomethylation at all 3 CpG sites of COX2, EGR1, and SOCS3.
J. A. Rusiecki <sup>57</sup>	2017	Pesticide	Human (695 males)	GSTp1, MGMT	Non-specific HPEEs may contribute to increased DNAm in GSTp1, and in some groups, reduced DNAm in MGMT and LINE-1.
Y. Wang <sup>58</sup>	2017	Arsenical	Human	SFRP1	Following treatment with As <sub>2</sub> O <sub>3</sub> for 48 h, the SFRP1 gene was demethylated
S. E. Wirbisky-Hershberger <sup>59</sup>	2017	Triazine	Animal (zebrafish)	Global DNA methylation	An embryonic atrazine exposure decreases global methylation levels and the expression of dnmt4 and dnmt5.
A. B. Benitez-Trinidad <sup>60</sup>	2018	Occupational pesticide	Human (190 individuals)	LINE-1	Occupational pesticide exposure and external factors appears to modify the DNA methylation pattern measured through LINE-1.
C. Giuliani <sup>61</sup>	2018	Herbicide	Human	CYP1A1	Past environmental exposure to dioxin (AO/TCDD) shapes the DNA methylation profile of regions in CYP1A1 gene.
D. Hernandez-Cortes <sup>62</sup>	2018	Organophosphate	Animal (mice)	Ogg1	The results showed that Me-Pa significantly decreased the global DNA methylation pattern and significantly increased the methylation of two CpG sites within Ogg1 promoter and one CpG site within Nrf2 promoter.
V. F. S. Kahl <sup>63</sup>	2018	Pesticides	Human	Global DNA methylation	Global DNA methylation was significantly decreased in tobacco farmers.



V. F. S. Kahl <sup>64</sup>	2018	Pesticide mixtures	Human	Global DNA methylation and p16	Exposed group showed significantly shorter telomeres and DNA hypomethylation, as well as p16 hypermethylation.
S. Kim <sup>65</sup>	2018	Organochlorine	Human (109 Korean mother-child pairs)	IGF2	Higher levels of p,p'-dichlorodiphenyltrichloroethane (p,p'-DDT) in maternal serum were associated with hypermethylation of insulin-like growth factor 2 (IGF2). In multiple-POP models, a significant and positive association between DDTs and IGF2 methylation was also observed.
J. Y. Lee <sup>66</sup>	2018	Organochlorine	Human (364 healthy Korean subjects)	CDH1	Serum concentrations of OCPs or PCBs compounds were higher in CDH1 methylation-positive subjects than in methylation-negative ones.
Y. K. Leung <sup>67</sup>	2018	Organochlorine	Human (72 participants)	The cord blood DNA	In males-only, methylation changes was seen for p,p'-DDE in and 1,473 CpG sites.
K. C. Paul <sup>68</sup>	2018	Organophosphate	Human	Global DNA methylation	Among the 70 CpGs located in 41 genes, 14 were also differentially methylated in saliva samples.
Y. Song <sup>69</sup>	2018	Organochlorine	Animal (rats)	H19 and Gtl2	Gestational exposure to p,p'-DDE impaired the testis histology and decreased the sperm fertility with H19 and Gtl2 hypomethylation in F1 offspring.
D. A. Van Der Plaats <sup>70</sup>	2018	Occupational pesticide	Human (1561 subjects)	Global DNA methylation	In total for all analyses, high pesticide exposure was genome-wide significantly associated with differential DNA methylation of 31 CpGs annotated to 29 genes.
X. Yu <sup>71</sup>	2018	Organochlorine	Human (24 subjects)	BRCA1	The DNA methylation level of the identified CpGs of BRCA1 increased with increased exposure to dichlorodiphenyltrichloroethane (DDT) and the level of gene expression in the identified CpGs of BRCA1 decreased with increased exposure to Dichlorodiphenyltrichloroethane (DDT).

M. Abolhassani <sup>72</sup>	2019	Organochlorine and organophosphorous	Human (72 participants)	p16	significantly hypermethylation of p16 promoter in CRC patients.
A. L. Gomez <sup>73</sup>	2019	Organophosphorus	Animal (rats )	ESR1	GBH also altered the abundance of ESR1 transcript variants by hypermethylation of ESR1 promoters.
J. Goodrich <sup>74</sup>	2019	Organophosphorus	Human (1000 infants)	Global DNA methylation	Profenofos and vinclozolin were associated with methylation at <10 sites.
J. F. Herrera-Moreno <sup>75</sup>	2019	Occupational pesticide	Human (288 participants)	Global DNA methylation	Decreased DNA methylation of the CDKN2B gene was observed in pesticide-exposed groups compared to the non-exposed group.
M. Huang <sup>76</sup>	2019	Bipyridinium herbicides	Human	Global DNA methylation	The results of global DNA methylation revealed a significant decrease in PQ-exposed groups.
K. T. Kelsey <sup>77</sup>	2019	Agent Orange	Human (37 participants)	H19	36 gene regions, including the region of the imprinted gene H19 to have altered DNA methylation associated with high exposure compared to the low exposure group.
S. Kim <sup>78</sup>	2019	Organochlorine	Human (106 Korean mother)	DIO3 and MCT8	In utero exposure to DDTs may influence the DNA methylation of DIO3 and MCT8 genes in the placenta, in a sexually dimorphic manner.
J. Kochmanski <sup>79</sup>	2019	Organochlorine	Animal (Mouse)	Nr4a2 and Lmx1b	Significant, sex-specific differentially methylated CpGs (DMCs) and regions (DMRs) by developmental dieldrin exposur, including DMCs at the Nr4a2 and Lmx1b genes.
D. Mahna <sup>80</sup>	2019	Pyrethroid	Animal (mice)	p53	The gene promoter region of p53 gene show alteration in methylation status in the test animal sample as compared to the control.
K. Okamura <sup>81</sup>	2019	Arsenical	Animal (mice)	TMEM54, CD74	DNA methylation levels of regions around the transcriptional start sites of Tmem54 and Cd74 were decreased and the

					expression of these genes were significantly increased in the hepatic tumors of F2 males of the arsenite group.
D. M. Paredes-Céspedes <sup>82</sup>	2019	Pesticides	Human	WRAP53 $\alpha$	An association between %5mC of the WRAP53 $\alpha$ gene with micronutrient intake and pesticide exposure in mestizo sprayers, whereas changes in %5mC of the WRAP53 $\alpha$ gene was associated with body mass index in the indigenous group.
N. V. Barzi <sup>83</sup>	2020	Organophosphorus	Animal (mouse)	Caspase9	The percentage of Caspase9 DNA methylation in embryos collected from the CPF group was higher compared to the others.
Y. He <sup>84</sup>	2020	Arsenical	Human	PANDAR	Arsenic metabolism ability and exposure affected the expression of PANDAR, DNA damage, and DNA methylation.
J. C. Nwanaji-Enwerem <sup>85</sup>	2020	Agent Orange	Human (37 male)	FOXK2	Significant negative associations of dioxin level and DNAm-age sperm with methylation levels of FOXK2 - a gene previously reported to be hypomethylated in infertile men.
M. Ouidir <sup>86</sup>	2020	Organochlorine	Human (260 pregnant women)	TUSC3	Higher PFUnDA was associated with increased methylation at 3 CpG sites (cg13996963, cg12089439, cg18145877) annotated to TUSC3, and increased methylation at those 3 CpG sites was correlated with decreased expression of TUSC3 in the placenta.
L. Sai <sup>87</sup>	2020	Organophosphorus	Animal (rat)	PIK3CD	High methylation gene PIK3CD may play a key role in epigenetic regulation of multiple pathways, such as Ras signaling pathway, AGE-RAGE signaling pathway in diabetic complications, HIF-1 signaling pathway, VEGF signaling pathway, and glioma and Fc epsilon RI signaling pathway in rats exposed to CPF.

M. Teng <sup>88</sup>	2020	Conazole fungicides	Animal (zebrafish)	Global DNA methylation	Propiconazole disrupted the steroidogenic pathway and caused changes in global DNA methylation that induced reproductive toxicity.
A. I. Vester <sup>89</sup>	2020	Pyrethroid	Animal (male)	<i>Nr3c1</i>	There was a significant increase in average percent methylation of a CpG site at chr18: 39489427 ( <i>Nr3c1</i> ) in males exposed to deltamethrin and CORT compared to unexposed males.
E. Woźniak <sup>90</sup>	2020	Organophosphorus	Human	Global DNA methylation	The obtained results have revealed significant reduction of global DNA methylation level in PBMCs exposed to glyphosate.
H. C. Wu <sup>91</sup>	2020	Organochlorine	Human (316 daughters)	CCDC85A, CYP1A1 and ZFPM2	We observed DDT DMRs in three genes, CCDC85A, CYP1A1 and ZFPM2.
H. Ergun <sup>92</sup>	2021	Organochlorine	Animal (rat)	Global DNA methylation	DNA methylation could be modified by exposure to glyphosate
C. Maurice <sup>93</sup>	2021	Organochlorine	Animal (rat)	Global DNA methylation	Developmental exposure to an environmentally relevant Arctic POPs mixture impaired sperm quality and pregnancy outcomes across two subsequent, unexposed generations and altered sperm DNA methylation.
M. R. Rytel <sup>94</sup>	2021	Agent Orange	Human	SLC9A3, LYNX1, and TNRC18	3 CpGs in the adipose tissue (contained within SLC9A3, LYNX1, and TNRC18) were marginally significantly hypomethylated, and 1 CpG in whole blood (contained within PTPRN2) was marginally significantly hypermethylated with high TCDD burden.
A. Saad-Hussein <sup>95</sup>	2021	Occupational pesticide	Human (100 pesticides)	XRCC1, PON1, GSTP1 and GST	The results of this study revealed that most genotypes in XRCC1, PON1, GSTP1 and GST genes were associated with LINE-1 hypomethylation among UE group.

			exposed workers)		
F. Salimi <sup>96</sup>	2021	Organochlorine	Human	MGMT	The results indicated that OCPs lead to PTC development through MGMT gene promoter hypermethylation.
M. S. Vidali <sup>97</sup>	2021	Organochlorine	Human	Global DNA methylation	Extensive dose-dependent hypomethylation was observed, even at low concentrations, in stimulated PBMC treated with PCB-118 and PCB-153 as well as a small but statistically significant hypomethylation in HCB-treated stimulated cells.
W. Wang <sup>98</sup>	2021	Organochlorine	Animal (mouse)	Global DNA methylation	Insecticides pose risks of developmental toxicity through DNA methylation.
R. Golestanian <sup>99</sup>	2022	Organophosphorus	Human	C/EBP	Treatment with 10 $\mu$ M Diazinon significantly increased the CYP3A4 gene transcription by approximately 27-fold, which was correlated with the hypermethylation of 3 CpGs in C/EBP binding sites, including -5998, -5731 and -5725.
Y. Huang <sup>100</sup>	2022	Others	Animal (mouse)	mBOs	The results of RRBS-Seq sequencing showed that the methylation modification at DMR level in Rotenone-treated mBOs group was significantly higher than that in Ctrl group.
A. Katić <sup>101</sup>	2022	Pyrethroid	Animal (rat)	Igf2 and H19	Exposure to $\alpha$ -cypermethrin had no effect on the average CpG methylation levels within the differentially methylated regions (DMRs) of the Igf2 and H19 imprinted genes under these experimental conditions.
K. Larsen <sup>102</sup>	2022	Organophosphorus	Animal (pig)	IL18	In a CpG island of the promoter for IL18, we observed significantly reduced DNA methylation for certain individual CpG positions.

R. M. Lucia <sup>103</sup>	2022	Organophosphorus	Human (392 postmenopausal women)	MSH4, KCNA6, ABAT, and NDUFAF2/ERCC8	Four regions, within the promoters of the MSH4, KCNA6, ABAT, and NDUFAF2/ERCC8 genes, were associated with glyphosate levels, along with an association between ESR1 promoter hypomethylation and AMPA.
D. M. Paredes-Céspedes <sup>104</sup>	2022	Pesticides	Human (190 Huichol indigenous persons)	CDKN2B	The farmer group presented a higher methylation percentage of CDKN2B than the non-farmer group, but no differences in CDKN2A were observed between groups.
A. Rafeeina <sup>105</sup>	2022	Organochlorine	Human	ABL1	OCPs, especially alpha-hexachlorocyclohexane, beta-hexachlorocyclohexane, gamma-hexachlorocyclohexane, 2,4 dichlorodiphenyldichloroethylene, and 4,4 dichlorodiphenyltrichloroethane may induce methylation at the ABL1 promoter level.
S. Wang <sup>106</sup>	2022	Organophosphorus	Animal (zebrafish)	Global DNA methylation	Long-lasting DNA methylation changes in genome after embryonic ATZ exposure.
C. H. Chang <sup>107</sup>	2023	Organophosphate	Human	PON1	A negative association between urinary OP metabolites and PON1 promoter mean methylation levels was found.
Z. R. Guler <sup>108</sup>	2023	Neonicotinoid	Human	Global DNA methylation	Global DNA methylation significantly increased after imidacloprid exposure at 100 µM, and thiamethoxam exposures at 200 µM and 500 µM.
A. Katić <sup>109</sup>	2023	Pyrethroid	Animal (rat)	LINE-1	We observed not statistically significant decrease in DNA methylation levels of all three CpG sites within repetitive element LINE-1 with increasing concentrations of $\alpha$ -cypermethrin.

T. Mehtiyev <sup>110</sup>	2023	Organophosphorus	Human	H3K27me3, H3K9me3, and H3K9ac	Glyphosate at concentrations ranging from 50–250 µM and AMPA at concentrations ranging from 50–500 µM significantly increased global levels of DNA methylation and global histone modifications, including H3K27me3, H3K9me3, and H3K9ac.
M. D. P. Navarrete-Meneses <sup>111</sup>	2023	Pyrethroid	Human	BMMCs, PBMCs	We found that permethrin does not induce DNA hypermethylation but can induce hypomethylation, and that malathion generated both types of events.
A. Rafeeina <sup>112</sup>	2023	Organochlorine	Human	CDKN2B and MGMT	The rise in the OCP levels was associated with an increase in methylation at the promoter level of CDKN2B and MGMT as well as a decrease in the relative expression of H4K16ac and H3K4me3.
F. Salimi <sup>113</sup>	2023	Organochlorine	Human	TSHR, p16	Further TSHR methylation and less p16 methylation were observed in PTC than in BTN.
C. S. Silva <sup>114</sup>	2023	Arsenical	Animal (zebrafish)	Global DNA methylation	Sodium arsenite significantly reduced global DNA methylation in the zebrafish larvae.
S. Stöber <sup>115</sup>	2023	Arsenical	Human	Global DNA methylation	Chronic low-dose arsenite exposure can lead to global hypomethylation.

<b>Supplementary Table 2 Characteristics of 65 studies of DNA methylation and T2D.</b>				
Ref.	Year	Type of study	Genes	Main conclusion
E. Walaszczyk <sup>116</sup>	2018	Review	ABCG1, LOXL2, TXNIP, SLC1A5 and SREBF1	Methylation changes of the CpGs located in SREBF1, ABCG1 and CPTA1, LOXL2, TXNIP were associated with type 2 diabetes.
H. R. Elliott <sup>117</sup>	2017	Human	Global DNA methylation	Around half of known type 2 diabetes SNPs are associated with variation in DNA methylation.
A. González-Izquierdo <sup>118</sup>	2017	Human	538 genes	Comparing DNA methylation levels between IR and IS, 982 CpG sites were identified with significant differences between both groups. These differentially methylated CpGs (DMCpGs) were associated with 538 genes.
B. A. Hidalgo <sup>119</sup>	2017	Human	Global DNA methylation	In combined multiethnic analysis, methylation at a total of 208 cytosine guanine dinucleotides (CpGs) were significantly associated with FG, 761 CpGs with logFI, and 109 CpGs with HbA1c.
Q. Huang <sup>120</sup>	2017	Human	PTPN1	The results indicated a significant correlation between PTPN1 promoter methylation and the risk of T2D.
S. Rodríguez-Rodero <sup>121</sup>	2017	Human	HOOK2	HOOK2, demonstrated a significant correlation between differentially hypermethylated regions on the gene body and the presence of type 2 diabetes.
J. Thongsroy <sup>122</sup>	2017	Human	Global DNA methylation	The DM group possess the lowest Alu methylation.
P. Volkov <sup>123</sup>	2017	Human	NR4A3, PARK2, PID1, SLC2A2, and SOCS2	457 genes, including NR4A3, PARK2, PID1, SLC2A2, and SOCS2, that had both DMRs and significant expression changes in T2D islets.
F. Barajas-Olmos <sup>124</sup>	2018	Human	Global DNA methylation	Analysis of DNA methylation profiles revealed several loci with differential methylation between individuals with and without T2D, in all tissues.



H. Elliott <sup>125</sup>	2018	Human	KCNQ1	Only in KCNQ1 did methylation show any evidence of being on a causal pathway to disease.
A. S. Norhashimah <sup>126</sup>	2018	Animal (mice)	PTX3	Only PTX3 gene showed different DNA methylation levels between NDC and T2D.
R. Ortiz <sup>127</sup>	2018	Human	FKBP5	FKBP5 methylation may be a marker of higher metabolic risk in T2DM.
J. Shen <sup>128</sup>	2018	Human	9698 genes	A total of 9,698 genes were demonstrated to be differentially methylated in obese patients with T2D compared with non-obese healthy controls.
C. Wang <sup>129</sup>	2018	Human	MFSD1 and ARHGEF1	Major facilitator superfamily domain containing 1 (MFSD1) was found to be a methylation associated gene at hypermethylation site of cg16289538 in Han group. Rho guanine nucleotide exchange factor 1 (ARHGEF1) was the susceptible gene corresponding to the methylation sites of cg18800192 and cg00759295 in Kazak group.
L. Yin <sup>130</sup>	2018	Human	PTEN	PTEN methylation in T2DM patients was significantly lower than that in NGT groups.
S. Yu <sup>131</sup>	2018	Human	3'GC	Methylation level of the 3'GC was higher in T2DM patients than in non-T2DM individuals.
A. Arpón <sup>132</sup>	2019	Human	Global DNA methylation	This study demonstrated the association between DNA methylation in some specific CpGs and HOMA-IR values.
A. Cardona <sup>133</sup>	2019	Human	Global DNA methylation	One MVP, cg00574958 at CPT1A, with a possible direct causal role in T2DM.
S. Garcia-Calzon <sup>134</sup>	2019	Human	TXNIP	The methylation loci cg19696031 of the TXNIP gene in whole blood is strongly associated with HbA1c and blood glucose levels in a population of newly-diagnosed, drug-naïve T2D individuals.
K. A. C. Meeks <sup>135</sup>	2019	Human	TXNIP	The most strongly associated DMP-cg19693031, TXNIP showed hypomethylation in T2D cases compared with controls.

M. Ouni <sup>136</sup>	2019	Human	IGFBP-2	A methylation score based on seven type 2 diabetes-related CpGs in the IGFBP-2 gene was associated with higher type 2 diabetes risk.
X. Chen <sup>137</sup>	2020	Human	IRS1, PRKCE, FTO, PPARGC1A, KCNQ1, ATP10A, GHR, CREB1, PRKAR1A and HNF1B	10 top type 2 diabetes mellitus-related differentially methylated genes, including IRS1, PRKCE, FTO, PPARGC1A, KCNQ1, ATP10A, GHR, CREB1, PRKAR1A and HNF1B.
Z. N. Wang <sup>138</sup>	2020	Human	TXNIP	We found that cg19693031 in TXNIP gene was the lowest P-value site in the association analysis between DNA methylation and fasting plasma glucose and HbA1c.
D. Zhang <sup>139</sup>	2021	Human	TXNIP	TXNIP methylation is associated with T2DM incidence in a Chinese population.
K. Cao <sup>140</sup>	2021	Human, animal (mice)	ND6	With the observation of specific ND6 hypermethylation in both T2DM patients and insulin resistant mice.
R. H. Chung <sup>141</sup>	2021	Human	G6PC2	Our analysis results suggest that rs2232326 and rs2232328 in G6PC2 may affect DNA methylation at CpGs near the gene and that the methylation may have downstream effects on fasting glucose.
S. M. Hafez <sup>142</sup>	2021	Human	IGFBP-1	DNA methylation levels of the IGFBP-1 gene are higher in T2D patients than in healthy control.
N. Hizon <sup>143</sup>	2021	Human	Global DNA methylation	We identified 2,982 differentially methylated CpGs
H. Kim <sup>144</sup>	2021	Human	BMP8A, NBPF20, STX18,	We identified 8 DMSs (each at BMP8A, NBPF20, STX18, ZNF365, CPT1A, and TRIM37, and 2 at TXNIP) that were significantly associated with the risk of

			ZNF365, CPT1A, TRIM37, TXNIP	T2D ( $P < 9.0 \times 10^{-8}$ ), including 3 that were previously known (DMSs in TXNIP and CPT1A).
Z. Wang <sup>145</sup>	2021	Human	TXNIP	cg19690313 on TXNIP correlates with HbA1c and fasting plasma glucose levels.
R. K. Abdulzahra <sup>146</sup>	2022	Human	PRKCZ	Around 36% of T2DM patients showed a PRKCZ methylation, whereas, about 0% PRKCZ methylation was in the control group.
P. Baca <sup>147</sup>	2022	Human	Global DNA methylation	We identified 11 120 DMCs and 96 DMRs distributed across all chromosomes, with the greatest density of epigenomic alterations at the MHC locus.
F. Chen <sup>148</sup>	2022	Human	TRIM67	Placental DNA methylation levels in the TRIM67 promoter region were markedly elevated in GDM and were associated with blood glucose and lipid levels during healthy pregnancy.
F. P. Chilunga <sup>149</sup>	2022	Human	Global DNA methylation	We identified three differentially methylated positions (DMPs) for homeostatic model assessment of insulin resistance (HOMA-IR) at 5% FDR.
A. Domingo-Relloso <sup>150</sup>	2022	Human	SREBF1, ABCG1 and HDAC1	Our results suggest that differences in peripheral blood DNA methylation are related to cross-sectional markers of glucose metabolism and insulin activity.
E. Fraszczyk <sup>151</sup>	2022	Human	Global DNA methylation	The meta-analysis identified 76 CpG sites that were differentially methylated in individuals with incident type 2 diabetes compared with control individuals.
Y. He <sup>152</sup>	2022	Human	FURIN	The hypermethylation levels in FURIN promoter were associated with an increased risk for incident diabetes in Chinese adults.
D. L. Juvinao-Quintero <sup>153</sup>	2022	Human	DHCR24	We found strong evidence of causality of DNAm at cg25536676 (DHCR24) on T2D, where an increase in transformed residuals of DNAm at this site were associated with 43% higher risk of T2D.
M. S. Ravari <sup>154</sup>	2022	Human	IL-6 and GPX1	The DNA methylation levels of the IL-6 and GPX1 promoter in the peripheral blood are not related to the occurrence of T2D.

C. Sarnowski <sup>155</sup>	2022	Human	CPT1A	DNA methylation at cg00574958 (CPT1A) was significantly associated with clinical diagnosis of cognitive status and two AD biomarker measures.
M. Toure <sup>156</sup>	2022	Human	CD36	The CD36 gene methylation was significantly 1.36 times more frequent in obese and obese diabetic compared to lean control.
H. H. Tsai <sup>157</sup>	2022	Human	cg19693031	Summarily, methylation at cg19693031 was inversely associated with fasting blood glucose in a dose-dependent manner.
W. J. Wang <sup>158</sup>	2022	Human	CYP1A2, GFRA1, HDAC4, LIMS2, NAV3, PAX6, UPK1B, DPP10, CPLX1, CSMD2, GPR133, NRXN1, PCSK9, PENK, PRDM16, PTPRN2, TNXB	We validated 7 hypermethylated (CYP1A2, GFRA1, HDAC4, LIMS2, NAV3, PAX6, UPK1B) and 10 hypomethylated (DPP10, CPLX1, CSMD2, GPR133, NRXN1, PCSK9, PENK, PRDM16, PTPRN2, TNXB) genes reported in previous epigenome-wide association studies.
P. Xu <sup>159</sup>	2022	Human	IGFBP-1, IGFBP-2, MC4R, SOCS3, chemerin, CAMTA1, PIK3R5 and TNF- $\alpha$	Methylation changes of many key molecules, such as IGFBP-1, IGFBP-2, MC4R, SOCS3, chemerin, CAMTA1, PIK3R5 and TNF- $\alpha$ , which play an important role in the pathogenesis of GDM.
K. Ziarniak <sup>160</sup>	2022	Animal (rat)	Kiss1r	Kiss1r promoter was hypermethylated in the liver, suggesting gene silencing.
P. Firdous <sup>161</sup>	2023	Human	HNF1 $\alpha$	The expression of HNF1 $\alpha$ was found to be upregulated (p value 0.0349*) in majority of MODY (60%) and T1D (72%) cases

N. S. Hasan <sup>162</sup>	2023	Human	IGFBP1	There was DNA hyper methylation levels of IGFBP1 gene at each of the six CpG sites in T2DM patients than control.
D. L. Juvinao-Quintero <sup>163</sup>	2023	Human	DHCR24	We identified one CpG mapping to a gene related to the metabolism of lipids (DHCR24) as a novel causal biomarker for risk of type 2 diabetes.
T. Rönn, J. K. Ofori <sup>164</sup>	2023	Human	RHOT1	RHOT1 methylation in blood is associated with future T2D.
H. Seo, J. H. Park <sup>165</sup>	2023	Human	PDE1C, DIP2C, FLJ90757, PRSS50, and TDRD9	A DMR associated with PDE1C showed hypermethylation, whereas DMRs associated with DIP2C, FLJ90757, PRSS50, and TDRD9 showed hypomethylation.
H. O. Smail <sup>166</sup>	2023	Human	TCF7L2	Hypermethylation of DNA in the promoter region in diabetic and prediabetic groups compared to the healthy controls.
J. Thongsroy <sup>167</sup>	2023	Human	Alu	Alu methylation in type 2 DM patients progressively decreases with increasing HbA1c levels.
W. Wang <sup>168</sup>	2023	Human	SLC6A18	Three CpGs mapped to SLC6A18 gene were validated in a community population, with a hypermethylated direction in diabetic patients.
X. Wang <sup>169</sup>	2023	Human	ChREBP	Peripheral blood ChREBP methylation is elevated in T2DM patients.
X. Wang <sup>170</sup>	2023	Human	Global DNA methylation	Among the 12 patients in the exploratory cohort, we identified 5178 hypomethylated and 4787 hypermethylated regions involving 1613 genes in the Tibetan group.

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