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REVIEW ARTICLE

Shining the Light on Sunshine: a systematic review of the influence of sun exposure on type 2 diabetes mellitus-related outcomes

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Summary

Prospective observational studies uniformly link vitamin D deficiency with the incidence of type 2 diabetes mellitus (T2DM), yet trials supplementing participants at risk of T2DM with vitamin D to reduce progression to T2DM have yielded inconsistent results. Inconsistencies between supplementation trials may be due to insufficient dosing or small sample sizes. Observational studies may also have reported spurious associations due to uncontrolled confounding by lifestyle or genetic factors. Alternatively, observational and intervention studies may not be entirely comparable. Observational studies show an association between higher vitamin D status, which is predominantly derived from sun exposure, and decreased incidence of T2DM. Trials intervene with vitamin D supplementation, and therefore may be missing alternate causes of the effect of sun exposure, as seen in observational studies. We propose that sun exposure may be the driving force behind the associations seen in observational studies; sun exposure may have additional benefits beyond increasing serum 25-hydroxyvitamin D (25OHD) levels. We performed an electronic literature search to identify articles that examined associations between sun exposure and T2DM and/or glucose metabolism. A best evidence synthesis was then conducted using outcomes from analyses deemed to have high methodological quality. Ten eligible full-text articles were identified, yielding 19 T2DM-related outcomes. The best evidence analysis considered 11 outcomes which were grouped into six outcome types: T2DM, fasting glucose, glucose tolerance, fasting insulin, insulin secretion and insulin sensitivity. There was moderate evidence to support a role of recreational sun exposure in reducing odds of T2DM incidence. High-level evidence was lacking; evidence presented for other outcomes was of low or insufficient level. This review highlights significant gaps in research pertaining to sun exposure and T2DM-related outcomes. Further research is encouraged as we aim to identify novel preventative strategies for T2DM.

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Background

The recent International Diabetes Federation (IDF) Diabetes Atlas (6th edition) describes a snapshot of the global diabetes burden in 2013 and projects this forward to the year 2035.[1] Currently, an estimated 382 million global citizens have diabetes, costing around $1437 USD in 2013 for each person affected by the condition. Projections based on current trends predict that 592 million people will be living with diabetes by 2035; one in ten people will be affected, with an inordinate amount of funding required globally to treat diabetes and manage diabetic complications ($627 billion USD in 2035).

The effectiveness of vitamin D supplementation in diabetes prevention is a focus of current research. Vitamin D supplementation trials have yielded inconsistent results,[2] possibly due to insufficient vitamin D doses, heterogeneity in participant glycaemic and/or vitamin D status at baseline between studies, low supplementation compliance, or to insufficient power, particularly in post hoc analyses. Yet in two recent meta-analyses of prospective observational studies, higher serum 25-hydroxyvitamin D (25OHD) was associated with a lower risk of T2DM.[3,4] Observational studies may be reporting spurious associations due to uncontrolled confounding by lifestyle or genetic factors, or the association may be due to reverse causality; low serum 25OHD may be a marker, rather than a cause of ill health (most recently posited by Autier *et al.*[5]).

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There is an alternative explanation. In many parts of the world, the majority of our vitamin D store derives from the absorption of energy from solar ultraviolet radiation (UVR, specifically UVR of wavelength 280–315 nm; UVB[6]) by a cholesterol metabolite in the skin. In 1995, Scragg *et al.*[7] proposed that low levels of sun exposure, resulting in low 25OHD levels, could increase the risk of impaired glucose tolerance and T2DM. But, it is possible that there are pathways through which sun exposure protects against the development of T2DM other than by increasing 25OHD levels. Therefore, when comparing observational with intervention studies, vitamin D supplementation trials may be failing to capture additional benefits of sun exposure beyond increases in serum 25OHD levels. Instead of viewing vitamin D as being the factor driving associations with T2DM, it is timely to search for the independent effects of sun exposure itself.

Given the public health impact of T2DM, novel methods of prevention are of great consequence. If identified, a preventative effect of sun exposure on T2DM could easily translate into public health policy. In the face of the inconsistent results reported from observational and intervention studies, we performed a systematic review to examine the evidence of an effect of sun exposure or artificial UVR on the prevalence or incidence of T2DM or on measures of glucose metabolism in adults.

Methodology for article identification

Where appropriate, PRISMA guidelines for the reporting of systematic reviews and meta-analyses were followed.[8] Searches for pre-existing reviews on sun exposure and T2DM end-points, using Thomsom Reuters' Web of Science (formerly known as ISI Web of Knowledge), Scopus (Science Direct), PubMed and The Cochrane Collaboration, yielded no results. We undertook a search for full-text articles with sun exposure and either T2DM or glucose metabolism or both outcomes. The electronic search was conducted within Web of Science and Scopus; search terms are shown in Table 1. Restrictions were placed on title (to omit experimental rodent studies), language (to omit publications in languages other than English), article type (to omit reviews) and publication date (1966 through to July 2012). Briefly, the sun exposure terms captured exposure to radiation from the sun or artificial UVR and were measured as one or any combination of the following: time outdoors, time between certain latitudes or in different climates, composite indices comprising sun exposure duration and body surface area exposed to sun, solar irradiance at the skin measured by polysulphone ultraviolet wristwatch methods, ambient UVR, latitude, season, time of year or sun-seeking behaviour such as sunbathing or sun bed use. T2DM was defined by self-report, clinical diagnosis, hospital records, registry linkage, medication use or standard diagnostic glucose metabolism test results. Glucose metabolism was defined as any one or more of the following: fasting glucose, fasting insulin, HbA1c, test results from oral glucose tolerance and glucose clamp techniques or composite indices manipulating these glucose metabolism measurements.

Three researchers (CS-L, SLB, KMS) searched titles, abstracts and full articles of the resulting output to determine eligibility of the articles against predetermined criteria before checking reference lists of eligible publications for additional potentially eligible articles. Peer-reviewed full-text articles which were published in English and comprised cohort, case–control or cross-sectional study designs, and were population, community, clinic or institution based (with short-term institutionalization of <1 week) were eligible for inclusion. Articles on gestational diabetes mellitus, type 1 diabetes mellitus and diabetes insipidus were excluded, maintaining a more homogenous group of study populations and outcomes. Studies were also excluded if they (i) investigated T2DM in people younger than 18 years of age; (ii) consisted of a source population who were completely diabetic or a population in which all individuals experienced limited or excessive sun exposure or were matched on sun exposure (including studies conducted solely within the tropics); (iii) were intervention studies (for example vitamin D supplementation trials or ecological studies reporting diabetes outcomes in different geographical regions without analysis of latitudinal differences); (iv) provided only unadjusted data for an association between sun exposure and T2DM-related outcomes. Although age, obesity and physical activity are key confounders in the association between sun exposure and T2DM-related outcomes, adjustment for these factors did not determine article eligibility. Instead, the degree to which the eligible articles controlled for these factors influenced their risk-of-bias assessment and therefore their inclusion into the best evidence synthesis. We did not include abstracts or search the grey literature.

Results

Article identification

The electronic search strategy initially yielded 10 232 citations (Fig. 1); following the exclusion of immediately obvious duplicates, 8630 articles remained for the multistage screening process. Reasons for exclusion included the following: basic science, non-human animal and plant studies (n = 4857; 56%), irrelevant human studies/other (n = 2345: 27%), therapeutic or imaging studies (n = 853; 10%), studies with irrelevant exposure or outcome variables (n = 410; 5%), and grey literature (n = 157; 2%). From this screening process, eight eligible articles were identified for inclusion in this review. We (CS-L, SLB) conducted a manual search of the reference lists of those eight articles and identified a further two eligible articles bringing the final number of eligible manuscripts to 10. These 10 articles yielded 19 outcomes.

Quality assessment of T2DM-related outcomes

Data on outcomes from studies eligible for review were extracted and recorded electronically. Using individually validated questions from the Viswanathan and Berkmans' Observational Studies Risk of Bias and Precision Item Bank,[9] eligible

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Table 1. Medical Subject Heading (MeSH) and keyword search terms

Diabetes terms	"diabet* OR prediabet* OR t2 dm OR tiidm OR niddm OR (blood OR plasma OR fasting OR post?prandial OR tolerance* OR metabolism OR intolerance* OR clamp*) AND glucose) OR (blood AND sugar*) OR (insulin AND (resistance OR sensitivity)) OR hyperinsulin?emia OR hyperglyc?emia OR (glyc?emic AND (index OR indices)) OR (HbA1c OR (Hb AND A1c)) OR ((glycosylated OR glycated) AND H?emoglobin*) OR glycoh?emoglobin "
Sun exposure terms	"sun* OR season OR "electromagnetic radiation" OR ultraviolet OR uv OR uvr OR daylight OR light OR solar OR latitude OR outdoor OR non*melanoma OR heliotherapy OR phototherapy OR "vitamin D" OR 25 hydroxy* OR 25 dihydroxy* OR calcifediol OR cholecalci* OR calcitriol OR ergocalci* "
Restrictions on title	""type 1" OR "type I" OR gestational OR insipidus OR child* OR adolescen* OR rat* OR mice OR mouse "

Relevant search symbols applied to individual databases: * allows for variations in word ending; ? allows for variation in spelling.

articles were evaluated in terms of risk of bias, precision and plausibility for each outcome (contact first author for further information). Given the scarcity of the literature and the heterogeneity of published articles on this topic, we determined *a priori* to perform a best evidence synthesis. Selection of outcomes for the best evidence synthesis was dependent upon these criteria. Four of the 19 outcomes were excluded from the synthesis based on the risk of bias assessment: fewer than half of the risk of bias domains were graded as 'low risk of bias' (homeostasis model of assessment-insulin resistance (HOMA-IR),[10] random

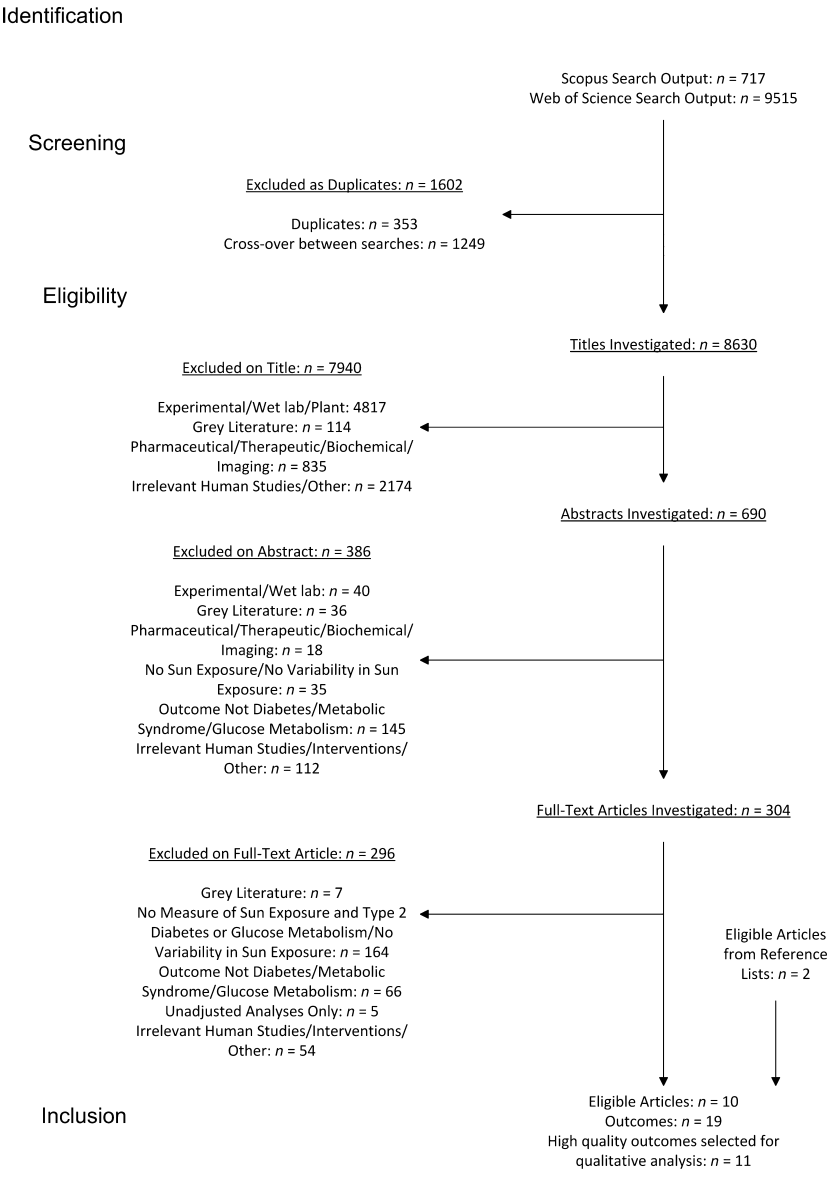

Fig. 1 Flowchart of articles identified as relevant for inclusion.

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glucose,[11] HbA1c,[12] insulin sensitivity index (ISI)-Matsuda)[13]. Precision and plausibility were compromised in an additional four outcomes: insufficient sample size was likely, no power/sample size estimate was described *a priori* (T2DM,[10] impaired glucose tolerance (IGT),[10] and fasting insulin[14]), and the analysis protocol was suspect for one outcome (fasting glucose[15]).

Best evidence synthesis

Eleven high-quality outcomes included in the best evidence synthesis are described in Table 2, alongside a summary of associations. These outcomes were collated to determine the strength of evidence across six groups of comparable outcomes (subsequently referred to as 'outcome types'): T2DM incidence, fasting glucose, glucose tolerance, fasting insulin, insulin secretion and insulin sensitivity. The strength of evidence was assessed across each outcome type according to fields described by Owens *et al.*,[16] leading to a label assignment of 'low-', 'moderate-' or 'high-'level evidence or 'insufficient' evidence where findings were inconclusive. This assessment accounted for causal directness (the causal distance between the exposure and outcome) and the consistency in direction and magnitude of the effect measures reported across an outcome type (Table 3). Table 4 summarizes the quality of evidence for each outcome type. Four of these outcome types comprised only a single outcome (T2DM incidence, glucose tolerance, fasting insulin and insulin secretion), making consistency of findings across these outcome types impossible to assess. Only one study showed a 'direct' link between sun exposure and T2DM: self-reported sun exposure over a mean follow-up period of 11 years,[17] while other studies typically explored cross-sectional associations using season or another temporal division of the year to represent sun exposure.

Given the scarcity of information regarding sun exposure and diabetes-related outcomes, a 'moderate' level of evidence was the highest level of evidence obtained. Furthermore, this 'moderate' level of evidence was based on analyses performed on the one high-quality outcome: this review found moderate evidence for recreational sun exposure reducing odds of T2DM incidence (and for no effect of occupational sun exposure). There was low-level evidence to suggest that higher levels of sun exposure (i) increased fasting insulin, (ii) reduced insulin secretion in response to a glucose load and (iii) did not affect glucose levels post-2-h glucose load. There was insufficient evidence to suggest an effect of sun exposure on fasting glucose or insulin sensitivity.

Sun exposure and T2DM

The highest level of evidence (moderate) for an association between sun exposure and T2DM outcomes in adults originates from the study by Lindqvist *et al.*[17] The article reports a reduction in odds of developing T2DM given increased recreational (rather than occupational) sun exposure. This disparity between the results for recreational and occupational sun exposure could be due to the frequency of sun exposure (perhaps leading to tolerance), duration, intensity and site of exposure (sun protective clothing and behaviour differences between the two settings), or perhaps selection biases for such work (for example, fair-skinned people may avoid occupational sun exposure or a less healthy lifestyle may be associated with manual labour). A similar disparity between recreational and occupational sun exposure is well described for risk of developing melanoma.[19] Considering results from grey literature (which were therefore not eligible for inclusion into the present review), seasonality in T2DM incidence supports the association between sun exposure and T2DM incidence; T2DM incidence is lowest in summer.[18] These results may stimulate further research into the epidemiologic and mechanistic relationship between sun exposure and T2DM outcomes as the wide availability of sunlight in most locations means this is potentially a simple and effective method for prevention of T2DM. Furthermore, research on this topic may have additional important public health implications, such as modifying sun exposure recommendations.

Sun exposure and glycaemia

Evidence for an association between sun exposure and fasting serum glucose level is lacking. Although results reporting on the potential effect of sun exposure on fasting glucose are somewhat inconsistent, they are not necessarily contradictory (Table 2): while three studies reported higher levels of fasting glucose in winter or the colder months compared with other periods of the year,[14,20,21] one study reported no association between fasting glucose levels in summer compared with winter.[10] These results are in agreement with a small collection of unadjusted analyses from other studies assessing variation in fasting glucose throughout the year (analyses not included in the review due to solely reporting unadjusted results).[14,21–24] Typically, the lowest glucose levels occur during summer and levels peak in winter or early spring. One of these analyses went beyond simply observing trends in fasting glucose throughout the year: fasting plasma glucose was positively correlated with a measure of available sun and inversely correlated with temperature.[21] Temperature, available sunlight and season may be markers for physical activity levels, rather than strictly reflecting sun exposure levels. Physical activity is difficult to measure accurately and precisely, leading to spurious associations with glycaemia despite one study controlling for differences in activity levels.[20] Considering that the unadjusted analyses and three of four of the studies included in the best evidence synthesis (including the study adjusting for physical activity) are in agreement, it is possible that future research may confirm that sun exposure reduces fasting glucose.

Sun exposure, glucose tolerance, insulin sensitivity and pancreatic function

We found low-level evidence for an association between sun exposure and fasting insulin levels; fasting serum insulin was higher in summer than in winter.[25] Unadjusted analyses from ineligible articles are less conclusive. Fasting insulin levels peaked in the warmer, lighter months, and although not significant, this is in line with the findings reported in this review.[24] Others

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Table 2. Description of studies assessed as having high-quality outcomes and a summary of their associations, presented by outcome type*

First Author *et al.*, year of publication (ref)	Study location, Year(s) of study	Study design (L, CS), Source of participants	Sample size, Percentage, Female	Age (years), Mean (SD) or range	Sun exposure measure(s)	Diabetes outcome measure		Control for confounding variables	Summary of associations between outcome and exposure†
						Outcome	Ascertainment		
T2DM									
Lindqvist *et al.* (2010)[17]	Sweden, Baseline: 1990–1992 Follow-up: 2000–2002	L Population-based cohort study: Melanoma Inquiry of Southern Sweden Study	*n* = 23 962 (537 cases) 100%	25–64	Self-reported recreational and occupational sun exposure (including sun bed use)	T2DM Incidence	Self-reported cross-checked with national and hospital registries	Age Analysis restricted to women	Decreased odds of developing T2DM given: Sunbathing during summer [OR = 0·5 (95% CI: 0·4–0·6)] Sunbathing during winter vacation [OR = 0·5 (95% CI: 0·3–0·6)] Sunbathing during vacation abroad [OR = 0·7 (95% CI: 0·6–0·8)] Sun bed use [OR = 0·7 (95% CI: 0·5–0·8)] No difference detected in the odds for developing T2DM given working outdoors during summer. [OR = 1·1 (95% CI: 0·9–1·3)]
								Age, BMI Analysis restricted to women	Decreased odds of developing T2DM given: Sunbathing during summer [OR = 0·6 (95% CI: 0·5–0·8)] Sunbathing during winter vacation [OR = 0·6 (95% CI: 0·4–0·8)] Sun bed use [OR = 0·7 (95% CI: 0·6–0·9)] No difference detected in the odds for developing T2DM given: Sunbathing during vacation abroad [OR = 0·8 (95% CI: 0·7–1·0)] Working outdoors during summer [OR = 1·0 (95% CI: 0·8–1·2)]
								Age, BMI, education level, parity, oral contraceptive use Analysis restricted to women	Decreased odds of developing T2DM given: Sunbathing during summer [OR = 0·7 (95% CI: 0·5–0·9)] Sunbathing during winter vacation [OR = 0·7 (95% CI: 0·5–0·9)] Sun bed use [OR = 0·8 (95% CI: 0·6–0·9)] No difference detected in the odds for developing T2DM given: Sunbathing during vacation abroad [OR = 0·9 (95% CI: 0·7–1·0)] Working outdoors during summer [OR = 1·0 (95% CI: 0·8–1·2)]
								Age, BMI, smoking status, physical exercise Analysis restricted to women	Decreased odds of developing T2DM given: Sunbathing during summer [OR = 0·6 (95% CI: 0·5–0·8)] Sunbathing during winter vacation [OR = 0·6 (95% CI: 0·5–0·9)] Sun bed use [OR = 0·7 (95% CI: 0·6–0·9)] No difference detected in the odds for developing T2DM given Sunbathing during vacation abroad [OR = 0·8 (95% CI: 0·7–1·0)] Working outdoors during summer [OR = 1·0 (95% CI: 0·8–1·0)]

(continued)

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Table 2. (continued)

First Author *et al.*, year of publication (ref)	Study location, Year(s) of study	Study design (L, CS), Source of participants	Sample size, Percentage, Female	Age (years), Mean (SD) or range	Sun exposure measure(s)	Diabetes outcome measure		Control for confounding variables	Summary of associations between outcome and exposure†
						Outcome	Ascertainment		
Fasting glucose									
Berglund *et al.* (2012)[10]	Sweden, 1991–1995	CS Population-based cohort study: The Uppsala Longitudinal Study of Adult Men	*n* = 1117 (winter: *n* = 810, summer: *n* = 307) 0%	71 (0)‡	Season (winter *vs* summer)	Fasting glucose (log function)	Fasting plasma glucose	Age Analysis restricted to men	No difference detected between fasting glucose levels in summer compared with winter: ($P = 0{\cdot}28$)
Chen *et al.* (2006)[20]	Taiwan 2000–2003	CS Community based cross-sectional study: recruitment from five Kinmen townships	*n* = 7938 (winter: *n* = 5577, summer: *n* = 2361) 57%	57·1 (11·9)	Season (winter *vs* summer)	Impaired fasting glucose	Fasting plasma glucose ≥ 110 mg/dl	Unadjusted	Higher prevalence of impaired fasting glucose in winter compared with summer: [OR = 1·6 (95% CI: 1·5–1·8)
								Age, sex, BMI	Higher prevalence of impaired fasting glucose in winter compared with summer: [OR = 1·6 (95% CI: 1·4–1·8)]
								Age, sex, BMI, alcohol, smoking, PA, seafood, visceral food, fish, education	Higher prevalence of impaired fasting glucose in winter compared with summer: [OR = 1·6 (95% CI: 1·4–1·8)]
								Age, sex, BMI, alcohol, PA, seafood, fish, education, high blood pressure, low HDL-C, hypertriglyceridemias	Higher prevalence of impaired fasting glucose in winter compared with summer: [OR = 1·6 (95% CI: 1·4–1·9)]
Mavri *et al.* (2001)[14]	Slovenia, Recruited: 2001 Follow-up: <1 year	L Institution based case-control study: recruitment from hospital medical staff and through disease registry	*n* = 82 40%	30–62	Season (categorical)	Fasting glucose	Fasting serum glucose	Sex	In participants free of CAD: Higher fasting glucose levels in the cold months compared with the warmer months: ($P < 0{\cdot}003$) In AMI survivors: Higher fasting glucose levels in the cold months compared with the warmer months: ($P < 0{\cdot}001$) In all participants: Higher fasting glucose levels in the cold months compared with the warmer months: ($P < 0{\cdot}0001$)
Suarez *et al.* (1982)[21]	United States of America, 1972–1984	CS Community based cross-sectional study: recruitment from California	*n* = 4541 55%	20–79	Season (categorical)	Fasting glucose	Fasting plasma glucose	Age, BMI Analysis stratified by sex	Highest fasting glucose levels in winter, lowest in spring compared with other seasons: ($P < 0{\cdot}0001$)
Glucose tolerance									
Berglund *et al.* (2012)[10]	Sweden, 1991–1995	CS Population-based cohort study: The Uppsala Longitudinal Study of Adult Men	*n* = 1117 (winter: *n* = 810, summer: *n* = 307) 0%	71 (0)‡	Season (winter *vs* summer)	2-hour postload glucose (log function)	Plasma glucose 2 h after 75 g-OGTT glucose load	Age Analysis restricted to men	No difference detected between 2-h postload glucose levels in summer compared with winter: ($P = 0{\cdot}58$)
Fasting insulin									
Chen *et al.* (2008)[25]	Taiwan, 2000–2003	CS Community based cross-sectional study: recruitment from Kin-Chen, Kinmen	*n* = 2175 (winter: *n* = 1492, summer: *n* = 683) 55%	55·4 (11·3)	Season (winter *vs* summer)	Fasting insulin (log function)	Fasting serum insulin	BMI, systolic blood pressure, HDL-C, triglycerides, fasting plasma glucose, uric acid, smoking, alcohol drinking	Higher fasting insulin levels in summer compared with winter: ($P < 0{\cdot}0001$) Regression coefficient: $\beta = -0{\cdot}2052$, Partial $R^2 = 0{\cdot}0460$

(continued)

Table 2. (continued)

First Author *et al.*, year of publication (ref)	Study location, Year(s) of study	Study design (L, CS), Source of participants	Sample size, Percentage, Female	Age (years), Mean (SD) or range	Sun exposure measure(s)	Diabetes outcome measure		Control for confounding variables	Summary of associations between outcome and exposure†
						Outcome	Ascertainment		
Insulin secretion									
Berglund *et al.* (2012)[10]	Sweden, 1991–1995	CS Population-based cohort study: The Uppsala Longitudinal Study of Adult Men	*n* = 1117 (winter: *n* = 810, summer: *n* = 307) 0%	71 (0)‡	Season (winter *vs* summer)	Insulin Secretion (square-root function)	AUC-insulin during 2-h 75 g-OGTT	Age Analysis restricted to men Age, BMI, WC, energy intake, vitamin D, smoking, glucose tolerance state (T2DM, IGT, or NGT), medication (oral hypoglycaemic agents and antihypertensives), PA Analyses restricted to men Age, M\I Analyses restricted to men	Greater insulin secretion in winter compared with summer: (P = 0·007) Greater insulin secretion in winter compared with summer: (P = 0·024) No difference detected between AUC-insulin in summer compared with winter: (P = 0·30)
Insulin sensitivity									
Berglund *et al.* (2012)[10]	Sweden, 1991–1995	CS Population-based cohort study: The Uppsala Longitudinal Study of Adult Men	*n* = 1117 (winter: *n* = 810, summer: *n* = 307) 0%	71 (0)‡	Season (winter *vs* summer)	Insulin Sensitivity Index (M\I, square-root function)	Euglycaemic insulin clamp	Age Analysis restricted to men Age, BMI, WC, energy intake, vitamin D, smoking, glucose tolerance state (T2DM, IGT, or NGT), medication (oral hypoglycaemic agents and antihypertensives), PA Analyses restricted to men	Greater insulin sensitivity in summer compared with winter: (P = 0·0003) Greater insulin sensitivity in summer compared with winter: (P = 0·0006)
Chen *et al.* (2008)[25]	Taiwan, 2000–2003	CS Community based cross-sectional study: recruitment from Kin-Chen, Kinmen	*n* = 2175 (winter: *n* = 1492, summer: *n* = 683) 55%	55·4 (11·3)	Season (winter *vs* summer)	Insulin resistance (HOMA-IR, log function)	Fasting plasma glucose and serum insulin	BMI, systolic blood pressure, triglycerides, FPG (Age, sex, HDL-C, cholesterol, uric acid, smoking, alcohol drinking and PA not significant in stepwise regression modelling)	Greater insulin resistance in summer compared with winter: (P < 0·0001) Regression coefficient: β_2 = −0·1538, Partial R^2 = 0·0214
Isken *et al.* (2011)[13]	Germany, 2002–2009	CS Population-based cohort study: The Metabolic-Syndrome-Berlin-Potsdam (MeSyBePo) Cohort Study	*n* = 2385 NR	51·9 (0·3)	Semi-annual change: January to June *vs* July to December	Insulin sensitivity (HOMA-%S, log function)	Fasting serum glucose and insulin	Age, sex, BMI, WHR, T2DM status, chronic drug use, smoking habit	Greater insulin sensitivity in the second half of the year (two-thirds of summer, all of autumn and one-third of winter) compared with the first half of the year: (P = 0·0008) Regression coefficient: β = 0·06, R^2 = 0·35

AMI, Acute myocardial infarction; AUC, Incremental area under the curve; BMI, body mass index; CAD, Coronary artery disease; CS, Cross-sectional; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; HOMA-%S, insulin sensitivity index (homeostasis model insulin sensitivity derived from fasting insulin and fasting glucose levels); HOMA-IR, insulin resistance index (homeostasis model of insulin resistance: a normalized product of fasting insulin and fasting glucose levels); IGT, impaired glucose tolerance; L, longitudinal; M\I, insulin sensitivity index (glucose disposal rate divided by mean plasma insulin concentration during euglycaemic insulin clamp); NGT, normal glucose tolerance; NR, not reported; OGTT, oral glucose tolerance test; PA, physical activity; SD, standard deviation; T2DM, Type 2 diabetes mellitus; WHR, waist to hip ratio.

*Other eligible studies not meeting the criteria for high-quality outcomes are not presented (HOMA-IR,[10] random glucose,[11] HbA1c,[12] ISI-Matsuda,[13] T2DM,[10] IGT,[10] and fasting insulin[14]).

†*P*-value or odds ratio (OR) with 95% confidence interval (95% CI) presented.

‡Participants, born between 1920 and 1924, were all 71 years of age.

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Table 3. Grading of level of evidence across analogous outcomes

Consistency*	Directness*	Level of quality of evidence*
Consistent	Direct	High
	Indirect	Moderate
Unknown (single study)	Direct	Moderate
	Indirect	Low
Inconsistent	Direct	Insufficient
	Indirect	Insufficient

*As defined by Owens *et al.*[16]

found fasting insulin to be increased in autumn.[22,23] While overall the results are inconclusive, we believe that the adjustments made by the included study – particularly for BMI – have led to a more accurate representation of the association between sun exposure and fasting insulin, suggesting that sun exposure increases fasting insulin levels. However, this review also presents low-level evidence suggesting that sun exposure decreases insulin secretion following glucose loading with a 2-h 75 g-oral glucose tolerance test (OGTT).[10] An unadjusted analysis shows the same pattern, with insulin secretion increasing dramatically in the colder, darker months and decreasing again in the warmer, lighter months.[24] We found little evidence to support any association between sun exposure and postload glucose levels. There were equivalent plasma glucose levels following a 2-h 75 g-OGTT in summer compared with winter.[10]

Evidence for an association between sun exposure and insulin sensitivity is lacking. Although the findings seem contradictory, results using three different measurements may be describing different underlying phenomena related to sun exposure: an increase in hepatic insulin resistance (measured using HOMA-IR)[25] *vs* an increase in whole body insulin sensitivity (which is mainly reflective of insulin sensitivity of muscle, measured using M/I; glucose disposal rate divided by mean plasma insulin concentration during euglycaemic insulin clamp).[10] Otherwise, these differences may be due to variability in control for confounders. The temporal division of the year employed as the exposure variable by Isken *et al.*[13] (January to June *vs* July to December) is likely to capture medium-term changes in HOMA-%S[13] caused by sun exposure. These changes may be due to vitamin D production, with the increase in insulin sensitivity during the latter two-thirds of summer and into the first third of winter being due to a six-eight week lag in 25OHD levels following sun exposure[26] or to medium-term immunological effects. Photoimmunomodulation involves many complex pathways with much left undiscovered, so the possible role of immunology is not well understood. An unadjusted analysis reported no seasonal pattern in insulin sensitivity index (Si; from the frequently sampled, intravenous glucose tolerance test) according to a sine curve-based model.[27] These results may be limited by the model specifications (for example cycle length), or due to a lack of adjustment for confounding variables, such as age and body mass index (BMI). Overall, findings from these three articles raise questions regarding the pathways through which sun could act to influence insulin sensitivity, highlighting the importance of exploring the possibility of differential effects in organs and in tissues (particularly the pancreas, liver, adipose tissue and skeletal muscle).

Discussion

Higher serum 25OHD has been associated with a lower risk of T2DM in many prospective observational studies, including our own.[28] This strong inverse association has been reinforced by two meta-analyses which compared T2DM incidence between the highest and the lowest categories of 25OHD [OR: 0·67 (95% CI: 0·57–0·75)[4] and RR: 0·62 (95% CI: 0·54–0·70)[3]]. Summary effect measures were not materially altered in sensitivity analyses in which individual studies were removed,[3,4] or by adjustment for confounders.[3] Song *et al.*[3] went on to show that each 10 nmol/l increment in 25OHD conferred a 4% lower risk of developing T2DM. While prospective observational studies present strong evidence for an inverse association between 25OHD and T2DM, results from vitamin D supplementation trials have

Table 4. Final synthesis presenting the level of quality of evidence for each outcome type

Outcome type	Causal directness* between exposure and outcome measures	Consistency* across outcomes	Level of Quality of Evidence*	Direction of Association
T2DM incidence	Direct	Unknown†	Moderate	↓
Fasting glucose	Indirect	Inconsistent	Insufficient	Not applicable
Glucose tolerance	Indirect	Unknown†	Low	No association
Fasting insulin	Indirect	Unknown†	Low	↑
Insulin secretion	Indirect	Unknown†	Low	↓
Insulin sensitivity	Indirect	Inconsistent	Insufficient	Not applicable

T2DM, Type 2 diabetes mellitus.
*As defined by Owens *et al.*[16]
†Consistency across the outcome type cannot be determined as only one outcome exists in the category.

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been inconclusive.[2] As sun exposure yields the majority of our serum 25OHD, supplementation trials may be overlooking other pathways through which sun exposure may influence T2DM-related outcomes. Briefly, these pathways are reviewed:

Circadian rhythm

Sunlight, primarily in the blue light spectrum, is the primary external time cue. It synchronizes a wide range of complex biological processes via neurological pathways, through the central nervous system and into peripheral tissues. Circadian rhythm is rigidly controlled in pancreatic islet cells,[29] and the circadian clock machinery has been found to regulate glucose sensing, insulin gene expression and insulin secretion.[29,30] Indeed, various mutations in circadian clock machinery lead to hyperglycaemia, hypoinsulinaemia and reduced beta-cell mass[29,31] and have been associated with T2DM.[32] Insulin sensitivity also displays circadian rhythmicity in skeletal muscle.[33] Melatonin, the key neurohormone regulating circadian rhythm, is directly responsive to sunlight and has been found to reduce insulin secretion[34,35] and to improve insulin sensitivity and glucose tolerance.[36] Given that sunlight is the primary time cue, this research suggests that sunlight ultimately moderates glucose metabolism through circadian rhythm alterations involving neuroendocrine pathways.

Photoimmunomodulation

Ultraviolet radiation exposure of the skin may also influence T2DM-related outcomes via suppression of pro-inflammatory and upregulation of anti-inflammatory immune processes. These immunoregulatory and anti-inflammatory qualities may have a role in reducing the chronic systemic inflammation which is frequently observed in T2DM. UVR exposure has well-characterized effects on the immune system.[37,38–42] Briefly, UVR is absorbed by chromophores in the skin such as DNA, lipids, 7-dehydrocholesterol and urocanic acid. UVR-induced damage following both suberythemal and erythemal doses of UVR[43] results in the migration of UVR-damaged antigen presenting cells (dermal dendritic cells[44] and Langerhans cells[45,46]) to local lymph nodes where they present antigen in a defective manner,[47] inducing antigen-specific immune tolerance (regulatory T cells which modify immune reactivity to a particular antigen).[47,48] UVR exposure to the skin induced tolerance to self-antigens in clinically diagnosed T2DM[49] and therefore may be important in reducing immunological and inflammatory aspects of T2DM.

To our knowledge, two interventions examined the effect of UVB exposure to the skin on T2DM-related outcomes in humans.[50,51] UVA and (independently) UVB were shown to have no significant effect on glucose or insulin levels in one study,[50] whereas the other reported an increase in glucagon-induced insulin secretion following the administration of UVB.[51] In contrast, our findings suggest that sun exposure may have the opposite effect on insulin secretion. This may be due to differences in study design including the UV spectrum of the delivered dose, intervention compared with observation, UVB radiation exposure coupled with glucagon administration compared with summer and winter values post-2-h OGTT. Many answers regarding the potential role of photoimmunoregulation in the development of T2DM remain to be revealed.

Temperature, Thermogenesis and Cellular Stress

Although vitamin D production is enhanced by an increase in skin temperature,[52,53] heat from the sun may initiate small changes in glucose metabolism independently of vitamin D production. Heat has been linked to improvement in peripheral insulin sensitivity[54] and has been suggested as a possible therapy in T2DM for decreasing fasting plasma glucose.[55] Heat induces vasodilatation in peripheral tissues including skeletal muscle, thus increasing perfusion with circulating factors, including glucose and insulin. Additionally, heat treatment has been shown to moderate insulin resistance instigated with a high-fat diet.[54] This mechanism might play a role in the potentially differential effects of sun exposure on hepatic and peripheral glucose uptake, by affecting peripheral uptake. While pathologic mechanisms underlying this response remain uncertain, it is known that excessive heat (from sun exposure or other sources) induces a stress response involved in adaptation pathways, with amplification of heat-shock proteins aiding the ability to adapt to various biological pressures. These heat-shock proteins may be involved in glucose and lipid oxidation[56] and may therefore influence glucose metabolism in peripheral tissues. Diabetic individuals in regions with large summer–winter differences experience seasonal changes in HbA1c values wherein HbA1c levels were reduced in summer.[57]

Cold temperature may also affect glycaemia. Cold-activated brown adipose tissue (BAT) plays a crucial role in nonshivering thermogenesis and has been identified in humans.[58] Following transplantation of BAT in mice, glucose tolerance and insulin sensitivity were improved, body weight and fat mass were reduced, and insulin resistance stemming from high-fat feeding was completely attenuated.[59] BAT biology sits at the intersection between temperature, photoperiod (day/night length) and diet-related features of circadian rhythm, and glucose metabolism. BAT activity increases in the colder, darker winter period.[60] *Rev-erbα*, a cellular clock protein, controls this circadian response to cold temperature and also glucose uptake in BAT.[61] Finally, melatonin may act via 'browning' of adipose to exert its effect on metabolism and weight loss.[62] Through coupling of the circadian and temperature effects of sun exposure on BAT biology, BAT may help protect against T2DM development. Sun exposure may be involved in the development of T2DM through temperature changes, BAT activity and cellular stress responses.

Taken in context, we suggest that sun exposure may prevent T2DM development through circadian control of endocrine and metabolic processes, regulation of immune processes, cellular stress, temperature changes and BAT activity. However, the reviewed papers did not directly measure markers of circadian modulation, photoimmunomodulation, temperature, BAT activity or cellular stress as products of sun exposure; season was the common exposure variable in these articles.

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Sun exposure measurements

We advise caution in the interpretation of these findings, given that time-of-year variants were the predominant sun exposure variable in eligible articles. Season is a social construct (not directly observable) which is perceived and labelled differently by societies across the world, tying a sense of temporality to climate and environmental changes. It is an operational definition encompassing many features, not just sun exposure. Although season may reflect available radiation from the sun as well as personal sun exposure, it is likely to also be measuring changes in other factors including diet, metabolism, adaptive behaviour (including clothing worn and physical activity levels) and even other biological substances which display cyclic rhythms such as adiponectin[63]. Notably then, sun exposure could be the primary driver of seasonal physiological changes including modification in glucose and insulin metabolism.

Future prospective cohort studies might employ longitudinal study designs and large sample sizes and measure sun exposure directly, at the level of the individual, whether by self-report, ambient UVR, personal UVR dosimeters or some combination thereof. Advancing research into pathways other than through vitamin D synthesis would also be invaluable. We encourage investigations into the epidemiologic and mechanistic relationships between sun exposure and T2DM-related outcomes.

Sun exposure and T2DM-related outcomes

The present review examined the potential effects of sun exposure, as distinct from vitamin D status, on T2DM-related outcomes. We found moderate evidence that recreational sun exposure reduces odds of T2DM incidence and low-level evidence to suggest that sun exposure affects fasting insulin and insulin secretion.

A previous study has postulated that sun exposure protects against the development of T2DM through raising serum 25OHD levels.[7] Here, we hypothesize that sun exposure protects against the development of T2DM via pathways additional to the increase in 25OHD. Our findings suggest that sun exposure may decrease fasting glucose levels by increasing fasting insulin levels, thereby stimulating glucose uptake. This may be coupled with a reduction in systemic inflammation and oxidative stress in target tissues and organs (e.g. pancreas, muscle, liver and adipose), reviewed by Lamb and Goldstein.[64] Evidence presented here suggests that sun exposure may decrease insulin secretion following glucose loading. This was unexpected as it contradicts results from two studies linking vitamin D with increased insulin secretion,[51,65] in one of which there was an increase in glucagon-induced insulin secretion following UVB exposure.[51] Perhaps, the smaller quantum of insulin required in response to glucose loading, noted in this review, was a product of the increased fasting insulinaemia observed during summer. Postload glucose levels may in turn be stabilized throughout the year as increased fasting insulinaemia is then compensated for by a reduction in postload insulin secretion during summer. Our findings also suggest a differential effect of sun exposure on insulin sensitivity in muscle compared with liver, an increase in insulin sensitivity in muscle *vs* a decrease in insulin sensitivity in hepatic insulin sensitivity with greater sun exposure.

Methodological strengths and limitations

A major strength of this review is the systematic search for eligible articles, conducted in two electronic databases, with three researchers investigating the search output. Secondly, reference lists of eligible articles were searched by title, abstract and in full to capture additional eligible articles. Thirdly, the assessment of risk of bias, precision and overall plausibility was conducted at the outcome level, rather than the study level, using validated items from a databank created for this purpose.[9] Finally, only high-quality outcomes were selected for inclusion in the best evidence synthesis.

This review is subject to some methodological limitations. Publication bias was not addressed: (i) the studies reviewed were primarily from North America, Europe and Asia, so many other ethnic groups and climate settings were not included; (ii) grey literature, including conference abstracts, was excluded, potentially creating a bias in this review towards positive associations and publications from established researchers (more likely to be published in full-text articles); and (iii) articles published in languages other than English were excluded.

Limitations based on included studies

The two predominant limitations were that articles typically employed cross-sectional analysis methods and used time-of-year measurements to represent sun exposure. These design features are problematic: causality is harder to infer from cross-sectional studies compared with longitudinal studies, and time-of-year is a suboptimal sun exposure measurement. Furthermore, poor reporting or lack of transparency in the reporting meant that many studies were evaluated as having an 'unclear risk' for several risk of bias domains. Finally, physical activity is an important confounder which may have contributed to spurious associations due to being difficult to measure accurately and precisely and not being controlled for in many studies.

Conclusions

This review highlights significant gaps in health research pertaining to sun exposure and type 2 diabetes mellitus; literature on sun exposure and type 2 diabetes mellitus-related outcomes is sparse. Findings presented demonstrate with moderate-level evidence that recreational sun exposure protects against the development of type 2 diabetes mellitus. Ideally, additional epidemiologic studies would explore this association between sun exposure and type 2 diabetes mellitus incidence to make meta-analysis feasible. Further research to delineate pathways through which sun exposure might influence type 2 diabetes mellitus-related outcomes is important, as sun exposure represents a

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potentially inexpensive and relatively simple method for type 2 diabetes mellitus prevention.

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Conflicts of interest

CS-L wishes to declare a scholarship from CRESH. Other authors declare no conflict of interest.

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