Supplementary material

Supplementary Methods

To investigate the epidemiology of COVID-19 in relation to diabetes and microcirculation, a detailed analysis was conducted utilizing the aforementioned retrieved results. As shown in Figure 1, Pertinent determiners such as "COVID-19", "Corona Virus Disease 2019", "novel coronavirus", and "SARS-CoV-2" were employed. The analysis encompassed a time frame spanning from January 1, 2019 to December 31, 2023, resulting in the identification of 38 relevant publications. VOSviewer software was utilized to facilitate a comprehensive visualization of keyword co-occurrence.

Supplementary Results

Supplementary Figure 6 illustrates the co-occurrence mapping of keywords with high frequency within the domain of diabetes and microcirculation in the context of COVID-19. The analysis revealed that the current research focuses and emerging trends pertaining to diabetes and microcirculation in the context of COVID-19 are closely linked to "endothelial function", which highlights the significance of understanding the role of endothelial function in the context of COVID-19 and its impact on the pathophysiology of diabetes and microcirculation.

Supplementary Discussion

The link of diabetes, microcirculation, and their association with infectious diseases such as COVID-19 has become a focal point of contemporary medical research. Amidst a global pandemic, the interplay between these conditions has garnered significant scholarly attention, indicated by the data delineated in our supplementary materials. IDF Diabetes Atlas of 2022 has elucidated that individuals with diabetes, particularly those with glycated hemoglobin levels ≥ 7%, are at a substantially elevated risk—35 to 40% higher—of hospitalization and severe morbidity due to COVID-19. The susceptibility of diabetic patients to severe outcomes from COVID-19 infection is alarmingly

evident. A bidirectional nexus is hypothesized to underpin the relationship between COVID-19 and diabetes that COVID-19 may perturb insulin signaling and potentiate insulin resistance through cytokine storm syndromes[1]. Furthermore, the direct viral invasion of endothelial cells by SARS-CoV-2 contributes to microvascular complications, characterized by hypoxia, inflammatory cascades, and oxidative stress, which disrupt microcirculatory function[2,3]. This can lead to impaired perfusion and oxygenation of tissues, with subsequent implications for glucose metabolism. The therapeutic implications are clear, namely interventions aimed at preserving or restoring microcirculatory integrity should play a central role in the management of diabetes, particularly in the context of COVID-19. The dual challenge of diabetes and COVID-19 infection necessitates a concerted effort to optimize microcirculatory function to mitigate the risk of adverse outcomes.

The role of microRNAs in microcirculatory dysfunction-related diabetes

Supplementary Methods

MicroRNAs regulate gene expression and may participate in the pathophysiology of microcirculatory dysfunction-related diabetes. To explore the aspects of microRNAs in diabetes and microcirculation research, keyword of "microRNA" was employed to filter the relevant studies from the inception until December 31, 2023. Subsequently, VOSviewer and CiteSpace software were used to provide keyword co-occurrence networks and timezone visualization, respectively.

Supplementary Results

Followed by the search strategy, 98 research articles were finally identified. Keywords with high frequency in the research of diabetes, microcirculation, and microRNA were illustrated in Supplementary Figure 7A-E. In the co-occurrence network, "diabetic kidney disease" was linked with several keywords, including "microRNA", "type 2 diabetes", and "oxidative stress"

(Supplementary Figure 7A). In contrary, "coronary circulation" and "cardiovascular disease" showed limited associations with "endothelial cell", "endothelial dysfunction", and "nitric oxide" (Supplementary Figure 7B and E). The term of "gestational diabetes mellitus" presented a triadic association among "cell", "angiogenesis", and "blood-tumor-barrier" (Supplementary Figure 7C), while "diabetic retinopathy" holds considerable links among pivotal terms such as "microRNA", "type 2 diabetes", "angiogenesis", and "endothelial cell" (Supplementary Figure 7D).

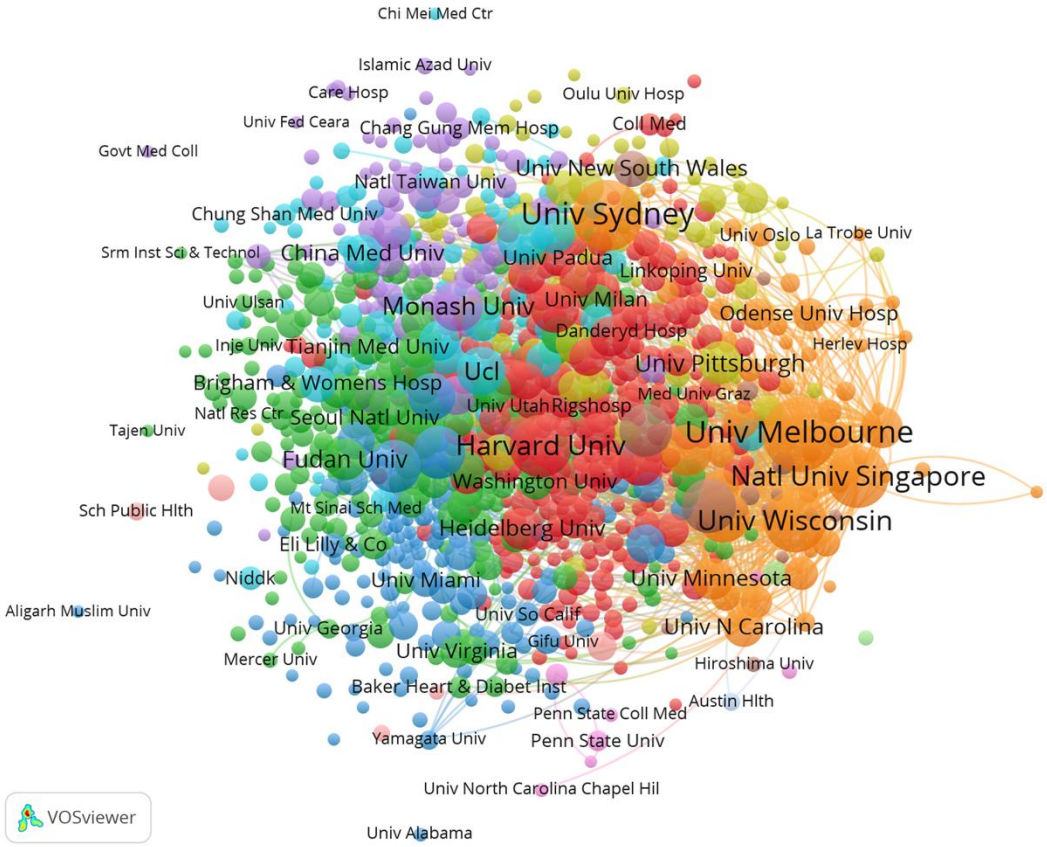
Additionally, the evolutionary trends in the fields of diabetes, microcirculation and microRNA research were depicted by a timezone visualization. As illustrated in Supplementary Figure 7F, "diabetic nephropathy" and "high glucose" appeared in 2010, and in 2014, the research focus shifted to "diabetic retinopathy", "expression", "endothelial cells", and other fields. Over the next decade, the co-occurrence links of keywords gradually expanded and formed a complex network in this research field. In the timezone, it can be found that "microRNA", "expression profile" and "type 2 diabetes" play vital roles in this field, revealing the emerging trend of microRNA in diabetes, microcirculation and microRNA research and its potential application value in clinical practice.

References

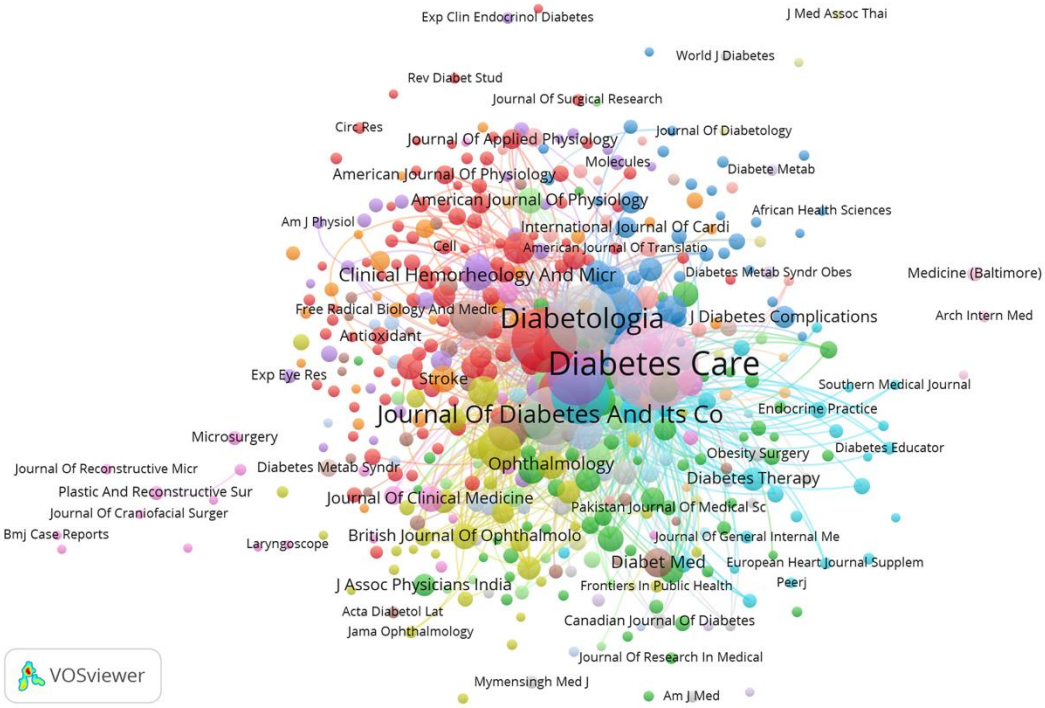
1 **Ren H**, Yang Y, Wang F, Yan Y, Shi X, Dong K, Yu X, Zhang S. Association of the insulin resistance marker TyG index with the severity and mortality of COVID-19. *Cardiovasc Diabetol* 2020; **19**: 58 [PMID: 32393351 DOI: 10.1186/s12933-020-01035-2]

2 **Lambadiari V**, Kousathana F, Raptis A, Katogiannis K, Kokkinos A, Ikonomidis I. Pre-Existing Cytokine and NLRP3 Inflammasome Activation and Increased Vascular Permeability in Diabetes: A Possible Fatal Link with Worst COVID-19 Infection Outcomes? *Front Immunol* 2020; **11**: 557235 [PMID: 33329516 DOI: 10.3389/fimmu.2020.557235]

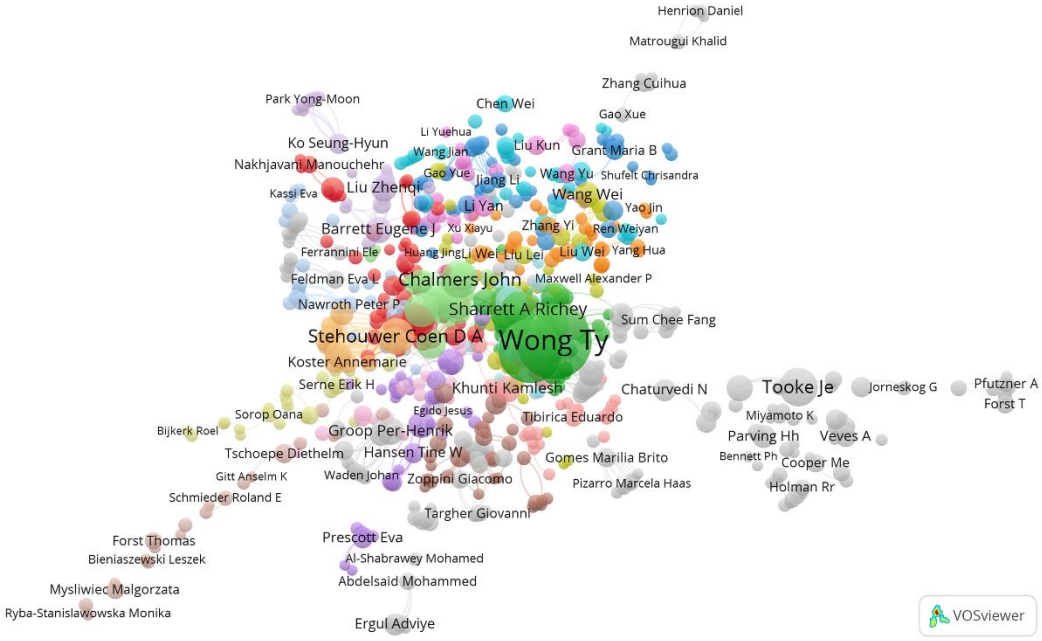
3 **Chelazzi C**, Villa G, Mancinelli P, De Gaudio AR, Adembri C. Glycocalyx and sepsis-induced alterations in vascular permeability. *Crit Care* 2015; **19**: 26 [PMID: 25887223 DOI: 10.1186/s13054-015-0741-z]



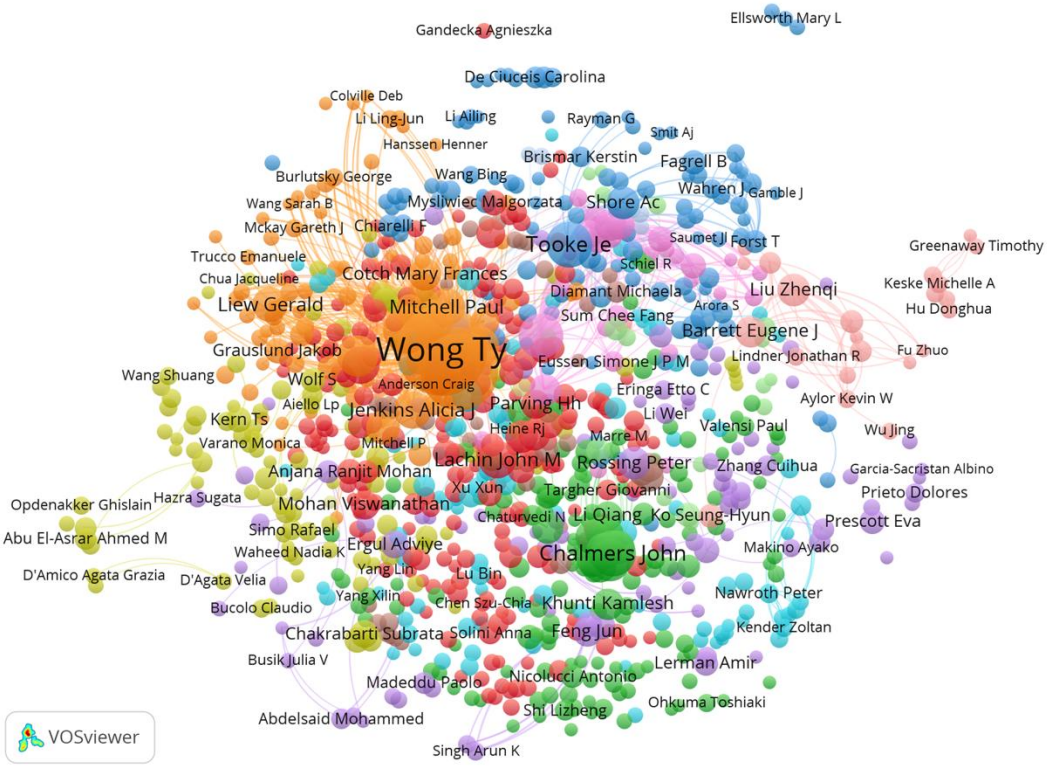
Supplementary Figure 1 Institutional citation network. This figure presents a network of institutions visualized as circles, where the size of each circle corresponds to the citation impact of the institution. Different colors categorize the institutions into distinct clusters, reflecting their research focus or geographic location. The connecting lines between circles illustrate citation relationships, with the spatial proximity of any two nodes indicating the strength of their bibliometric ties through co-citation.



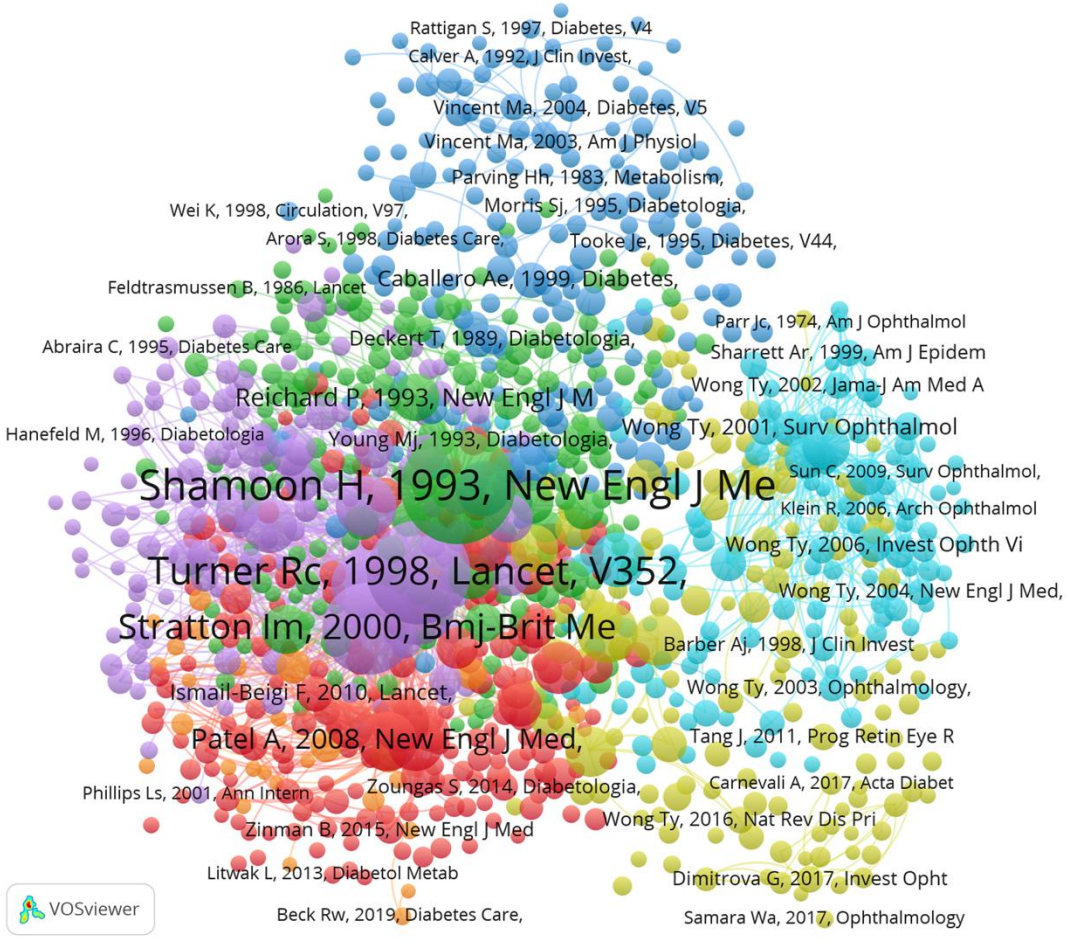
Supplementary Figure 2 Journal citation network. This visualization maps the citation network of academic journals as circles, with the size of each circle proportional to the journal's citation frequency. The color coding of the circles groups the journals into clusters, based on their disciplinary focus or impact factor. Lines between the journals represent citation links, where the distance between any two nodes reveals the extent of their co-citation relationship.



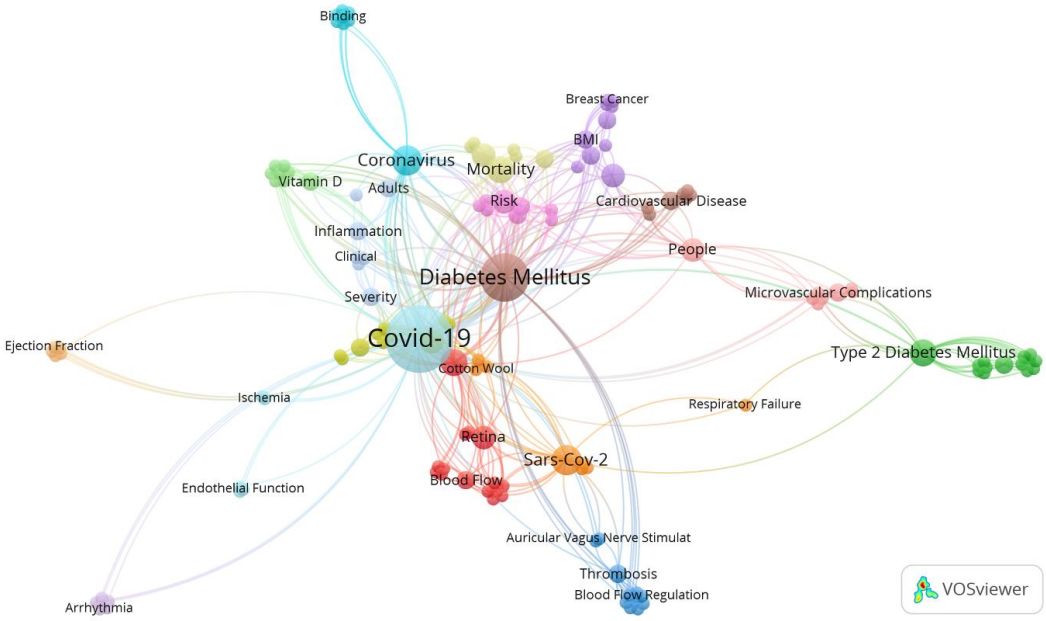
Supplementary Figure 3 Co-authorship network among researchers. Displayed here are circles representing individual authors, with the size of each circle denoting the extent of an author's collaborative engagements as measured by co-authorship frequency. Colors assign authors to specific clusters, reflecting their field of study or institutional affiliation. The lines between authors indicate collaborative links, with the closeness of two nodes suggesting a stronger co-authorship connection.



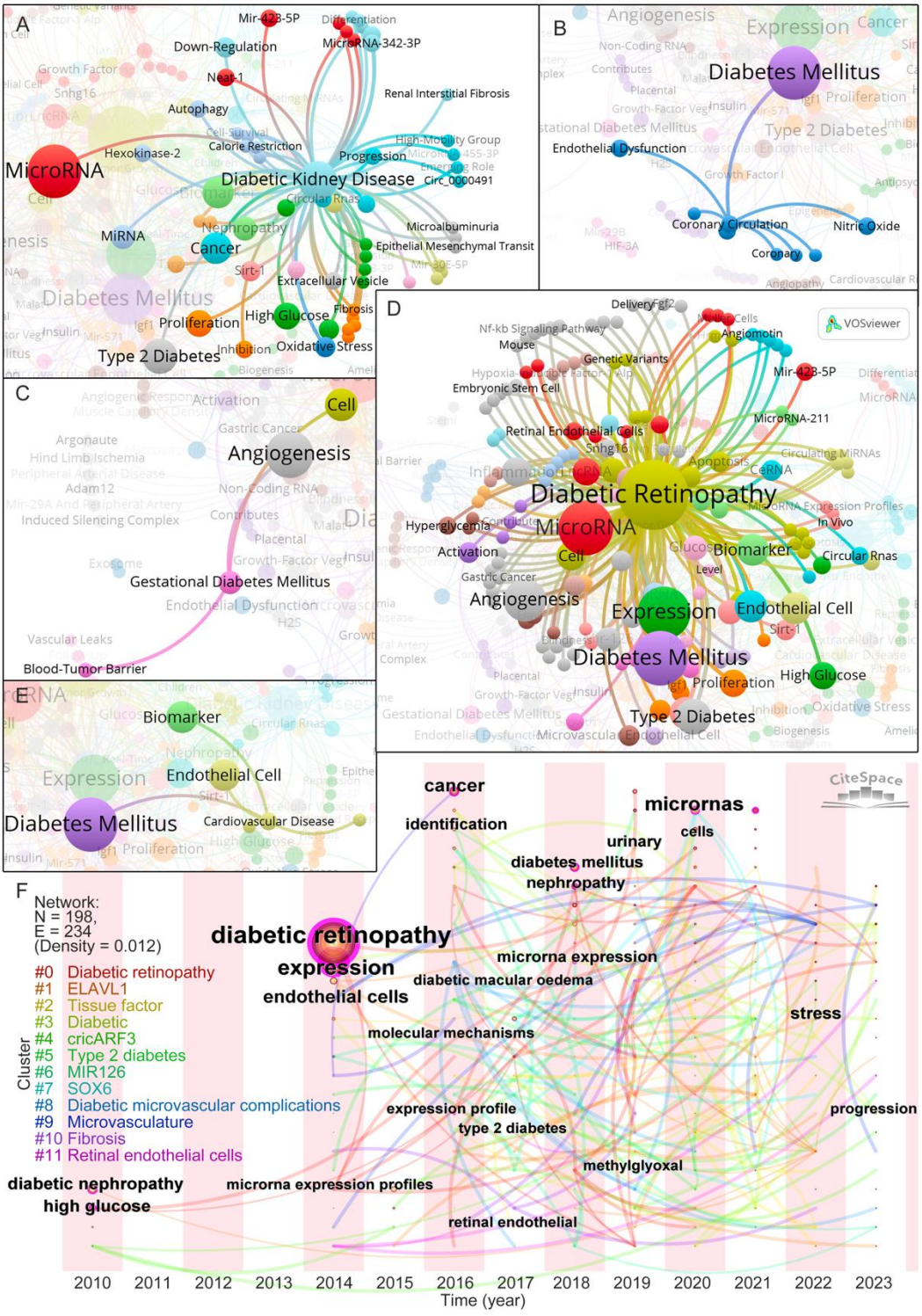
Supplementary Figure 4 Author citation network. This figure illustrates a citation network among authors, where each circle represents an author and the circle's size indicates the author's citation magnitude. Colors differentiate authors into clusters, which may correspond to their research specialties or affiliations. The lines connecting the authors signify citation relationships, with the spatial arrangement of nodes illustrating the extent of citation interconnections.



Supplementary Figure 5 Co-citation network of references. In this visualization, circles represent cited references, with the size of each circle reflecting the frequency of co-citation. The color of each circle indicates the cluster group of the reference, which relate to the research topic or publication type. Lines between references denote citation connections, and the distance between nodes indicates the level of bibliometric relation in terms of co-citations.



Supplementary Figure 6 Keyword co-occurrence network in diabetes, microcirculation, and coronavirus disease 2019 research. This figure maps the co-occurrence of keywords within the research domains of diabetes, microcirculation, and COVID-19. Each node's size is proportional to the frequency of the keyword's appearance in the literature, indicating its centrality in the discourse. Colors segregate keywords into clusters, likely reflective of thematic or disciplinary boundaries. Lines between keywords represent co-occurrence links, with the distance between nodes illustrating the degree of thematic overlap or interrelation based on their co-occurrence in academic publications.



Supplementary Figure 7 Detailed keyword co-occurrence networks and timezone in diabetes, microcirculation, and microRNA research. A-E: Panels present a detailed analysis of the co-occurrence relationships among keywords and their

associated terms in diabetes, microcirculation, and microRNA research. Each panel emphasizes a specific keyword, including "diabetic kidney disease", "coronary circulation", "gestational diabetes mellitus", "diabetic retinopathy", and "cardiovascular disease", respectively; F: Panel provides a timezone visualization, showing the keywords evolution in diabetes, microcirculation, and microRNA research. The node size indicates the volume of publications. The lines connecting nodes illustrate their co-occurrence relationships, with twelve colors represent different cluster groups.

Supplementary Table 1 The top 10 cited countries/regions

Rank	Countries/Regions	Citations	Documents	Links	Total link strength
1	United States	181,025	3,359	81	23480
2	United Kingdom	93,326	1,187	79	13866
3	Canada	45,791	433	73	5678
4	China	32,884	1,931	77	9024
5	Australia	32,683	697	79	10496
6	Italy	26,230	666	74	5375
7	Netherlands	22,601	450	71	4536
8	Japan	20,833	614	65	4135
9	Germany	20,085	652	69	4205
10	France	19,389	330	81	23480

Citations represents the total number of citations received by all documents published by a countries/region; Documents represents the number of publications published by a countries/region; Links means the number of connections among a countries/region and others; Total link strength means the total number of publications in which two countries/regions occur together.

Supplementary Table 2 The top 10 cited institutions

Rank	Institutions	Citations	Documents	Links	Total link strength
1	Radcliffe Infirmary	12755	242	167	896
2	University of Wisconsin	12039	215	185	774
3	Harvard University	15401	163	119	283
4	Royal Victoria Hospital	16118	163	129	513
5	University of Melbourne	11073	160	129	650
6	University of Sydney	9451	123	149	381
7	National University of Singapore	5885	117	147	358
8	Case Western Reserve University	8237	115	145	522
9	University of Oxford	1578	114	60	121
10	University of Washington	7067	113	135	261

Citations represents the total number of citations received by all documents published by an institution; Documents represents the number of publications published by an institution; Links means the number of connections among an institution and others; Total link strength means the total number of publications in which two institutions occur together.

Supplementary Table 3 The top 10 cited journals

Rank	Journals	Citations	Documents	Links	Total link strength
1	New England Journal of Medicine	48844	26	277	2469
2	Diabetes Care	40524	576	313	4215
3	Lancet	32922	34	263	1716
4	Diabetes Mellitus	18337	291	284	2032
5	Diabetologia	18030	329	299	2313
6	BMJ-British Medical Journal	13041	9	209	1151
7	Diabetes Research and Clinical Practice	7515	228	226	1319
8	Circulation	7341	57	152	486
9	Diabetic Medicine	7263	234	216	1343
10	Investigative Ophthalmology & Visual Science	6831	118	186	1095

Citations represents the total number of citations received by all documents published by a journal; Documents represents the number of publications published by a journal; Links means the number of connections among a journal and others; Total link strength means the total number of publications in which two journals occur together.

Supplementary Table 4 The top 10 productive authors and cited authors

Rank	Top 10 productive authors	Documents	Links	Total link strength	Citations	Top 10 cited authors	Documents	Links	Total link strength	Citations
1	Wong TY	202	96	745	12602	Holman RR	10	432	1101	17100
2	Klein R	147	64	431	14028	Turner RC	10	426	1056	16966
3	Klein BE	54	31	201	2250	Cull CA	6	411	994	16407
4	Tooke JE	53	6	56	1977	Matthews DR	10	430	1086	15354
5	Chalmers J	52	38	406	8048	Stratton IM	7	430	1061	15206
6	Stehouwer CD	50	40	296	1340	Klein R	147	582	9013	14028
7	Sharrett AR	44	36	197	2499	Manley SE	5	400	842	13483
8	Woodward M	44	45	397	7953	Wong TY	202	555	11510	12602
9	Wang JJ	42	45	207	1876	Chalmers J	52	398	2358	8048
10	Donaghue KC	41	25	162	1773	Woodward M	44	392	2230	7953

Documents represents the number of publications; Links represents the number of connections among an author and other authors; Total link strength means the total number of publications in which two authors occur together; Citations represents the total number of citations received by all documents published by an author.

Supplementary Table 5 The top 10 co-cited references

Rank	References	Citations	Links	Total link strength
1	Diabetes Control and Complications Trial Research G, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-986.	1052	879	8590
2	UKPDS group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-853.	885	831	8263
3	Stratton IM, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. BMJ. 2000;321(7258):405-412.	679	691	5519
4	UKPDS Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ.	440	644	4547

	1998;317(7160):703-713.			
5	Ohkubo Y, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: A randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28(2):103-117.	360	550	3425
6	UKPDS Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352(9131):854-865.	306	581	3137
7	Wilkinson CP, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110(9):1677-1682.	301	602	1944
8	ADVANCE Collaborative Group, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560-2572.	294	545	3321
9	Holman RR, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577-1589.	271	522	2937
10	Action to Control Cardiovascular Risk in Diabetes Study Group, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545-2559.	256	524	2969

Citations means the number of citations received by a document; Links represents the number of connections among a reference and other references; Total link strength means the total the number of publications in which two references occur together. UKPDS: the United Kingdom prospective diabetes study.

Supplementary Table 6 The top 8 keywords clusters

Cluster ID	Size	Clusters	Top 5 keywords
0	267	Oxidative stress	Intercellular adhesion molecule 1; Endothelial growth factor; Retinal microvascular cells; Atherosclerosis; Gene
1	190	Mortality	Parameters; Increases; Care; Risk factor; Morbidity
2	153	Microcirculation	Aldosterone; Capillary blood flow; Tolerance; Neuropathy; Morphology
3	137	Optical coherence tomography	Heart; Tumor necrosis factor; Atorvastatin; Vitamin D metabolites; Cardiac magnetic resonance
4	135	Microvascular complication	Hypertensive patients; Costs and cost analysis; β-cell function; Blood proteins; Pregnancy
5	126	Atherosclerosis risk	Diabetic peripheral neuropathy; Glomerular injury; Ace inhibition; Cardiovascular health; Genes
6	72	Diabetic neuropathy	Electrical stimulation; Microvascular blood flow; Cutaneous PO_2 measurements; Estimated glomerular filtration rate; Myocardial infarct
7	63	Metabolic syndrome	Lifestyle; Intima media thickness; Dilated cardiomyopathy; Aldose reductase inhibitor; Protein kinase C

Size represents the number of publications in the cluster.

Supplementary Table 7 The top 10 keywords

Rank	Keywords	Occurrences	Links	Total link strength
1	Diabetes mellitus	4264	999	29473
2	Microvascular Complication	1858	816	14148
3	Type 2 diabetes	1777	885	13098
4	Retinopathy	1218	811	9382
5	Risk	1212	813	9365
6	Disease	1138	870	8593
7	Complication	1021	838	7689
8	Diabetic retinopathy	1020	692	6346
9	Prevalence	1001	674	7642
10	Risk factor	997	777	8132

Links represents the number of connections among a keyword and other keywords; Total link represents the strength the total number of publications in which two keywords occur together.

Supplementary Table 8 Top 25 keywords with the strongest citation bursts

Keywords	Strength	Begin time (year)	End time (year)	Mean time (year)
IDDM	92.84	1990	2006	1990
NIDDM	63.85	1994	2005	1994
Diabetic retinopathy	59.35	2020	2023	1991
Diabetes mellitus	47.00	1993	2000	1959
Metabolic control	38.30	1991	2005	1991
Blood flow	33.64	1991	2002	1991
Blood pressure	33.22	2003	2010	1991
Diabetic kidney disease	33.04	2018	2023	2018
Insulin	31.56	1992	2005	1990
Coronary heart disease	28.72	1995	2008	1991
Rats	27.52	1991	2007	1991
Vasodilation	27.10	2000	2011	1994
Microalbuminuria	24.88	1994	2005	1993
Nitric oxide	23.90	1997	2010	1992
Protein kinase C	22.97	1992	2008	1992
Complications	21.32	1991	1999	1991
Optical coherence tomography angiography	20.00	2019	2023	2017
Autonomic neuropathy	19.30	1990	2008	1990
Responses	18.63	1992	2003	1992
Atherosclerosis risk	18.30	2003	2012	2002
Metabolic syndrome	17.43	2008	2014	2003
Vessel diameters	16.81	2007	2012	2007
Nitric oxide synthase	16.31	2004	2013	2000
Retinal microvascular Abnormality	15.00	2006	2016	2006
Nephropathy	14.97	1990	2002	1990

Strength means the total number of publications in which two countries/regions occur together; Mean time represents the average year of the keywords with strong citation bursts. IDDM: Insulin-dependent diabetes mellitus; NIDDM: Non-insulin-dependent diabetes mellitus.