Table 1S: Basic characteristics of included human studies (n=20)

Author, year	Country	Study design	Population	Age	Gender	Effect measures	Main findings
Barry et al., 2016	Canada	Cross-sectional study	Type 2 diabetes mellitus (T2DM) (n=24) Control (n=22)	T2DM (57.8±10.9) Control (53.4±10.7)	F (n=34) M (n=12)	Interleukin-6 (IL-6), interleukin-10 (IL-10), and tumour necrosis factor-α (TNF-α).	Type 2 diabetes mellitus (T2DM) group had significantly elevated levels of tumour necrosis factor (TNF)-α and interleukin (IL)-6 when compared to the control group. In addition, there was no significant difference in IL-10 levels between the two groups. However, the anti-inflammatory activity of IL-10 was lower in T2DM group compared to controls.
Cipolletta et al., 2005	UK	Cross-sectional study	T2DM (n=27) Control (n=12)	T2DM (50.6±16.1) Control (51.8±7.9)	F (n=20) M (n=19)	Monocyte chemoattractant protein-1 (MCP-1).	The expression of the scavenger receptor, CD36 on monocytes was significantly increased in the T2DM group compared to the controls group.
Corralles et al., 2007	Spain	Cross-sectional study	T2DM (n=55) Control (n=8)	T2DM (64±8) Control (64±9)	All 63 males	IL-6, TNF-α.	There was no significant difference in the levels of IL-1β, IL-6, and TNF-α released by monocytes and dendritic cells from T2DM and the control group. However, sub-analysis of $CD16^+$ monocytes and $CD16^+$ dendritic cells showed significantly reduced the production of IL-6 and TNF-α, respectively.
Dai et al., 2015	China	Cross-sectional study	T2DM (n=17) Control (n=12) Obese-T2DM (n=15)	T2DM (44.25±6.75) Control (42.5±6.5)	F (n=23) M (n=21)	Glycated haemoglobin (HbA1c).	Obese -T2DM individuals had a significant increase in IFN-γ than T2DM individuals. Additionally, T2DM and Obese-T2DM individuals had increased IFN-γ than control.
Eftekharian et al., 2016	Iran	Cross-sectional study	T2DM (n=75) Control (n=72)	Not reported	Not reported	Total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), Neutrophil-lymphocyte ratio (NLR).	Total cholesterol, triglycerides, and low-density lipoprotein (LDL) levels were significantly increased in the T2DM group compared to the controls
Freirre et al., 2017	United States	Cross-sectional study	T2DM (n=83) Control (n=83)	T2DM (56.83±9.84) Control (40.62±11.46)	F (n=85) M (n=81)	IL-10, IL-1β, TNF-α, nuclear factor-kappa-β (NF-kβ), HbA1c	Increased frequency of neutrophils and elevated levels of cholesterol were reported in the T2DM group compared to controls.

Gacka et al.,2010	Poland	Cross-sectional study	T2DM (n=58) Control (n=22)	T2DM (51.75±13.75) Control (41.25±9.75)	F (n=42) M (n=38)	TNF-α	Expression of TNF-α and IL-8 genes was observed in only two members of the control group and undetectable in T2DM.
Ip et al., 2016	USA	Cross-sectional study	T2DM (n=22) Control (n=29)	T2DM (50.6±16.1) Control (51.8±7.9)	F (n=32) M (n=19)	IL-10, IL-1β, TNF-α	Elevated levels of IL-4, IL-5, IL-10, IL-13, and TNF-α were observed in individuals with T2DM compared to controls.
Jagannathan-Bogdan et al., 2011	United States	Cross-sectional study	T2DM (n=18) Control (n=16)	T2DM (49.95±8.75) Control (45.25±6.75)	F (n=22) M (n=12)	IL-17 and interferon-gamma (IFN- γ)	Individuals with T2DM had significantly increased the frequency of Th17 cells and IFN-γ levels when compared to controls.
Lin et al., 2018	China	Cohort	T2DM (n=20) Control (n=20)	T2DM (51.25±5.71) Control (54.3±7.39)	F (n=15) M (n=25)	NF-kβ, HbA1c, MCP-1, TC, TG	The expression of monocyte chemoattractant protein (MCP) -1 on monocytes as well as its serum levels and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kβ) signaling were significantly increased in T2DM group compared to controls.
Malandrino et al., 2015	Spain	Cohort	T2DM (n=11) Control (n=36)	T2DM (66.1±8.6) Control (61.6±10.6)	F (n=21) M (n=26)	IL-6, HDL, TC, TG, full blood glucose (FBG)	There was increased expression of carnitine palmitoyltransferase (CPT1A) on adipose tissue-resident macrophages compared to adipocytes. There were no significant differences in anti-inflammatory markers including IL-10 and IL-4 in cells with or without palmitate CPT1A.
Moreno-Navarrete 2009	Spain	Cross-sectional study	T2DM (n=135) Control (n=94)	T2DM (58.18±10.7) Control (49.8±11.3)	All 229 males	NF-kβ, IL-6, IL-8.	T2DM group showed increased levels of neutrophils when compared to the control group. There was a reduction in the expression of IL-6, IL-8, and MCP-1 in LPS-stimulated THP-1 cells relative to LPS-stimulated cells in the diabetic patient compared to control.
Mraz et al., 2011	Czech Republic	Cross-sectional study	T2DM (n=12) Control (n=15)	T2DM (57.7±9.34) Control (54.1±6.97)	F (n=12) M (n=15)	C-reactive protein (CRP), TNF-α, IL-6, IL-8	Individuals with T2DM had increased serum triglycerides, C-reactive protein (CRP), TNF-α, IL-6, and IL-8 levels when compared to the control group.
Ozturk et al., 2013	Turkey	Cross-sectional study	T2DM (n=97) Control (n=218)	T2DM (66.78±4.12) Control (72.81±6.17)	F (n=148) M (n=167)	NLR, CRP	There was statistical significance in the levels neutrophil-lymphocyte ratio (NLR) and CRP.

Shiny et al., 2014	India	Cross-sectional study	T2DM (n=237) Control (n=286)	T2DM (47±8) Control (39±7)	Not reported	HbA1c, TC, TG, NLR, HDL, LDL, Homeostatic model assessment of insulin resistance (HOMA-IR)	Individuals with T2DM had a significantly higher NLR, blood pressure and serum cholesterol levels compared to individuals with impaired glucose tolerance (IGT) and controls. However, there was no significant difference in monocytes, basophils and eosinophils levels amongst all groups
Shurtz-Swirskeit et al., 2001	Israel	Cross-sectional study	T2DM (n=18) Control (n=16)	T2DM (51.5±10) Control (48.35±5.45)	F (n=18) M (n=16)	Not reported	Individuals with T2DM had significantly elevated peripheral polymorphonuclear leukocyte count compared to controls.
Ulu et al., 2013	Turkey	Cross-sectional	T2DM (n=58) Control (n=45)	T2DM (50.31±5.2) Control (48.35±5.45)	F (n=69) M (n=34)	NLR	Individuals withT2DM had significantly elevated NLR compared to the controls.
Vaidyula et al., 2006	USA	Cross-sectional study	T2DM (n=10) Control (n=5)	T2DM (38.3±2.7) Control (39.6±2)	F (n=8) M (n=7)	Not reported	Individuals with T2DM had increased monocytes tissue factor when compared to controls.
Van Diepen et al., 2017	Netherlands	Cross-sectional study	T2DM (n=45) Control (n=72)	T2DM (60.3±1.6) Control (54.2±1)	F (n=56.68) M (n=58.32)	HbA1c	Individuals with T2DM had increased circulating succinate levels compared to the controls. The expression of succinate receptor-1 was increased in M2 compared to M1 macrophages this was improved following differentiation of monocytes to macrophages.
Yang et al 2012	China	Cross-sectional study	T2DM (n=28) Control (n=20)	T2DM (52±8) Control (49±6)	F (n=23) M (n=25)	IL-6	Individuals with T2DM had significantly increased monocytes ($CD14^+$ $CD16^+$) derived IL-6 and CRP levels when compared to controls.

Table 2S: Characteristics of included animal studies (n=8)

Author, year	Country	Strain, model	Age	Duration on diet (Weeks)	Effect measure	Main findings
Buras et al., 2015	USA	Male C57BL6/J Diabetes induced model of obesity (DIO) Induced by HFD (60% kcal derived from fats)	6	Not reported	TNF-α	High- fat diet (HFD)-fed mice developed obesity and slight hyperglycaemia. Interestingly, the levels of tumour necrosis factor-α (TNF-α) and interleukin-1 β (IL-1β) remained the same despite the reversal of hyperglycaemia. Proinsulin-secreting macrophages had increased adipose visceral macrophages that were undetectable in the control group.
Van Diepen et al., 2017	Netherland	$Sucnr^{-/+}$ Male C57BL/6 background DIO induced by HFD (60% kcal derived from fats)	8-12	2-16	IL-1β, IL-6, TNF-α, and MCP-1	Mouse adipose tissue on HFD showed increased expression of succinate receptor 1 (Sucnr1) mRNA in matured adipocyte compared to a stromal vascular fraction. Adipose tissue of HFD-fed mice showed a reduced number of macrophage markers F4/80 and CD68 compared to HFD-fed wild type (WT) mice.
Dror et al., 2017	Switzerland	C57BL/6N. DIO induced by HFD (58% kcal derived from fats, 25% carbohydrate,16% protein)	4	20 - 25	IL-1β, IL-6, and TNF-α	HFD-feeding increased circulating levels of IL-1β in WT mice. In Il1b−/− mice IL-1β was undetectable. Increased peritoneal macrophages and genes that code for inflammatory markers including IL-1β in ornamental fat.
Hong et al., 2009	USA	Male C57BL/6 DIO Induced by HFD (55% Kcal derived from fats)	10	3	IL-6, TNF-α	The deletion of macrophages resulted in decreased levels of neuroprotection D1 (NPD1) in mice wounds. Treatment db/db-macrophages by NPD1 decreased TNF-α, leukotriene-B4 (LTB4), and 8-isoprostane levels compared to the control. In addition, IL-10 increased as a result of administration of NPD1 and NPD1-treated db/db-macrophages. Macrophage depletion caused by dichloroethylene-diphosphonate (Clodronate) loaded liposomes therapy resulted in a decrease of F4/80 macrophage in db/db mice skin w ound.
Jia et al., 2014	United States	Male C57BL/6 Cre-conditional toll-like receptor (Tlr4) induced by electroporation of bacterial artificial chromosomes with Tlr4 into EL350 bacteria.	Not report ed	6-7	TNF-α	Circulating levels and mRNA expression of TNF-α, IL-6, IL-1β, and monocyte chemoattractant protein 1 (MCP-1), were significantly decreased in obese $Tlr4^{LKO}$ mice white adipose tissue (WAT) compared to HFD-fed controls. The decrease in TNF-α level was induced by LPS treatment. Additionally, WAT of HFD-fed $Tlr4^{LKO}$ mice, mRNA expression of CD11c, M1 macrophage marker, also decreased.
Kimball et al., 2017	United States	Male C57BL/6 DIO Induced by HFD derived from 60% kcal of fats).	Not report ed	10-12	IL-1β	Mixed lineage leukaemia-1 (Mll1) gene expression was significantly increased in macrophages following an injury. Mll1 expression was elevated in T2DM monocytes compared to the control group, showing an abnormal expression of MLL1 in prediabetic wound macrophages

Lee et al., 2016	Korea	C57BL/6 Autophagy related-7 (Atg7) conditional knockout (cKO) mice, was obtained by crossing Atg7 conditional wild type mice (cWT) with Lys-Cre mice.	Not reported	Not reported	IL-1β, IL-6, TNFα	Low Atg7 mRNA expression in peritoneal macrophage of Atg7 cKO mice. Atg7 cKO ob/ob mice glucose levels were above normal range compared to Atg7 cWT ob/ob mice. Lipopolysaccharide (LPS) induced low secretion of IL-1β. LPS coupled with palmitic acid treatment significantly increased the secretion of IL-1β in macrophages of Atg7 cKO mice compared to Atg7 to the control mice.
Prattichizo et al., 2018	Spain	Male C57BL/6 DIO induced by the admin of streptozotocin and citrate buffer.	Not reported	25	IL-6, IL-10, TNF-α, and MCP-1	Non-macrophagic, non-endothelial (ECs) showed increased p21 and transforming growth factor-β expression. Both macrophages and ECs showed expression senescence-associated secretory phenotype compatible markers. In comparison to the control group, circulating angiogenic cells showed a significant increase in the mRNA expression of p16 and IL-8.

Table 3S: Clinical and metabolic characteristics of included human studies

Author, year	SS	Gender	Anthropometric measurements		Cardiovascular risk factors			
		Male (%)	**BMI**	**Waist circumference**	**FBG**	**DBP**	**SBP**	**Insulin**
Barry et al., 2016	46	12 (26.1)	2 [-1.19, 5.19]	6.8 [-2.79, 16.39]	4.91[3.72, 6.11] [a]	Not reported	Not reported	Not reported
Cipolletta et al., 2005	40	19 (47,5)	0.90 [-3.49, 5.29]	Not reported	Not reported	4.00 [-0.54, 8.54]	9.00 [0.23, 17.77]	Not reported
Corralles et al., 2007	63	63 (100)	-7.90 [-11.15, -4.65]	Not reported	1.48 [0.69, 2.26] [a]	Not reported	Not reported	2.68 [1.80, 3.56]
Dai et al., 2015	29	15 (51.7)	1.05 [0.23, 1.87]	Not reported	Not determined	Not reported	Not reported	Not reported
Freirre et al., 2017	166	81 (48.9)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Gacka et al., 2010	80	38 (47,5)	6.94 [4.90, 8.98]	0.14 [0.09, 0.19]	1.47 [0.92, 2.01] [a]	7.21 [1.72, 12.70]	16.91 [8.10, 25.72]	-1.66 [-2.93, -0.38]
Ip et al., 2016	51	19 (37,3)	-2.0 [-4.34, 0.34]	Not reported	1.51 [0.88, 2.15] [a]	Not reported	Not reported	Not reported
Jagannathan-Bogdan et al., 2011	34	12 (35,3)	13.25 [8.09, 18.41]	Not reported	Not reported	Not reported	Not reported	Not reported
Lin et al., 2018	40	25 (62.3)	1.11 [0.79, 1.43]	Not reported	5.32 [3.94, 6.69] [a]	4.91 [3.47,6.33]	3.32 [0.76, 5.83]	2.03 [1.07, 2.99]
Malandrino et al., 2015	47	26 (55.3)	-0.25 [-0.88, 0.38]	-2.80 [-4.39, -1.21]	16.19 [12.71, 19.68] [a]	-1.00 [-4.07, 2.07]	0.00 [-5.00, 5.00]	Not reported
Moreno-Navarrete 2009	229	229 (100)	1.88 [0.88, 2.88]	0.05 [0.03, 0.07]	0.98 [0.70, 1.25] [a]	Not reported	Not reported	0.80 [0.29, 1.30]
Mraz et al., 2011	29	0 (0)	28.20 [22.98, 33.42]	Not reported	1.37 [0.52, 2.23] [a]	Not reported	Not reported	Not reported
Ozturk et al., 2013	315	167 (53)	Not reported	Not reported	2.09 [1.80, 2.38] [a]	Not reported	Not reported	Not reported
Shinny et al., 2014	523	Not reported	1.50 [0.77, 2.23]	4.60 [2.79, 6.41]	1.63 [1.43, 1.83]	2.20 [0.48, 3.92]	9.40[6.35, 12.45]	Not reported
Shurtz-Swirskeit et al., 2001	34	16 (47,1)	Not reported	Not reported	11.32 [8.38, 14.25] [a]	Not reported	Not reported	Not reported
Ulu et al., 2013	103	34 (33)	0.08 [-1.50, 1.66]	Not reported	1.48 [1.04, 1.92] [a]	Not reported	Not reported	0.14 [-0.60, 0.88]
Vaidyula et al., 2006	15	7 (46,7)	0.10 [-1.70, 1.90]	Not reported	-2.44 [-3.92, -0.96] [a]	Not reported	Not reported	Not reported

Van Diepen et al., 2017	117	Not determined	2.9 [2.63, 3.17]	0.08[0.07,0.09]	20.21[17.57,22.9] [a]	Not reported	Not reported	Not reported
Yang et al 2012	48	25 (52,1)	-0.70 [-2.12, 0.72]	Not reported	0.47 [-0.12, 1.05] [a]	0.00 [-4.93, 4.93]	2.00 [-2.25, 6.25]	Not reported

Footnote
Data presented as Mean Difference, 95% CI except for data indicated by [a] Standardized Mean Difference, 95%CI.
SS: Sample size, FBG: Fasting blood glucose, SBP: systolic blood pressure, DBP: diastolic blood pressure

Table 4S: Primary and secondary outcomes and the effect measure of included human studies

Study	IL-6	TNF-α	IL-1β	TG	TC	LDL	HDL	CRP	HbA1c	WBC	M	N	NLR
Barry et al., 2016	0.00 [0.26, 0.26]	0.80 [0.18, 1.4]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cipolletta et al., 2005	NR	NR	NR	NR	-0.03 [-0.71, 0.65]	-0.31 [-0.99, 0.37]	-1.74 [-2.54, -0.95]	NR	NR	NR	NR	NR	NR
Corralles et al., 2007	-0.08 [-0.82, 0.67]	-0.15[-0.9, 0.59]	-0.50 [-1.26, 0.25]	NR	NR	NR	NR	0.56 [0.32, 0.81]	1.90 [1.10, 2.70] [a]	NR	NR	NR	NR
Freire et., a2017	NR	0.05 [-0.26, 0.59]	-0.00 [-0.31, 0.30]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Eftekharian et al., 2016	NR	NR	NR	1.26 [0.91, 1.61]	2.44 [2.01, 2.87]	0.64 [0.31, 0.97]	-0.20 [-0.52, 0.13]	NR	NR	NR	NR	NR	NR
Gacka et al., 2010	NR	NR	NR	0.71 [0.20, 1.21]	NR	NR	-0.68 [-1.19, -0.18]	NR	2.50 [2.05, 2.95] [a]	NR	NR	NR	NR
Ip et al., 2016	NR	NR	NR	NR	NR	NR	NR	NR	2.85 [2.16, 3.54] [a]	NR	NR	NR	NR

Lin et al., 2018	NR	NR	NR	1.86 [1.11, 2.62]	1.55 [0.84, 2.27]	2.34 [1.51, 3.16]	NR	NR	11.86 [10.54,13.18] [a]	NR	NR	NR	NR
Malandrino et al., 2015	0.72 [0.12, 1.31]	NR	NR	3.03 [2.10, 3.96]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Moreno-Navarrete 2009	Not reported	0.20 [-0.07, 0.46]	NR	1.27 [0.99, 1.56]	NR	NR	NR	NR	1.50 [1.19, 1.81] [a]	NR	NR	-0.19 [-0.76, 0.39]	NR
Mraz et al., 2011	1.14 [0.31, 1.96]	1.23 [0.39, 2.06]	NR	1.36 [0.51, 2.22]	-0.28 [-1.05, 0.48]	NR	NR	1.49 [0.62, 2.36]	3.14 [1.88, 4.40] [a]	NR	NR	NR	NR
Ozturk et al., 2013	NR	NR	NR	NR	-0.06 [-0.30, 0.18]	0.10 [-0.15, 0.34]	-0.88 [-1.13, -0.63]	0.03 [-0.71, 0.78]	NR	0.56 [0.31, 0.80]	NR	0.25 [0.01, 0.49]	-0.14 [-0.32, 0.04] [a]
Shinny et al., 2014	NR	NR	NR	0.17 [-0.00, 0.34]	0.48 [0.30, 0.65]	0.09 [-0.09, 0.26]	-0.04 [-0.21, 0.13]	NR	0.70 [0.55,0.85] [a]	NR	-0.15 [-.32, 0.03]	0.77 [0.59, 0.95]	0.70 [0.55,0.85] [a]
Shurtz-Swirskeit et al., 2001	NR	NR	NR	2.32 [1.43, 3.22]	0.41 [-0.27, 1.09]	NR	NR	NR	2.22 [2.12, 2.32]	NR	NR	NR	NR
Ulu et al., 2013	NR	NR	NR	0.47 [0.08, 0.87]	NR	0.08 [-0.31, 0.47]	-0.35 [-0.74, 0.04]	NR	NR	NR	NR	NR	NR
Vaidyula et al., 2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Van Diepen et al., 2017	NR	NR	NR	4.47 [3.78, 5.16]	-1.99 [-2.44, -1.53]	-4.75 [-5.47, -4.02]	ND	NR	ND	NR	NR	NR	NR
Yang et al 2012	2.97 [2.12, 3.81]	NR	NR	0.47 [-0.11, 1.05]	0.00 [-0.57, 0.57]	-0.66 [-1.25, -0.07]	-0.28 [-0.85, 0.30]	1.21 [0.58, 1.83]	0.20 [-0.11, 0.51] [a]	-0.42 [-1.00, 0.16]	0.00 [-0.57, 0.57]	0.62 [0.35, 0.89]	NR

Footnote:

Data presented as Standardised Mean Difference (SMD), 95% CI, [a] represent data reported as a mean difference

NR: Not reported, ND: Not determined

Table 5S: Summary of findings. Type 2 diabetes mellitus (T2DM) compared to Control (normoglycaemia)

Type 2 Diabetes mellitus (T2DM) compared to Control (normoglycaemia) in T2DM

Patient or population: T2DM
Comparison: Control (normoglycaemia)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control (normoglycaemia)	**Risk with Type 2 Diabetes mellitus (T2DM)**				
Monocytes activation	The mean monocytes activation ranged from **-0.4195 - 66.5** SD	MD **0.47 SD higher** (0.1 higher to 0.84 higher)	-	991 (7 observational studies)	⊕◯◯◯ VERY LOW [a,b,c,d]	
Cardiovascular disease risk factors (CVDs)	The mean Cardiovascular disease risk factors ranged from **1.05-207.73** SD	mean **0.37 SD higher** (0.13 higher to 0.61 higher)	-	6867 (13 observational studies)	⊕◯◯◯ VERY LOW [a,d,e,f,g]	
Animal narrative	no data pooling was carried out in all animal studies [h]			(7 RCTs)	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 6Sa: Quality ratings and risk of bias assessment for included studies assigned to each study using the Downs and Black (DB) scale.

Author	Reporting/10	External validity score/3	Internal validity score/7	Selection bias score/6	Total Numerical score/26	Rating
Barry et al., 2016	8	0	3	3	14	Poor
Cipoletta et al., 2005	7	1	3	2	13	Poor
Corralles et al., 2007	6	0	4	0	10	Poor
Dai et al., 2015	9	3	4	2	18	Fair
Eftekharian et al., 2016	7	2	3	2	14	Poor
Freirre et al., 2017	7	0	1	1	9	Poor
Gacka et al., 2010	6	1	3	2	12	Poor
Ip et al., 2016	7	1	2	0	10	Poor
Jagannathan-Bogdan et al., 2016	5	0	3	0	8	Poor
Lin et al., 2018	8	3	1	2	14	Poor
Malandrino et al., 2015	8	2	2	2	14	Poor
Moreno-Navarette et al., 2009	8	3	2	1	14	Poor
Mraz et al., 2011	9	0	2	1	12	Poor
Ozturk et al., 2013	7	0	2	0	9	Poor
Shiny et al., 2014	10	2	3	4	19	Fair
Shurtz-Swirskeit et al., 2001	7	0	2	0	9	Poor
Ulu et al., 2013	7	1	2	1	10	Poor
Vaidyula et al., 2006	7	0	2	1	10	Poor
Van deepen et al., 2017	7	0	2	1	10	Poor
Yang et al., 2012	8	1	2	1	12	Poor
Median (range)	7 (5-10)	1 (0-3)	2 (1-4)	1 (0-4)	12 (8-19)	
Kappa [95%CI], % agreement	0.6 [0.08-1.0] 80.0%	0.33 [-0.971-.00] 66.67%	0.71 [0.15-1] 85.71	0.33 [-0.49-1] 66.67%		

Table 6Sb: Quality scores, Kappa results assessed by ARRIVE guideline for animal studies.

Domain	Introduction/4	Methods/9	Results/4	Discussion score/3	Overall score/20	Rating
Dale Buras et al., 2015	4	5	1	3	13	Fair
Van Deepen et al., 2017	4	9	3	3	19	Good
Dror et al., 2017	4	7	2	3	16	Good
Hong et al., 2009	4	5	2	3	14	Fair
Jia et al., 2014	4	9	2	3	18	Good
Kimball et al., 2017	4	5	2	2	13	Fair
Lee et al., 2016	4	7	2	3	16	Good
Pratichizzo et al., 2018	4	9	2	2	17	Good
Median	4 (4-4)	7 (5-9)	2 (1-3)	3 (2-3)	16 (13-19)	
%, Kappa value[95%CI]	100, K= 1[1.00-1.00]	62.50, K= 0.25[0.47-0.97]	87.50, K=0.75 [0.26-1.00]	100, K= 1 [1.00-1.00]		

Table 6Sc: Quality assessment of individual included studies in the review using the Joanna Briggs Institute (JBI) Critical Appraisal tools for use in JBI Systematic Reviews.

Author, year	1	2	3	4	5	6	7	8	9	Quality /9	Comment
Dale Buras et al., 2015	1	1	1	1	1	0	1	1	1	8	Good
Van Deepen et al., 2017	1	0	0	1	1	1	1	1	1	7	Good
Dror et al., 2017	1	1	1	1	1	1	1	1	1	9	Good
Hong et al., 2009	1	0	1	1	0	0	1	1	1	6	Fair
Jia et al., 2014	1	0	1	1	1	1	1	1	1	8	Good
Kimball et al., 2017	1	1	0	1	0	0	0	0	1	4	Poor
Lee et al., 2016	1	1	0	1	1	0	1	1	1	7	Good
Pratichizzo et al., 2018	1	1	1	1	1	1	1	1	0	8	Good
Median (range)	1 (1-1)	1(0-1)	1 (0-1)	1(1-1)	1(0-1)	0.5(0-1)	1 (0-1)	1 (0-1)	1 (0-1)	7.5 (4-8)	
%, Kappa[95%CI]	100, K=1 [1-1]	66.67, K=0.33 [-0.32-0.99]	66.67, K=0.33 [-0.32-0.99]	100, K= 1 [1.0-1.0]	55.55. K=0.11[-0.58-0.80]	66.67, K= 0.33[-0.32-0.99]	88.89, K= 0.78 0.34-1.00]	88.89, K=0.78 0.34-1.00]	88.89, K=0.78 [0.34-1.00]		

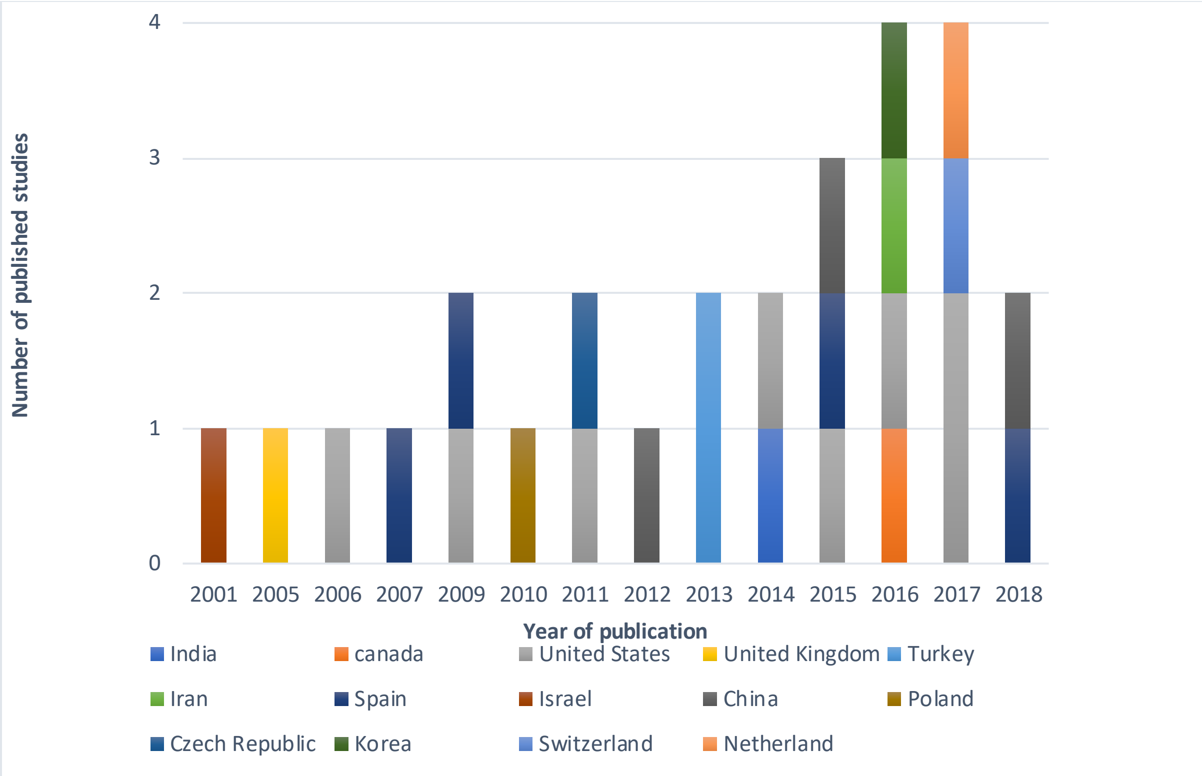


Figure 1S: Publication trends on monocyte activation and cardiovascular risk factors in T2DM

Study or Subgroup	T2DM Mean	T2DM SD	T2DM Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Fasting blood glucose (FBG)								
Barry et al., 2016	9.8	0.8	24	5.8	0.8	22	3.0%	4.91 [3.72, 6.11]
Corralles et al., 2007	147	44	55	85	7	8	3.5%	1.48 [0.69, 2.26]
Gacka et al., 2010	8.48	2.79	58	4.9	0.79	22	3.7%	1.47 [0.92, 2.01]
Ip et al., 2016	171.25	41.5	22	113	35	29	3.6%	1.51 [0.88, 2.15]
Lin et al., 2018	11.18	1.73	20	4.52	0.15	20	2.8%	5.32 [3.94, 6.69]
Malandrino et al., 2015	8.425	0.275	11	5.575	0.13	36	1.1%	16.19 [12.71, 19.68]
Moreno-Navarette et al., 2009	144.44	68.3	135	92.8	7.6	94	3.9%	0.98 [0.70, 1.25]
Mraz et al., 2011	8.51	3.84	12	4.84	0.62	15	3.4%	1.37 [0.52, 2.23]
Shiny et al., 2014	8.84	3.9	237	4.53	0.35	286	3.9%	1.63 [1.43, 1.83]
Shurtz-Swiskeit et al., 2001	155	7.2	18	91.5	2.3	16	1.4%	11.32 [8.38, 14.25]
Ulu et al., 2013	175.86	68.86	58	97.13	15.4	45	3.8%	1.48 [1.04, 1.92]
Vaidyula et al., 2006	95	4	10	113	11	5	2.7%	-2.44 [-3.92, -0.96]
Van Deepen et al., 2017	11.6	0.5	45	5.1	0.1	72	1.6%	20.24 [17.57, 22.90]
Yang et al., 2012	5.9	0.8	28	5.5	0.9	20	3.7%	0.47 [-0.12, 1.05]
Öztürk et al., 2013	183.43	82.89	97	84.14	13.7	218	3.8%	2.09 [1.80, 2.38]
Subtotal (95% CI)			**830**			**908**	**45.6%**	**3.26 [2.47, 4.04]**
Heterogeneity: Tau² = 1.98; Chi² = 429.39, df = 14 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 8.16 (P < 0.00001)								
Glycated haemoglobin (HbA1c)								
Corralles et al., 2007	7.2	1.5	55	5.3	1	8	3.5%	1.29 [0.52, 2.07]
Gacka et al., 2010	7.37	1.71	58	4.87	0.24	22	3.7%	1.69 [1.13, 2.25]
Ip et al., 2016	8.125	1.63	22	5.275	0.23	29	3.5%	2.60 [1.83, 3.36]
Lin et al., 2018	9.02	0.17	20	5.37	0.08	20	0.4%	26.93 [20.68, 33.17]
Moreno-Navarette et al., 2009	6.3	1.8	135	4.8	0.32	94	3.9%	1.07 [0.79, 1.35]
Mraz et al., 2011	6.66	2.15	12	3.52	0.62	15	3.3%	2.03 [1.07, 2.99]
Shiny et al., 2014	8.5	2.2	237	5.5	0.3	286	3.9%	2.00 [1.79, 2.21]
Shurtz-Swiskeit et al., 2001	7.12	0.18	18	4.9	0.1	16	1.0%	14.65 [10.88, 18.41]
Yang et al., 2012	5.8	0.6	28	5.6	0.5	20	3.7%	0.35 [-0.23, 0.93]
Subtotal (95% CI)			**585**			**510**	**26.7%**	**2.48 [1.63, 3.34]**
Heterogeneity: Tau² = 1.31; Chi² = 162.47, df = 8 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 5.69 (P < 0.00001)								
Insulin								
Corralles et al., 2007	11.33	4.475	11	5.05	1.05	36	3.4%	2.68 [1.80, 3.56]
Gacka et al., 2010	70	7	10	141	72	5	2.9%	-1.66 [-2.93, -0.38]
Malandrino et al., 2015	35.3	12.8	12	16.3	4.26	15	3.3%	2.03 [1.07, 2.99]
Mraz et al., 2011	12.66	6.97	58	7.6	3.91	22	3.7%	0.80 [0.29, 1.30]
Vaidyula et al., 2006	14.2	10	55	12.8	9.8	8	3.5%	0.14 [-0.60, 0.88]
Subtotal (95% CI)			**146**			**86**	**16.8%**	**0.84 [-0.31, 2.00]**
Heterogeneity: Tau² = 1.54; Chi² = 40.63, df = 4 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 1.43 (P = 0.15)								
Homeostatic model of insulin resistance (HOMA-IR)								
Gacka et al., 2010	4.8	3.13	58	1.7	0.9	22	3.7%	1.13 [0.61, 1.65]
Malandrino et al., 2015	8.173	5.4875	11	1.358	0.3025	36	3.4%	2.58 [1.71, 3.44]
Shiny et al., 2014	4.6	2	237	1.6	1	286	3.9%	1.95 [1.74, 2.16]
Subtotal (95% CI)			**306**			**344**	**11.0%**	**1.83 [1.16, 2.49]**
Heterogeneity: Tau² = 0.27; Chi² = 10.81, df = 2 (P = 0.004); I² = 82%								
Test for overall effect: Z = 5.38 (P < 0.00001)								
Total (95% CI)			**1867**			**1848**	**100.0%**	**2.33 [1.91, 2.76]**
Heterogeneity: Tau² = 1.21; Chi² = 666.61, df = 31 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 10.71 (P < 0.00001)								
Test for subgroup differences: Chi² = 13.87, df = 3 (P = 0.003), I² = 78.4%								

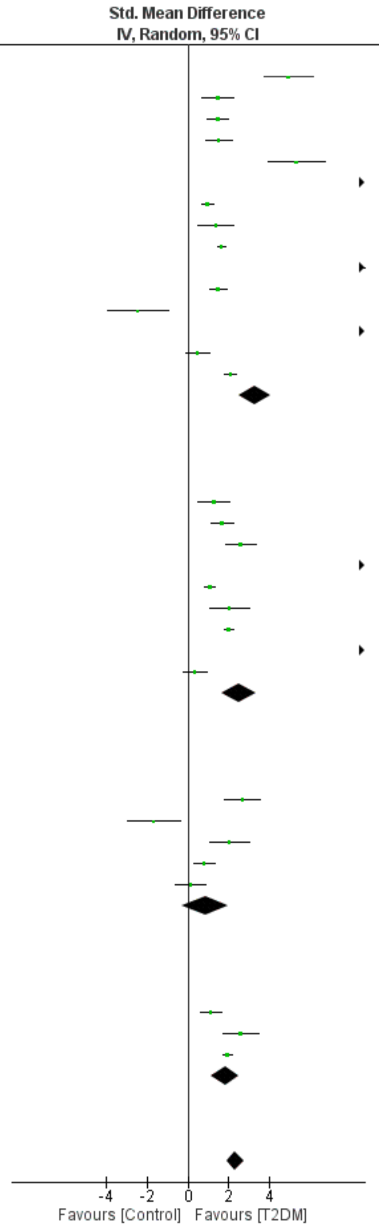
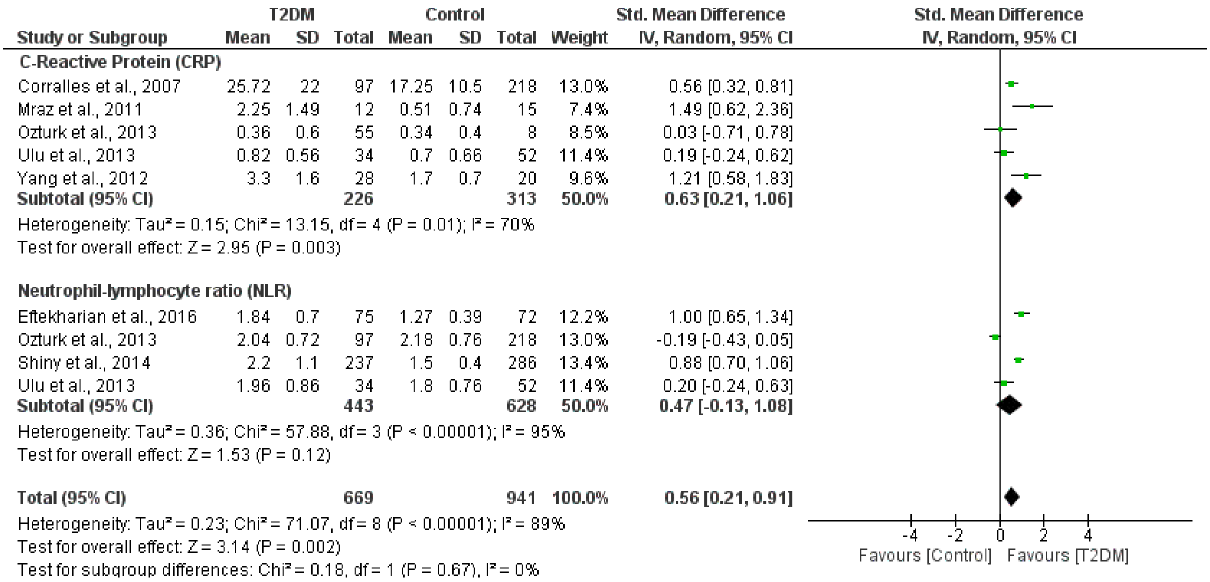


Figure 2S: Forest plot of glucose metabolism. Overall pooled estimate [SMD=1.94, 95% CI (1.52; 2.36), $p<0.00001$, $Chi^2=1048.79$, $I^2=96\%$, $p<0.0001$].



Study or Subgroup	T2DM Mean	T2DM SD	T2DM Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
C-Reactive Protein (CRP)								
Corralles et al., 2007	25.72	22	97	17.25	10.5	218	13.0%	0.56 [0.32, 0.81]
Mraz et al., 2011	2.25	1.49	12	0.51	0.74	15	7.4%	1.49 [0.62, 2.36]
Ozturk et al., 2013	0.36	0.6	55	0.34	0.4	8	8.5%	0.03 [-0.71, 0.78]
Ulu et al., 2013	0.82	0.56	34	0.7	0.66	52	11.4%	0.19 [-0.24, 0.62]
Yang et al., 2012	3.3	1.6	28	1.7	0.7	20	9.6%	1.21 [0.58, 1.83]
Subtotal (95% CI)			**226**			**313**	**50.0%**	**0.63 [0.21, 1.06]**
Heterogeneity: Tau² = 0.15; Chi² = 13.15, df = 4 (P = 0.01); I² = 70%								
Test for overall effect: Z = 2.95 (P = 0.003)								
Neutrophil-lymphocyte ratio (NLR)								
Eftekharian et al., 2016	1.84	0.7	75	1.27	0.39	72	12.2%	1.00 [0.65, 1.34]
Ozturk et al., 2013	2.04	0.72	97	2.18	0.76	218	13.0%	-0.19 [-0.43, 0.05]
Shiny et al., 2014	2.2	1.1	237	1.5	0.4	286	13.4%	0.88 [0.70, 1.06]
Ulu et al., 2013	1.96	0.86	34	1.8	0.76	52	11.4%	0.20 [-0.24, 0.63]
Subtotal (95% CI)			**443**			**628**	**50.0%**	**0.47 [-0.13, 1.08]**
Heterogeneity: Tau² = 0.36; Chi² = 57.88, df = 3 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 1.53 (P = 0.12)								
Total (95% CI)			**669**			**941**	**100.0%**	**0.56 [0.21, 0.91]**
Heterogeneity: Tau² = 0.23; Chi² = 71.07, df = 8 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 3.14 (P = 0.002)								
Test for subgroup differences: Chi² = 0.18, df = 1 (P = 0.67), I² = 0%								

Figure 3S: Forest plot of Inflammatory markers in individuals with T2DM versus control.

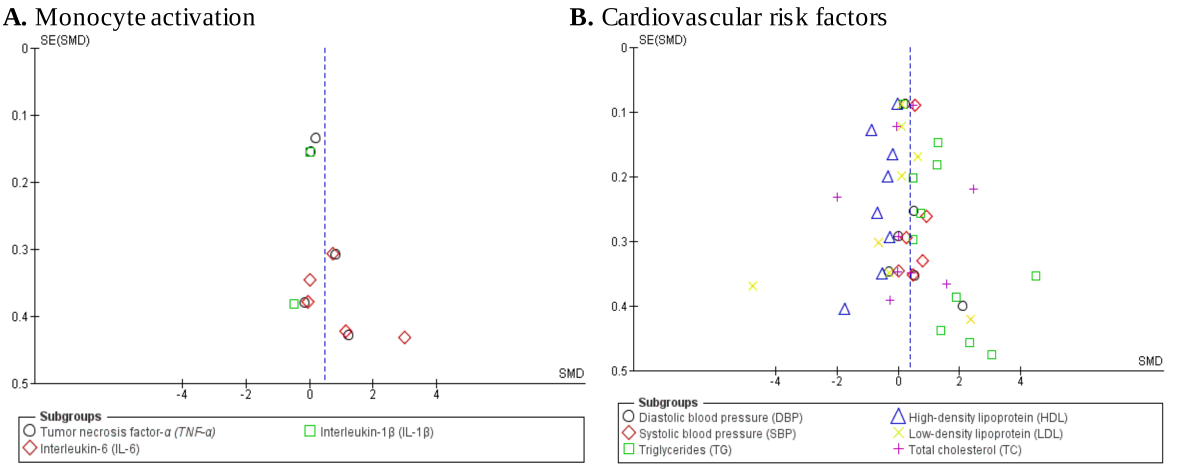


Figure 4S: Funnel plot of monocytes activation and cardiovascular risk factors showing perfect symmetry. Hence, there was no publication bias in these studies. Figure a: Monocyte activation, Figure b: Cardiovascular risk factors.