Institutet för miljömedicin - IMM

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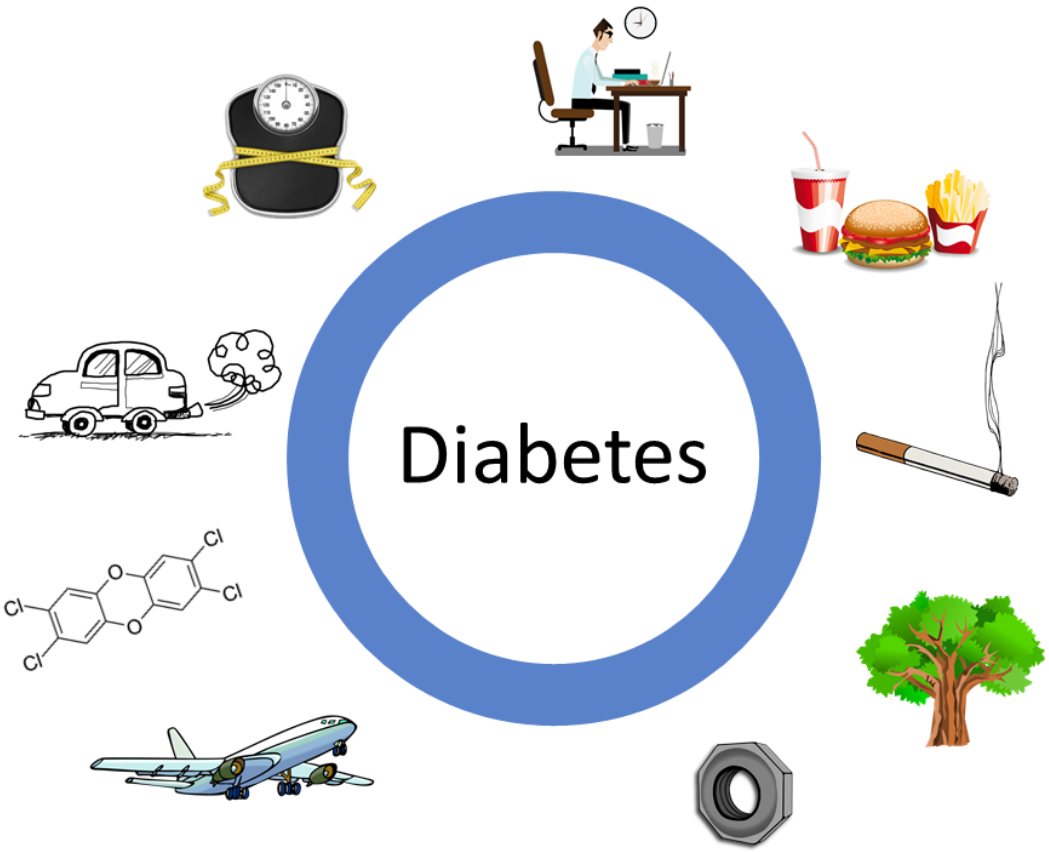
Environmental and lifestyle factors related to development of diabetes

Miljöfaktorer och levnadsvanor relaterade till utvecklandet av diabetes

IMM
Institute of Environmental Medicine
Institutet för miljömedicin

Karolinska Institutet

ENVIRONMENTAL AND LIFESTYLE FACTORS RELATED TO DEVELOPMENT OF DIABETES



MILJÖFAKTORER OCH LEVNADSVANOR RELATERADE TILL UTVECKLANDET AV DIABETES

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PREFACE

This report summarizes existing research on the relationship between lifestyle, environmental factors and the risk of diabetes. The report is prompted by an increased interest in the possible importance of environmental factors in the development of diabetes. Our emphasis is on type 2 diabetes, which is the most common form of diabetes, and the diabetes type most extensively researched. In addition, the more limited research on the influence of lifestyle and the environment for development of autoimmune forms of diabetes, such as type 1 diabetes and LADA (latent autoimmune diabetes in adults), is discussed. Lifestyle factors covered by the report include obesity, physical activity, tobacco use and dietary habits and among environmental factors we have included environmental chemicals, metals, noise, air pollution, and green environments. In addition, infections are discussed in relation to autoimmune diabetes. The aim of the report is to summarize current knowledge in the area and to point at knowledge gaps and further research needs. The report is published by the Institute of Environmental Medicine (IMM), a department at Karolinska Institutet where research is conducted on the influence of the environment on disease development. IMM also provides Swedish authorities with expertise in environmental health risk assessment. The report is authored by researchers active at IMM in the areas of lifestyle, environmental factors, and diabetes. Diabetes is a very common disease and the prevalence is increasing in Sweden as well as globally. Knowledge about the influence of lifestyle and environmental factors on diabetes risk is important as these factors are potentially modifiable and may be targeted in the prevention of diabetes.

FÖRORD

I denna rapport sammanfattas befintlig forskning kring sambandet mellan levnadsvanor, miljöfaktorer och risken för diabetes. Rapporten föranleds av ett ökat intresse kring den möjliga betydelsen av miljöfaktorer vid utvecklandet av diabetes. Tonvikten ligger på typ 2-diabetes som är den vanligaste formen av diabetes, för vilken kunskapsunderlaget också är mest omfattande. Utöver detta diskuteras den mer begränsade forskningen kring betydelsen av levnadsvanor och miljö för utvecklandet av autoimmuna former av diabetes som typ 1-diabetes och LADA (latent autoimmun diabetes hos vuxna). Till levnadsvanor som berörs i rapporten hör övervikt, fysisk aktivitet, tobaksbruk och kostvanor och bland miljöfaktorer behandlas vissa kemikalier, metaller, luftföroreningar, buller, samt mängden grönska i närområdet. Betydelsen av infektioner diskuteras också i relation till autoimmun diabetes. Syftet är att ge ett kunskapsunderlag samt peka på kunskapsluckor där behovet av ytterligare forskning är särskilt stort. Rapporten är skriven på engelska för att göra den tillgänglig för en internationell publik. En omfattande svensk sammanfattning finns på sidorna 7-12. Rapporten är utgiven av Institutet för Miljömedicin (IMM), en institution vid Karolinska Institutet där man bedriver forskning kring miljöns betydelse för sjukdomsutveckling. IMM är också ett nationellt expertorgan inom miljömedicinsk riskbedömning. Medverkar i rapporten gör flera av IMM:s forskare verksamma inom forskning kring miljöfaktorer, levnadsvanor och diabetes. Diabetes är en mycket vanlig sjukdom vars förekomst ökar i Sverige liksom i resten av världen. Kunskap om hur levnadsvanor och miljöfaktorer påverkar risken att utveckla diabetes är viktig eftersom dessa faktorer går att påverka och därmed kan bidra till att minska insjuknandet.

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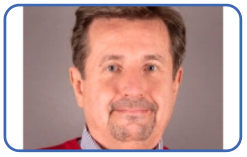

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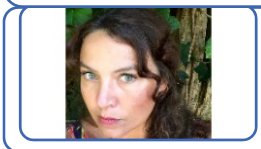

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SAMMANFATTNING

BAKGRUND

Diabetes är vanlig sjukdom vars förekomst ökar världen över. I Sverige har 8 % av den vuxna befolkningen diabetes och förekomsten spås öka till 10 % år 2050. Den ökande diabetesförekomsten drivs i första hand av en åldrande befolkning samt förbättrad överlevnad bland personer som drabbats av diabetes. Diabetes ökar risken för allvarliga sjukdomar som hjärtinfarkt, stroke och förtida död. Sjukdomen leder inte bara till lidande för den enskilde utan medför också höga och stigande samhällskostnader för vård och produktionsbortfall.

Diabetes är ett samlingsnamn för en grupp metabola sjukdomar som alla kännetecknas av en oförmåga att hålla blodsockernivåerna på en jämn nivå, men där flera olika sjukdomsmekanismer kan vara involverade. Kroniskt förhöjda blodsockernivåer ger på sikt skador i nerver och blodkärl. Typ 2-diabetes är den vanligaste diabetesformen och svarar för >85 % av alla fall. Sjukdomen orsakas av en kombination av nedsatt insulinkänslighet, s.k. insulinresistens, och defekt insulinfrisättning. Den drabbar i första hand vuxna och risken ökar kraftigt med stigande ålder. Typ 1-diabetes är en autoimmun sjukdom som orsakas av att det egna immunförsvaret förstör de insulinproducerande beta-cellerna. Detta resulterar i irreversibel insulinbrist och sjukdomen kräver därför livslång insulinbehandling. Typ 1-diabetes står för 99 % av all diabetes hos barn men kan utvecklas i alla åldrar. LADA (latent autoimmune diabetes hos vuxna) är den vanligaste formen av autoimmun diabetes hos vuxna. Den autoimmuna processen vid LADA är mildare än vid typ 1-diabetes och sjukdomen har även drag av typ 2-diabetes eftersom nedsatt insulinkänslighet bidrar till sjukdomsutvecklingen. Risken att drabbas av typ 2-diabetes är hög, enligt en studie kommer en av fem svenskar att drabbas, men befintlig litteratur ger inte stöd för att risken ökar i Sverige. Risken för typ 1-diabetes bland barn är låg, i Sverige drabbas fyra per 10 000 barn årligen, men risken har fördubblats de senaste 20 åren. Förändringar i miljö eller levnadsvanor antas ligga bakom ökningen, men det är inte klarlagt vilka faktorer det rör sig om. Huruvida autoimmun diabetes hos vuxna blir vanligare är inte känt.

Både typ 2-diabetes och autoimmuna former av diabetes orsakas av en kombination av genetiska och miljömässiga faktorer. Man vet att livsstilsfaktorer, i första hand övervikt och stillasittande har stor betydelse för utvecklandet av typ 2-diabetes och det har också kunnat visas att det är möjligt att förebygga sjukdomen genom förändrade levnadsvanor. Vid sidan av kända riskfaktorer har man på senare år diskuterat om miljöfaktorer som kemikalier, vissa metaller, luftföroreningar, buller och gröna miljöer också kan påverka utvecklandet av typ 2-diabetes men här är kunskapsunderlaget mer begränsat. Om och hur levnadsvanor och miljöfaktorer påverkar den autoimmuna reaktion som leder till typ 1-diabetes och LADA vet man betydligt mindre om. Syftet med denna rapport är att summera befintlig kunskap baserat på i första hand epidemiologiska studier om miljö och levnadsvanors inverkan på typ 2-diabetes, typ 1-diabetes och LADA, identifiera kunskapsluckor samt peka på framtida forskningsbehov och metodologiska utmaningar.

LEVNADSVANOR

Resultat från ett stort antal epidemiologiska studier från olika delar av världen visar att övervikt, stillasittande, tobaksbruk och låg födelsevikt är förenat med en ökad risk för typ 2-diabetes. Dessa faktorer tycks primärt öka risken för diabetes genom att de leder till ökad insulinresistens. Sjukdomen är vanligare bland personer med låg socioekonomisk status, vilket till stor del förklaras av att man har högre förekomst av övervikt och andra riskfaktorer. I interventionsstudier har man bekräftat att det går att minska risken för typ 2-diabetes radikalt genom livsstilsförändringar som leder till viktminskning och ökad fysisk aktivitet. Övervikt är den enskilt viktigaste riskfaktorn och tycks svara för uppemot 80 % av alla fall. Särskilt hög risk har en person med både ärftlighet för diabetes och övervikt. När det gäller typ 1-diabetes hos barn ger befintliga studier delvis motsägelsefulla resultat och det är inte klarlagt hur miljöfaktorer påverkar utvecklandet av den autoimmuna reaktion som ger upphov till sjukdomen. Till de mest konsistenta fynden hör en ökad risk bland barn som exponerats för virusinfektioner, antingen perinatalt eller som barn, samt övervikt hos barnet. Forskning kring autoimmun diabetes hos vuxna är begränsad men det finns stöd för att faktorer med inverkan på insulinkänsligheten som övervikt och stillasittande även ökar risken för LADA. Att övervikt tycks vara en riskfaktor både för typ 2-diabetes och autoimmun diabetes är särskilt allvarligt eftersom andelen överviktiga barn och vuxna stiger världen över.

KOST

Det är väl belagt att kosten har betydelse för utvecklandet av typ 2-diabetes, främst genom det totala energiintaget, eftersom ett överskott av energi kan leda till övervikt som i sig är starkt kopplad till diabetesrisken. Kostens kvalitet är emellertid också av betydelse, då det visats att vissa kostfaktorer har direkta effekter på diabetesrisken genom påverkan på insulinkänslighet och/eller beta-cellsfunktion. Sockersötade drycker, såsom läsk, och rött kött, särskilt processade produkter såsom korv och bacon, är de enskilda kostfaktorer som med starkast evidens kopplats till ökad risk för typ 2-diabetes. När det gäller skyddande faktorer så har man i flertalet studier sett en lägre risk för typ 2-diabetes bland individer med högt intag av fullkorn. Även kaffeintag har konsekvent kopplats till minskad risk. Allt vi äter påverkar oss på olika sätt och därför är studier där man ser till kostens hela sammansättning viktiga. Det kostmönster som med starkast evidens har kopplats till minskad diabetesrisk är den så kallade medelhavskosten. I både interventionsstudier och epidemiologiska studier har man sett att individer som i hög utsträckning äter enligt detta kostmönster har lägre risk för diabetesinsjuknande. Medelhavskost karaktäriseras generellt av ett högt intag av nötter, olivolja och andra källor till omättade fetter, grönsaker, frukt, fisk och skaldjur och ett måttligt alkoholintag, men ett begränsat intag av rött kött och mejeriprodukter (med hög fetthalt). I relation till våra nationella rekommendationer så äter vi i Sverige generellt för lite frukt, grönsaker, fisk, fullkorn och kostfibrer. Samtidigt har vi ett högt intag av exempelvis läsk och saft. Genom att i större utsträckning följa de nationella kostråden i Sverige skulle även risken för typ 2-diabetes kunna minskas i befolkningen. Kostens roll i utvecklandet av autoimmun diabetes är betydligt mindre känd. Ett flertal kostfaktorer har föreslagits påverka utvecklandet av typ 1-diabetes hos barn, men kunskapsunderlaget är fortfarande begränsat och etablerade samband saknas. För LADA finns endast ett fåtal studier, men dessa indikerar att kosten kan ha betydelse. Det är därför mycket viktigt att fortsätta kartlägga kostens roll i utvecklandet av autoimmun diabetes för att på sikt bidra till att förebygga sjukdomen.

MILJÖKEMIKALIER

Flera kemikalier (både persistenta och icke-persistenta) och kemikaliegrupper har rapporterats kunna bidra till ökad diabetesrisk, bland annat dioxiner, polyklorerade bifenyler (PCB), klorerade bekämpningsmedel, perfluorerade föreningar (PFAS), bromerade föreningar, bisfenoler och ftalater. Vi bedömer att det epidemiologiska underlaget är tillräckligt för att dra slutsatsen att exponering för PCBer – speciellt de dioxinlika – och vissa klorerade bekämpningsmedel är kopplade till ökad risk för typ 2-diabetes. För PFAS, bromerade föreningar, bisfenoler och ftalater är epidemiologiska data ännu alltför begränsade för att dra starka slutsatser. För bisfenoler och ftalater bidrar den korta halveringstiden i kroppen till osäkerhet i exponeringsmätningen, vilket komplicerar bedömningen av eventuella samband i epidemiologiska undersökningar, även om experimentella data ger starkare stöd. Det finns en relativt stor mängd experimentella studier som ger kunskap om potentiella mekanismer genom vilka kemikalier kan bidra till utvecklingen av diabetes. En möjlig mekanism som är biologiskt trolig och som stöds väl av empiriska bevis är störd mitokondriell funktion och ökad produktion av reaktiva syreradikaler (ROS) som leder till oxidativ stress och skador på bukspottkörtelns insulinproducerande beta-celler. Andra möjliga mekanismer är till exempel störning av signalvägar under fostrets utveckling som leder till effekter på beta-cellers massa och funktion senare i livet, eller störning av signalvägar som reglerar glukos- och lipidmetabolism, vilket leder till störning av glukoshomeostas. Epigenetiska förändringar orsakade av kemisk exponering är också en föreslagen mekanism. Experimentella data indikerar att exponering för vissa kemikalier kan bidra till utvecklingen av typ 1-diabetes via toxiska effekter på immunsystemet, men det epidemiologiska stödet är bristfälligt. Mer kunskap om de mekanismer som kan ligga bakom samband mellan exponering för kemikalier och diabetes, såväl typ 2-diabetes som autoimmun diabetes, skulle kunna minska osäkerheterna kring kausala samband i epidemiologiska studier och bidra till starkare slutsatser.

METALLER

Metaller är persistenta och långvarig låghaltig exponering har kopplats till många negativa hälsoeffekter, och de delar även många toxiska egenskaper, till exempel framkallande av oxidativ stress och inflammation. Sammantaget väcker detta misstankar om att metaller kan inverka på utvecklingen av diabetes. Epidemiologiska studier ger stöd för ett samband mellan arsenikexponering och typ 2-diabetes i populationer med relativt hög arsenikexponering via dricksvatten (≥150 µg arsenik/L), men vid lägre exponeringsnivåer är bevisen fortfarande otillräckliga. För kadmium finns det begränsat med epidemiologiskt stöd för ett eventuellt samband med typ 2-diabetes. Den främsta orsaken är att de flesta studierna som påvisat samband har en tvärsnittsdesign medan de fåtal longitudinella studier som finns tillgängliga inte har visat något samband. För metylkvicksilver och bly är det epidemiologiska underlaget motstridigt och ibland väldigt begränsat, och därför kan ingen slutsats dras för dessa metaller. Detta gäller också för en koppling mellan metallexponering och autoimmun diabetes. Experimentella djurstudier har indikerat att exponering för metaller kan påverka flera utfall som förknippas med etiologin till diabetes, såsom beta-cellsdysfunktion, ökade blodsockernivåer, förändrat insulin-stimulerat glukosupptag och glukosstimulerad insulinsekretion.

LUFTFÖRORENINGAR OCH BULLER

Långtidsexponering för luftföroreningar och trafikbuller kan ge upphov till allvarliga negativa hälsoeffekter, främst i hjärt-kärlsystemet. Ett flertal epidemiologiska studier pekar också på en roll för dessa exponeringar då det gäller utveckling av metabola sjukdomar, såsom typ 2-diabetes och övervikt. I synnerhet visar epidemiologiska studier som publicerats under det senaste decenniet från olika delar av världen på samband mellan exponering för luftföroreningar och typ 2-diabetes. Det mest omfattande och entydiga underlaget gäller fina partiklar, d.v.s. $PM_{2.5}$. Epidemiologiska studier av samband mellan luftföroreningsexponering och blodglukosnivåer, insulinresistens och beta-cellsfunktion, samt experimentella studier, stödjer dessa samband och åskådliggör relevanta etiologiska mekanismer. Det finns färre epidemiologiska studier rörande trafikbullerexponering och typ 2-diabetes, men en majoritet av dessa har rapporterat samband, främst för vägtrafik- och flygplansbuller. Sannolika etiologiska mekanismer utgörs av bullerorsakade sömnstörningar och stressreaktioner. Vad gäller typ 1-diabetes hos barn i relation exponering för luftföroreningar och buller finns bara enstaka studier och för LADA är kunskapsunderlaget obefintligt.

GRÖNOMRÅDEN

Det finns starkt stöd för att ökad exponering för bostadsnära grönska (växtlighet) i urbana miljöer påverkar vissa aspekter av människors hälsa positivt. Omgivningsgrönskan har till exempel kopplats till minskad icke-olycksrelaterad dödlighet, ökad sannolikhet för normal födelsevikt, bättre mental hälsa samt bättre motorisk och kognitiv utveckling hos barn. Som underliggande förklaringar föreslås växtlighetens kapacitet att mildra effekten av andra, hälsoskadliga miljöexponeringar (såsom värmeböljor, buller och luftföroreningar), samt dess lindrande inverkan på mental och fysiologisk stress och främjande av hälsosamma mänskliga aktiviteter såsom motion och socialisering. Genom dessa mekanismer skulle exponeringen till omgivningsgrönska potentiellt kunna minska risken för typ 2-diabetes. Vår litteraturgenomgång visar att det finns visst stöd för den hypotesen, men det finns få långtidsstudier som är metodologiskt jämförbara och inga av dessa studier är baserade på svenska data. Majoriteten av resultat som kopplar typ 2-diabetes till omgivningsgrönska är baserade på tvärsnittsdata. De patofysiologiska processerna, som kan förklara ett eventuellt samband mellan omgivningsgrönska och typ 2-diabetes, är fortfarande okända. Sambandet mellan tillgång till grönområden och autoimmun diabetes har inte studerats.

SLUTSATS

Levnadsvanor har vid sidan av ärftlighet avgörande betydelse för utvecklandet av typ 2-diabetes. Befintlig forskning visar att hela tre fjärdedelar av alla fall kan tillskrivas övervikt, stillasittande, ohälsosamma kostvanor och rökning, samt att övervikt är den i särklass viktigaste riskfaktorn. Det finns också stöd för att enskilda kostfaktorer, utöver effekter på vikten, påverkar risken för typ 2-diabetes. En minskad risk ses i relation till intag av fullkorn och kaffe medan läsk och charkuterier som korv och bacon ökar risken.
Både experimentella djurstudier och epidemiologiska studier ger stöd för att kemikalier som ingår i gruppen PCB:er, framförallt de dioxinlika, och vissa klorerade bekämpnings-medel (som till exempel DDT och dess metabolit DDE) ökar risken för typ 2-diabetes. Många av dessa är numera förbjudna, men finns kvar i miljön på grund av att de är svårnedbrytbara. Vad gäller kortlivade kemikalier som bisfenol A och ftalater har dessa i cell- och djurstudier visat sig påverka mekanismer som har betydelse för glukostoleransen.

Däremot finns alltför få epidemiologiska studier med upprepad exponeringsmätning för att man ska kunna slå fast med säkerhet att dessa kemikalier ökar typ 2-diabetesrisken.

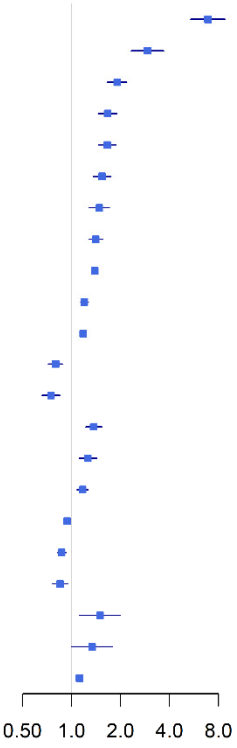
Via mat och dricksvatten exponeras vi för metaller som arsenik, kadmium, metylkvicksilver och bly. Data från experimentella djurstudier tyder på att detta skulle kunna öka risken för typ 2-diabetes. De epidemiologiska studierna på området är dock både få och ofta metodologiskt svaga. Det mest konsistenta fyndet är en ökad risk för typ 2-diabetes vid hög exponering för arsenik i dricksvattnet, detta gäller dock för väsentligt högre nivåer än de som förekommer i Sverige.

Epidemiologiska studier ger stöd för att långtidsexponering för luftföroreningar, framförallt fina partiklar, skulle kunna öka risken för typ 2-diabetes. Mekanistiska studier visar att dessa partiklar kan leda till systemisk inflammation vilket bland annat kan påverka insulinkänsligheten. Huruvida även exponering för buller ökar risken för typ 2-diabetes är inte klarlagt, även om ett fåtal epidemiologiska studier pekar i denna riktning.

Exponering för bostadsnära grönska i stadsmiljö skulle potentiellt kunna minska risken för typ 2-diabetes genom att stimulera till fysisk aktivitet och reducerad stress. Visst stöd för hypotesen ges från epidemiologiska studier men kunskapsunderlaget är i dagsläget mycket begränsat.

Figur 1. Levnadsvanor och miljöfaktorer som med starkt stöd i den vetenskapliga litteraturen kan kopplas till typ 2-diabetes. Relativa risker och 95% konfidensintervall (KI).

Riskfaktor	Relativ risk (95% KI)
BMI (fetma mot normalvikt)	6.88 (5.39-8.78)
BMI (övervikt mot normalvikt)	2.93 (2.33-3.68)
Stillasittande (mycket mot lite)	1.91 (1.66-2.19)
Midje-längdkvot (per 1 SDs ökning)	1.67 (1.46-1.90)
Midjemått (per 1 SDs ökning)	1.66 (1.47-1.88)
Midje-höftkvot (per 1 SDs ökning)	1.54 (1.36-1.75)
Depression (någonsin mot aldrig)	1.48 (1.28-1.74)
Utbildning (låg mot hög)	1.41 (1.28-1.55)
Rökning (nu mot aldrig)	1.39 (1.33-1.44)
TV-tittande (per 2 h/dags ökning)	1.20 (1.14-1.27)
BMI (per 1 kg/m2 ökning)	1.18 (1.15-1.20)
Födelsevikt (per 1 kg ökning)	0.80 (0.72-0.88)
Fysisk aktivitet på fritiden (hög mot låg)	0.75 (0.66-0.85)
Processat rött kött (per 50 g/dags ökning)	1.37 (1.22-1.54)
Socker-sötade drycker (per 1 glas/dags ökning)	1.26 (1.11-1.43)
Icke-processat rött kött (per 100 g/dags ökning)	1.17 (1.08-1.26)
Kaffe (per 1 kopp/dags ökning)	0.94 (0.93-0.95)
Fullkorn (per 30 g/dags ökning)	0.87 (0.82-0.93)
Medelhavskost (hög mot låg följsamhet)	0.85 (0.76-0.95)
DDE* (per 1 SDs ökning)	1.50 (1.12-2.00)
DL-PCB* (per 1 SDs ökning)	1.34 (1.00-1.79)
Luftföroreningar-PM2.5** (per 10 µg/m3 ökning)	1.12 (1.08-1.16)



** DL-PCBs- dioxinlika PCB, DDE- Dichlorodiphenyldichloroethylene (en metabolit av DDT). RR för DL-PCB och DDE baseras på data från en svensk studie då nya resultat från meta-analys saknas.*
***Koncentrationen av $PM_{2.5}$ i svenska storstäder är knappt 10 µg/m^3.*

För autoimmuna former av diabetes som typ 1-diabetes och LADA finns starkt belägg för att övervikt ökar risken, samt att vissa virusinfektioner ökar risken för typ 1-diabetes hos barn. Ett flertal andra levnadsvanor har kopplats till insjuknande i autoimmun diabetes hos barn eller vuxna men kunskapsunderlaget är alltför begränsat för att bestämda slutsatser ska kunna dras. När det gäller miljöfaktorer som kemikalier, metaller, luftföroreningar, buller och grönområden finns bara enstaka studier.

Figur 1 visar relativa risker för de levnadsvanor och miljöfaktorer som med starkt stöd i den vetenskapliga litteraturen kan kopplas till risken för typ 2-diabetes. Resultaten kommer från de senaste meta-analyserna inom området. De relativa riskerna kan inte omedelbart jämföras därför att riskfaktorerna mäts i olika enheter, figuren ger dock en överblick över kunskapsläget. Viktigt att notera är att betydelsen av en enskild faktor för folkhälsan beror dels på hur stor riskökning faktorn ger, samt utbredningen av exponeringen i befolkningen. Därigenom kan en faktor som luftföroreningar, som medför en relativt liten riskökning, ha stor betydelse eftersom en relativt stor andel av befolkningen är exponerad. För typ 2-diabetes är övervikt den dominerande riskfaktorn då den både medför en hög relativ risk och är vanligt förekommande i befolkningen. Övervikt kopplas även till en ökad risk för autoimmun diabetes. Att förebygga övervikt är därmed en central folkhälsoåtgärd för att minska diabetesinsjuknandet.

FORSKNINGSBEHOV

Hur miljöfaktorer som olika kemikalier, metaller, luftföroreningar, buller och tillgång till grönområden påverkar utvecklandet av typ 2-diabetes är ett viktigt ämne för framtida studier. Vad gäller levnadsvanor och kost finns omfattande forskning, dock saknas kunskap om hur enskilda kostfaktorer och kostmönster påverkar risken, samt hur levnadsvanorna samverkar med genetiska riskfaktorer vid utvecklandet av typ 2-diabetes. Det är också viktigt att klargöra betydelsen av levnadsvanor och miljöfaktorer vid utvecklandet av autoimmun diabetes hos barn och vuxna, inklusive samverkan med genetiska faktorer. I framtida epidemiologiska studier behöver man hantera de metodologiska problem som gör resultaten från många tidigare studier svårtolkade, framförallt avseende miljöfaktorernas betydelse. Det kräver god kontroll av störningsfaktorer, longitudinella data där exponering mäts före diabetesinsjuknandet, helst upprepade gånger, objektivt uppmätt exponering, exempelvis i form av biomarkörer, samt komplett identifiering av diabetesfall och diabetestyp. Experimentella studier för att öka förståelsen för de mekanismer som kan ligga bakom samband mellan exponering för olika miljöfaktorer och diabetes behövs för att ytterligare reducera osäkerheter orsakade av bland annat störningsfaktorer i epidemiologiska studier. Genom välgjorda interventionsstudier kan man få klarhet i vilka preventiva åtgärder som i praktiken kan minska diabetesinsjuknandet.

SUMMARY

BACKGROUND

Diabetes is a common, chronic disease and its prevalence is increasing worldwide. In Sweden, 8% of the adult population has diabetes and the prevalence is projected to increase to 10% by year 2050. The increasing prevalence of diabetes is primarily driven by an aging population and improved survival among people affected by the disease. Diabetes increases the risk of serious complications and may lead to myocardial infarction, stroke and premature death. The disease leads to suffering for the individual, and high costs for society in terms of health care and production loss.

Diabetes is a collective name for a group of metabolic diseases characterized by an inability to keep blood sugar at normal levels, where several partially different disease mechanisms may be involved. Chronically elevated blood sugar levels eventually cause damage to nerves and blood vessels. Type 2 diabetes is the most common type of diabetes and accounts for > 85% of all cases. The disease is caused by a combination of decreased insulin sensitivity, so-called insulin resistance, and defective insulin release. It primarily affects adults and the risk increases significantly with increasing age. Type 1 diabetes is an autoimmune disease caused by the immune system destroying the insulin-producing beta cells. This results in irreversible insulin deficiency and therefore the disease requires lifelong insulin therapy. Type 1 diabetes accounts for 99% of all diabetes in children but can develop at any age. LADA (latent autoimmune diabetes in adults) is the most common form of autoimmune diabetes in adults. The autoimmune process in LADA is milder than in type 1 diabetes and the disease also has features of type 2 diabetes, since reduced insulin sensitivity contributes to disease progression. The risk of developing type 2 diabetes is high; according to one study, the lifetime risk in Sweden is 20%. There is, however, no indication that the incidence has increased in Sweden during the last decade. Type 1 diabetes risk among children is low, in Sweden four out of 10,000 children are affected annually, but the incidence has doubled in the last 20 years. Changes in the environment or lifestyle are believed to explain the increase, but it is not clear which factors are involved. Whether autoimmune diabetes in adults is becoming more common is unknown.

Both type 2 diabetes and autoimmune forms of diabetes are caused by a combination of genetic and environmental factors. It is known that lifestyle factors, primarily obesity and a sedentary lifestyle, are of great importance for the development of type 2 diabetes and it has been shown that it is possible to prevent the disease through lifestyle modification. In addition to known risk factors, there is also concern that environmental factors such as certain chemicals and metals, air pollution, noise, and green space may influence development of type 2 diabetes, but research in this area is limited. How lifestyle and environmental factors affect the autoimmune response leading to type 1 diabetes and LADA is not clear. The purpose of this report is to summarize existing knowledge, primarily based on epidemiological studies, about the influence of environmental and lifestyle factors on the risk of type 2 diabetes, type 1 diabetes and LADA, to identify knowledge gaps and point out research needs and methodological challenges.

LIFESTYLE

Results from many epidemiological studies from different parts of the world show that overweight, sedentariness, tobacco use, and low birth weight are associated with an increased risk of type 2 diabetes. These factors appear to increase the risk of diabetes

primarily by leading to increased insulin resistance. The disease is more common among people with low socioeconomic status, which is largely explained by the higher prevalence of overweight and other unhealthy lifestyle risk factors. Intervention studies have confirmed that it is possible to radically reduce the risk of type 2 diabetes through lifestyle changes that lead to weight loss and increased physical activity. Being overweight is the single most important risk factor and has been estimated to account for up to 80% of all cases. Individuals with a combination of family history of diabetes and obesity are at particularly high risk of developing type 2 diabetes. Regarding type 1 diabetes in children, studies conducted to date have provided inconclusive results and it is not clear how environmental factors affect the development of the autoimmune response that gives rise to the disease. Among the most consistent findings are an increased risk among children exposed to certain viral infections, either perinatally or during childhood, as well as being overweight. Research on autoimmune diabetes in adults is limited, but there is evidence that factors with an impact on insulin sensitivity such as being overweight and sedentary also increase the risk of LADA. Being overweight seems to be a risk factor for both type 2 diabetes and autoimmune diabetes, which is particularly serious as the proportion of overweight children and adults is increasing globally.

DIET

It is well-established that diet has a role in the development of type 2 diabetes. Total energy intake is of importance since excess intake may result in overweight, which is strongly associated with diabetes risk. However, also the quality of the diet is of importance, as some dietary factors may have direct effects on insulin sensitivity and/or beta cell function and subsequently also on the risk of type 2 diabetes. Sugar-sweetened beverages and red meat, particularly processed meat products such as sausages and bacon, constitute the food groups with the strongest evidence of increased risk of type 2 diabetes. Regarding protective factors, many studies have found lower risk of type 2 diabetes among individuals with a high whole grain intake and habitual coffee consumption. Among dietary patterns evaluated in relation to type 2 diabetes, the strongest evidence is found for the Mediterranean diet, which is characterized by high intakes of nuts, olive oil, vegetables, fruit, fish and shellfish, and moderate alcohol intake, as well as limited intakes of red meat and (high fat) dairy products. High adherence to the Mediterranean dietary pattern has been associated with lower type 2 diabetes incidence in both intervention studies and epidemiological studies. In relation to Swedish dietary guidelines, the intakes of fruit, vegetables, fish, whole grain, and dietary fibers are too low, while the consumption of sugar-sweetened beverages is too high. Thus, higher adherence to national dietary guidelines could potentially reduce the incidence of type 2 diabetes in the population. The role of diet in the aetiology of autoimmune diabetes is far less understood. Based on studies published to date, it seems that diet may be of importance also in type 1 diabetes and LADA, but findings are inconclusive and the potential role of diet in autoimmune diabetes development is yet to be established.

ENVIRONMENTAL CHEMICALS

Certain environmental chemicals (both persistent and non-persistent) and chemical groups are of concern regarding contribution to diabetes risk, namely dioxins, polychlorinated biphenyls (PCBs), chlorinated pesticides, perfluorinated compounds (PFAS), brominated compounds, bisphenols and phthalates. We consider the epidemiological evidence adequate to conclude that exposure to PCBs, especially the dioxin-like PCBs, and chlorinated pesticides is associated with increased risk of type 2 diabetes. For PFAS, the brominated

compounds, bisphenols and phthalates epidemiological data are too limited to draw any firm conclusions. In addition, the short half-life of bisphenols and phthalates contributes to uncertainties in exposure measurements and complicates assessments of causal associations in epidemiological studies. However, experimental data give stronger support. A relatively large body of experimental studies is available that provides insights into potential mechanisms by which environmental chemicals could contribute to the development of diabetes. One potential mechanism that is well supported by empirical evidence as well as biological plausibility is mitochondrial dysfunction and increased production of reactive oxygen species (ROS), causing oxidative stress and damage to pancreatic beta cells. Other potential mechanisms are, for example, disruption of signalling pathways during foetal development that leads to effects on beta cell mass and function later in life, or disruption of signalling pathways that regulate glucose and lipid metabolism leading to disruption of glucose homeostasis. Epigenetic alterations caused by chemical exposure is another suggested mechanism. Some experimental data indicate that exposure to a few chemicals may contribute to development of type 1 diabetes via toxic effects on the immune system. Better understanding of the mechanisms underlying any association between exposure to environmental chemicals and diabetes would overcome some of the uncertainties caused by, for example, confounding factors and could thereby increase confidence in conclusions.

METALS

Metals are persistent and low-level exposure has been associated with various adverse health outcomes, and they share many toxicological properties, such as induction of oxidative stress and inflammation. Altogether, this raises concern about the involvement of metal exposure in the development of diabetes. Current epidemiological studies provide enough evidence of an association between arsenic exposure and type 2 diabetes in populations with relatively high arsenic exposure via drinking water (≥150 µg arsenic/L), whereas at lower exposure levels via drinking water and food the evidence is insufficient. For cadmium, the epidemiological evidence for an association with type 2 diabetes is limited, and studies finding an association are primarily of cross-sectional design, while the few available longitudinal studies do not support an association. For methylmercury and lead, epidemiological evidence is conflicting and/or scare, and therefore, no conclusion can be drawn. This also applies for a link between metal exposure and autoimmune diabetes. Experimental animal studies have indicated that metal exposure can affect endpoints associated with the aetiology of diabetes such as pancreatic beta cell dysfunction, increased gluconeogenesis and blood glucose levels, altered insulin-stimulated glucose uptake and glucose-stimulated insulin secretion.

AIR POLLUTION AND NOISE

Long-term exposure to air pollution and traffic noise can induce serious adverse health effects, primarily in the cardiovascular system. Increasing evidence also points to a role of these exposures for development of metabolic diseases, such as type 2 diabetes and overweight. Epidemiological studies published during the last decade from different parts of the world indicate that exposure to ambient air pollution can increase the risk of type 2 diabetes. The most extensive and consistent evidence relates to fine particulate, i.e. $PM_{2.5}$. Supporting evidence comes from epidemiological studies on air pollution exposure in relation to blood glucose levels, insulin resistance and beta cell function, as well as from experimental studies, illustrating relevant etiologic pathways. There are fewer epidemiological studies on environmental noise exposure and type 2 diabetes, but most of them reported positive associations, primarily for road traffic and aircraft noise. Plausible

etiological mechanisms have been indicated, such as noise induced sleep disturbances and stress reactions. Regarding type 1 diabetes in children and exposure to air pollution and noise, data are scarce and for LADA non-existent.

NEIGHBOURHOOD GREENNESS

Studies suggest that exposure to natural settings in urban context can have a range of positive outcomes for human health and wellbeing. Urban greenness is generally thought to affect health by mitigating the effect of harmful exposures (such as heat, noise and air pollution), relieving mental and physiological stress, and promoting health-beneficial human activities such as exercise and socializing. Increased neighbourhood greenness could potentially reduce the risk of type 2 diabetes through these mechanisms. Our literature review shows that there is some support for the hypothesis, however there are today very few prospective studies that are methodologically comparable. In addition, the pathophysiological processes that may be involved are still unknown.

CONCLUSION

Lifestyle factors are crucial for the development of type 2 diabetes, as many as three-quarters of all cases have been attributed to overweight, sedentariness, unhealthy diet and smoking. In addition, individual dietary factors seem to directly affect the risk of type 2 diabetes: A reduced risk is seen in relation to intake of whole grains and coffee, while sugar-sweetened soft drinks and processed meats such as sausage and bacon increase the risk. Some environmental chemicals, such as dioxin-like PCBs and chlorinated pesticides (e.g. DDT), can be linked to an increased risk of type 2 diabetes. In the case of short-lived chemicals such as bisphenol A and phthalates, there is support for diabetic effects from animals and cell studies, but the epidemiological evidence is limited. Firm conclusions cannot be drawn as to whether metals such as cadmium, methylmercury and lead increase the risk of diabetes as the epidemiological studies are too few and methodologically weak. The strongest support is seen for an increased risk of type 2 diabetes in relation to arsenic in drinking water, but this applies to substantially higher levels than those found in Sweden. Exposure to air pollution, especially fine particles, is associated with an increased risk of type 2 diabetes which is supported by mechanistic evidence. Whether exposure to noise increases the risk of type 2 diabetes is not clear, although the few studies available point in this direction. Increased exposure to neighbourhood greenness could potentially reduce the risk of type 2 diabetes by stimulating physical activity and reducing stress. Some support for the hypothesis is found in epidemiological studies, but the knowledge base is currently very limited. An overview of factors that has been firmly linked to type 2 diabetes is given in Figure 14 on page 108.

For autoimmune forms of diabetes such as type 1 diabetes and LADA, there is strong evidence that excess weight increases the risk, and furthermore, that certain viral infections increase the risk of type 1 diabetes in children. Several other lifestyle and dietary factors have been linked to the risk of autoimmune diabetes in children or adults, but there is not enough evidence to draw any definite conclusions. Regarding environmental factors such as chemicals, metals, air pollution, noise and proximity to urban greenness, their potential role in the development of autoimmune diabetes is largely unexplored.

To conclude, overweight and obesity are the strongest environmental risk factors for type 2 diabetes, and excess weight has also been linked to increased risk of autoimmune diabetes in children as well as in adults. Preventing obesity is thus a key public health measure to reduce diabetes incidence.

FUTURE DIRECTION

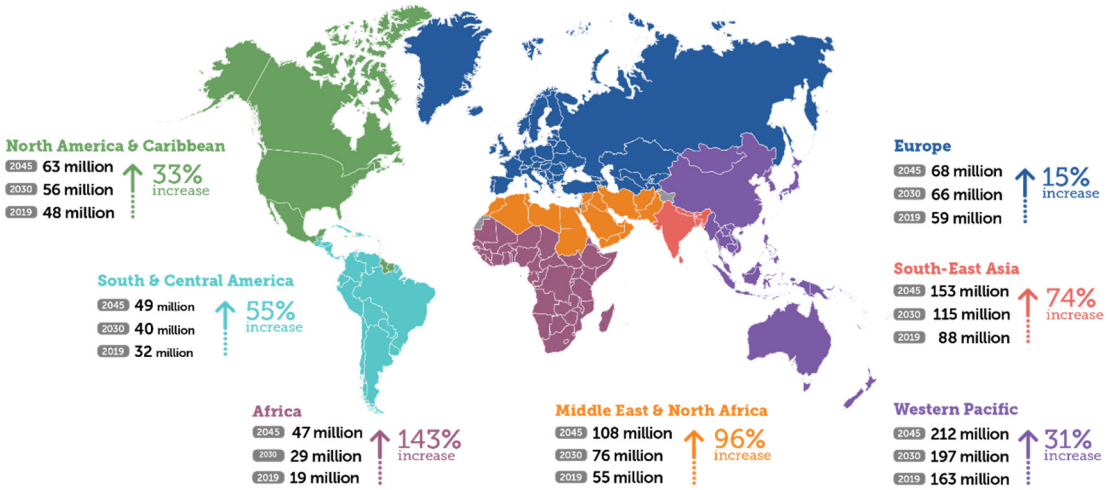
The role of the environment in the development of type 2 diabetes is an important topic for future studies. The influence of lifestyle factors has been studied in detail in relation to type 2 diabetes, but the influence of several individual dietary factors, and dietary patterns remains to be investigated, as well as the interaction between lifestyle and genetic factors. Regarding autoimmune diabetes, including both type 1 diabetes in children and LADA, there is a need to clarify the potential effect of both lifestyle and environmental factors, as well as their interaction with genetic factors. In future studies, it is important to overcome many of the methodological problems that have hampered many previous studies, especially those investigating environmental factors. This requires adequate control of confounding factors, longitudinal data where exposure is repeatedly assessed prior to diabetes onset, preferably with objectively measured exposure, for example in the form of biomarkers, and complete identification of diabetes cases and type of diabetes. Experimental studies to increase understanding of the mechanisms underlying any association between exposure to environmental factors and diabetes are needed to overcome some of the uncertainties caused, for example, by confounding factors in epidemiological studies.

DIABETES

OCCURRENCE

Diabetes is a metabolic disorder characterised by elevated blood glucose levels. It is a common chronic disease that, primarily by the complications it entails, leads to profound personal suffering and high costs for society in terms of sick leave, health care and premature death. Diabetes is a common and growing public health problem[1]. Prevalence is increasing in most countries around the world and most rapidly in urban areas of low- and middle-income countries[2]. In 2019, the global prevalence in the adult population was estimated to be 9.3% and the number of people with diabetes was estimated at 463 million. By 2045, prevalence of diabetes is estimated to rise to 10.9% and the number of affected individuals to 700 million (Figure 2). The rise has been attributed to demographic changes, including a larger proportion of people in higher ages, together with lifestyle changes, including rising levels of obesity and sedentariness, leading to increasing incidence of diabetes.

Figure 2. Number of people with diabetes worldwide and per region in 2019 and projections for 2030 and 2045 (age 20-79 years)[2].



In Sweden, one in five will develop diabetes during their lifetime[3] and prevalence has increased from 6.5% in 2006 to 8.1% in 2019 and 9.4% of men and 6.8% of women have diabetes (Figure 3). The condition increases with age and is more common in men than in women at every age (Figure 4). Importantly, incidence has been stable or even declining in Sweden since 2006[4] and similar trends have been reported from several western countries including the US[5], the UK[6], Scotland[7] and Norway[8]. The rising prevalence can instead be attributed to a shift in the age distribution of the population and reduced mortality in people with diabetes. The global rise in prevalence of diabetes is due to an increase in the number of individuals with type 2 diabetes (T2D). However, the incidence of type 1 diabetes (T1D) has been increasing over the last decades. A study published in 2019 with pooled data from 26 European countries indicates that the incidence of T1D in children increased by 3.4% annually between 1989 and 2013, resulting in a doubling over 20 years in Europe[9]. Every year, about 4 out of 10,000 children aged 0-15 years in Sweden develop T1D.

Figure 3. Diabetes prevalence in adults (≥20 years) in Sweden 2015-2019. Data from the Swedish Prescription Register*[10].

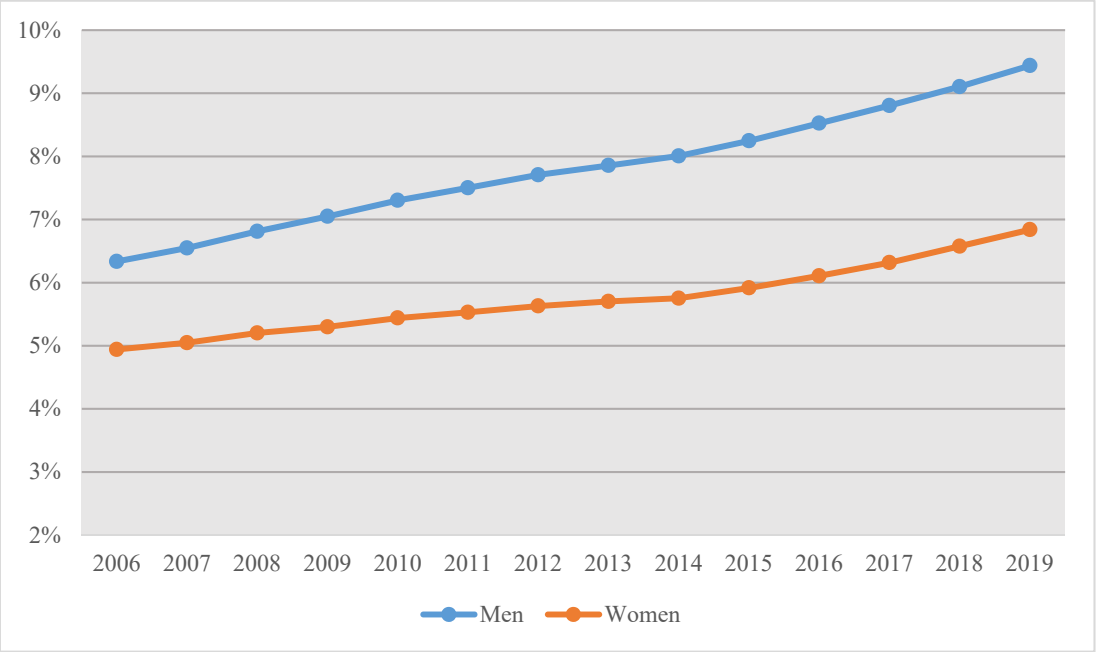
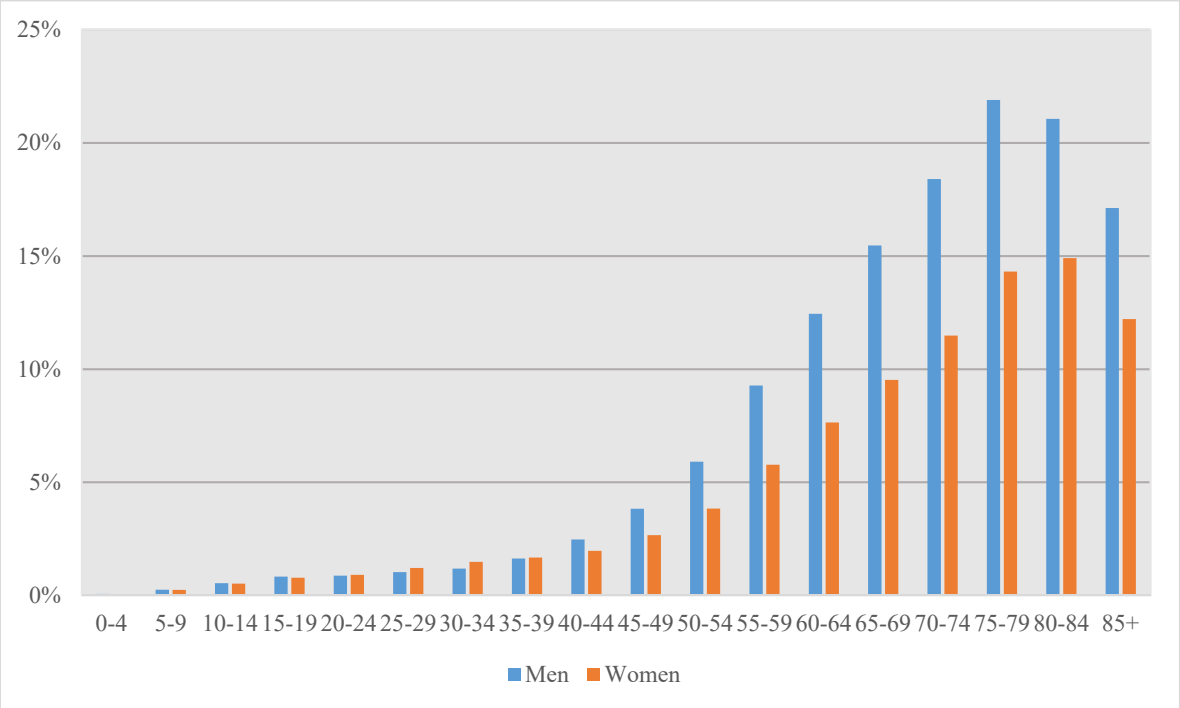


Figure 4. Prevalence (per 100) of diabetes by age and sex in Sweden in 2019. Data from the Swedish Prescription Register*[10].



**The proportions with prescriptions for diabetes medication was amplified by a factor 1.25 to account for the observation that 20% of all adult patients are treated non-pharmacologically[11].*

COMPLICATIONS

Diabetes causes a wide range of complications such as premature death, myocardial infarction, stroke, heart failure, kidney failure and painful diabetic neuropathy[12]. About a two-fold increased risk of coronary heart disease (CHD) and stroke is seen in people with diabetes after adjustment for other risk factors. Importantly, the risk of complications can be reduced substantially with good diabetes management[13]. Indeed, data from the Swedish National Diabetes Register indicate that it is possible to eradicate the excess risk of CHD completely with optimal treatment and lifestyle modifications. However, in poorly controlled T2D with early onset, the risk of CHD-death is increased 5-fold[14]. Moreover, individuals with T1D have a four-fold increased risk of CHD compared to individuals without diabetes, and the risk is increased more than ten-fold in those with poor glycaemic control[15]. Hence, the future disease burden will not only depend on incidence of diabetes but also on the extent to which the growing number of patients will develop complications. Because of its many comorbidities, diabetes has strong adverse effects on the ability to work and is associated with increased sickness absence and early retirement[16,17]. The high and increasing prevalence of diabetes will impose a major burden on individuals and society with negative effects on public health, the health care system and productivity. In Sweden, the costs for treating diabetes doubled between 2006 and 2014 because of increasing number of patients[18]. The risk of developing vascular disease in people with diabetes is influenced by environmental factors, primarily lifestyle factors such as obesity and smoking, but this will not be covered by the present report, which focuses on risk factors for development of diabetes.

DIAGNOSING DIABETES

Hyperglycaemia is the hallmark of diabetes and it is diagnosed on the basis of either a) fasting blood sugar levels ≥7 mmol/L, b) 2-hour oral glucose tolerance test ≥11 mmol/L, c) HbA1c ≥6.5% (48 mmol/mol) or d) in patients with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥11.1 mmol/L[19].

DIABETES TYPES

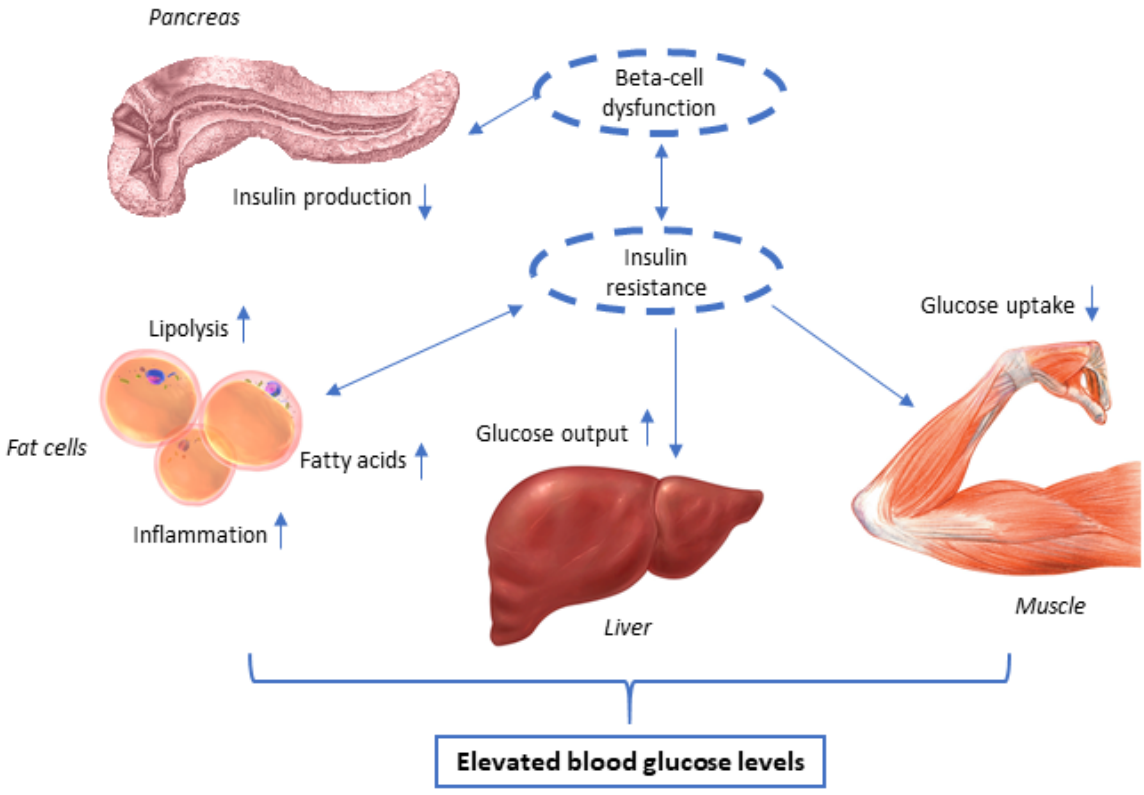
Diabetes is defined by the inability of the body to maintain glucose homeostasis, but the term includes several different conditions with distinct pathogenesis and potential risk factors. T2D is the most common form of diabetes accounting for 85-90% of all cases. This diabetes form affects primarily adults and prevalence increases dramatically with age; Figure 4 shows that 22% of all men and 14% of all women aged 75-79 years have diabetes, of which the vast majority have T2D. Autoimmune forms of diabetes like T1D and LADA account for most remaining cases, with T1D being the predominant diabetes form affecting children and LADA the most common form of autoimmune diabetes in adults[20]. In addition, there are monogenic forms of diabetes subtypes, gestational diabetes, and secondary diabetes, which will not be covered in this report.

TYPE 2 DIABETES

The main pathophysiological features of T2D are insulin resistance in skeletal muscle, liver and adipose tissue, together with impaired insulin secretion. Insulin resistance reduces peripheral glucose uptake and stimulates hepatic glucose output which leads to elevated blood glucose levels. The ensuing hyperglycaemia increases the demand on the beta cells for a compensatory rise in insulin secretion. This may eventually exhaust the beta cells and

lead to a progressive loss of beta cell function, resulting in insulin deficiency and subsequent diabetes[21]. The causes of insulin resistance include genetic factors as well as unhealthy lifestyle factors, most importantly adiposity. Besides insulin resistance and insulin deficiency, several other pathophysiological anomalies are involved in the development of hyperglycaemia (Figure 5). These include accelerated glucose production by the liver caused by elevated glucagon production, increased lipolysis and release of free fatty acids and pro-inflammatory cytokines, which is due to insulin resistance and inflammation in adipocytes. This exacerbates insulin resistance in the liver and muscles, leading to reduced glucose uptake which contributes to glucose intolerance. Oxidative stress may also be involved in the promotion of T2D since it may lead to inflammation through release of reactive oxygen species (ROS). Systemic inflammation is a well-known cause of insulin resistance and it has been suspected that environmental factors may contribute to the development of T2D through this pathway, i.e. by inducing oxidative stress. T2D typically develops over a long period of time (years) and gradually through a pre-diabetic state that is characterised by slightly elevated blood glucose levels. Symptoms of hyperglycaemia may be mild initially and therefore T2D may go undetected for some time.

Figure 5. Pathogenesis of type 2 diabetes.



AUTOIMMUNE DIABETES

T1D results from a pathophysiological process distinct from that of T2D; its main feature is insulin deficiency which is caused by autoreactive T-cells of the immune system that destroy the pancreatic beta cells and lead to declining insulin production22. This process may lead to an absolute deficiency of insulin production and exogenous insulin is needed to maintain normal glucose levels. The causes of such an autoimmune reaction include genetic factors. A triggering role of environmental factors has been suggested but the nature of such factors remains unclear. Presence of autoantibodies is a hallmark of T1D. In 1977 it was

first shown that about 10% of all individuals diagnosed with T2D also have autoantibodies[23]. The term LADA—latent autoimmune diabetes in adults—was introduced in 1993 to describe this patient group[24]. LADA is caused by a similar autoimmune activity as seen in T1D in children, but it is milder which is evidenced by the fact that these patients typically have remaining insulin production at time of diagnosis. Consequently, they may not need insulin treatment for several years following diagnosis. LADA is also characterized by insulin resistance, the main feature of T2D and has therefore been described as a hybrid of T1D and T2D (Table 1).

Table 1. Characteristics of type 2 diabetes, LADA and type 1 diabetes.

	Type 2 diabetes	LADA	Type 1 diabetes
Age at onset	Adulthood	Adulthood	Any age
Autoimmunity	No	Mild	Severe
Insulin deficiency	Mild	Moderate	Severe
Insulin resistance	Severe	Moderate	Possibly
Insulin treatment	Sometimes	Often	Always

GENETIC RISK FACTORS

Both T2D and the autoimmune forms of diabetes, i.e. T1D and LADA, have a strong genetic component as shown in both genetic and family history studies. Family history of diabetes is associated with an up to four-fold increased risk of T2D, a nine-fold increased risk of T1D, and a six-fold increased risk of LADA[25-27].

TYPE 2 DIABETES

The genetic influence on T2D seems to be spread across the whole genome and it is attributed to a large number of common genetic variants – each contributing a small amount to heritability of the disease[28]. More than 400 genetic loci have been linked to T2D, but together they only explain a small part of its heritability[29]. The strongest effect is conferred by variants in the transcription factor 7-like 2 (TCF7L2) gene, which is associated with a 30% risk increase. The majority of known genetic risk variants associated with T2D seems to influence insulin secretion rather than insulin resistance[28].

AUTOIMMUNE DIABETES

In T1D, the strongest genetic influence is conferred by genes in the human leukocyte antigen (HLA) complex which are responsible for approximately half of the genetic susceptibility[30]. The highest risk is conferred by HLA-DR3-DQ2 and HLA-DR4-DQ8 haplotypes, which are present in almost 90% of all children who develop diabetes in the Scandinavian countries[30]. The HLA genes encode the major histocompatibility complex (MHC) proteins that regulate the immune system. Polymorphisms are associated with insulin deficiency, likely due to an autoimmune-generated destruction of the beta cells[31]. In addition, T1D is associated with more than 60 loci outside the HLA complex such as the insulin gene (INS), PTPN22, CTLA-4, IL2RA and SH2B3[32]. The genetic make-up of LADA resembles that of T1D, including a strong link to genes in the HLA complex, especially the DR3-DQ2 and DR4-DQ8 haplotypes[33].

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METHODOLOGY

LITERATURE REVIEW

LIFESTYLE AND DIET

Since the literature on T2D in relation to lifestyle factors and diet is so comprehensive, we chose to base these chapters primarily on recently published umbrella reviews (reviews of meta-analyses) of epidemiological studies based on prospective cohort studies. In addition, evidence from individual studies, Mendelian randomization studies and randomized clinical trials is discussed. The literature on autoimmune diabetes is less extensive and there are few formal meta-analyses. To summarize current knowledge on lifestyle factors in relation to incidence of LADA and T1D we instead used recently published reviews, and individual studies deemed especially important.

ENVIRONMENTAL FACTORS

In 2019 literature searches were performed according to specified criteria for environmental chemicals, metals, air pollution, noise and green areas, respectively. These included both epidemiological studies, investigating the link between the selected exposures and diabetes, and experimental studies (cell-based and in animals) investigating diabetes-related endpoints as well as potential underlying mechanisms. Searches were conducted in Medline and Embase by information specialists from the library at Karolinska Institutet and were restricted to literature published in English and from the year 2000. The literature searches retrieved large amounts of relevant studies and reviews. In this report, we decided to first focus on summarizing existing reviews and only address individual studies where a more detailed review of data was considered appropriate. The review also includes a summary of information retrieved in the literature search regarding potential mechanisms by which the environmental exposures may contribute to the development of diabetes.

METHODOLOGICAL CONSIDERATIONS AND WEIGHT OF EVIDENCE

Most of the human evidence in this report is based on observational data, i.e. epidemiological studies without any experimental component. However, where available we have also included findings of randomized clinical trials and Mendelian randomization studies. Such study designs generally provide more conclusive evidence on causality than observational studies since the risk of bias is minimized. On the other hand, observational studies are generally more cost-efficient and may be the only option when toxic exposures are investigated.

Randomized clinical trials are the gold standard in terms of establishing a causal relationship between an exposure and disease. This study design implies that the exposure is randomized between study subjects and that the occurrence of exposure and determination of health effects are blinded. A few randomized clinical trials have addressed lifestyle factors in relation to T1D or T2D, primarily investigating the effect of physical activity and diet. In the area of environmental exposures like air pollution, noise, chemicals, metals and green areas, no randomized clinical trials are available.

Mendelian randomization is a study design that is being used increasingly in the medical field. This is a kind of natural experiment where genetic variants with a known function are used to evaluate whether there is a causal association between an exposure factor and

disease. In order to do this, you need a genetic variant that is known to be associated with the exposure of interest, e.g. by altering the biological response to that exposure. A major advantage of this design is that confounding is minimized, since genetic variants are distributed randomly at conception. However, this approach has limitations since several assumptions have to be fulfilled in order for the results of the Mendelian randomization study to be valid.

Research on the association between diabetes and lifestyle or environmental factors is primarily based on **epidemiological studies**. The quality of such studies depends on how well exposure and outcome (i.e. diabetes) is assessed. Self-reported information on exposure is commonly used, especially in studies of dietary factors and this is a limitation. Using biomarkers can improve the exposure assessment. Some environmental exposures are estimated from validated models, such as air pollution, noise and green space. It is also important to identify all incident cases of diabetes that occur during follow-up. This can be problematic since diabetes can go undiagnosed for several years, and also since individuals with T2D typically are treated in primary care and may therefore not be identifiable in hospital records of in-patient care registers. Finally, it is vital that confounding is minimized. It should also be noted that small effect sizes, common in studies on environmental factors and diabetes, are more sensitive to potential influence of confounding than large effects.

The epidemiological study design with the strongest weight of evidence is a prospective cohort study where exposure is measured prior to disease onset, and incidence of the disease is assessed during follow-up. However, for rare outcomes like T1D and LADA, a case-control design may be the most efficient way to include enough incident cases for meaningful analyses. Apart from the limitations mentioned above, a case-control study often relies on retrospective information on exposure, which may be subject to recall bias, especially problematic when it comes to the assessment of dietary intake. Cross-sectional studies can be valuable for hypothesis generation but are not suitable for causal inference since it cannot be determined whether the exposure preceded the outcome.

To what extent we can draw causal conclusion based on epidemiological data also depends on whether there is support for a causal effect from other types of studies including randomized clinical trials, Mendelian randomization studies, experimental studies in animals or other types of mechanistic studies. The number of studies in an area and consistency across those studies are also important for evaluation of the overall weight of evidence of a causal association between exposure and disease.

LIFESTYLE

SOFIA CARLSSON

INTRODUCTION

Lifestyle factors play a pivotal role in the promotion of T2D as shown in a large number of epidemiological studies from populations across the globe. Obesity and sedentariness are the strongest risk factors, especially in combination with family history of diabetes. Data from two landmark randomized clinical trials published in the early 2000s showed that lifestyle modification including weight loss and increased physical activity may dramatically reduce the incidence of T2D[1, 2]. Besides those factors, the risk of T2D has also been linked to individual dietary factors (discussed in the next chapter), tobacco use, low birth weight and psychosocial factors. Lifestyle factors have primarily been shown to influence the risk of T2D by promoting insulin resistance, the key feature of T2D. It is not clear if and how lifestyle factors influence the development of autoimmune forms of diabetes like T1D and LADA. Despite many efforts, it has proved difficult to identify any lifestyle or environmental factors that may trigger or promote the underlying autoimmune process[4-7]. Studies on T1D have primarily focused on children; follow-up of birth cohorts3 have been instrumental in identifying candidate risk factors for T1D. There is a shortage of studies on potential risk factors for T1D with adult onset, even though T1D may develop at any age. Therefore, data on the association between lifestyle factors and autoimmune diabetes in adults is limited to a small number of studies on LADA, all based on Scandinavian data[7]. In this section we summarize the vast literature on lifestyle factors and T2D and give an overview of some lifestyle factors that have been linked to T1D or LADA and the proposed role of infections.

TYPE 2 DIABETES

OVERWEIGHT/OBESITY

There has been a global rise in prevalence of overweight and obesity in parallel with the rise in diabetes prevalence. According to WHO, 39% of the population was overweight in 2016 and 13% was obese, which is nearly a tripling since 1975[8]. More than half of the Swedish population aged 16 to 84 years reported being overweight in 2018[9]. Obesity causes insulin resistance and about 70% of all obese individuals are insulin resistant[10]. Adiposity affects glucose metabolism primarily by increasing circulating free fatty acids. This results in increased storage of fat in muscles and the liver and may also impair insulin signalling which results in insulin resistance and consequently, reduced glucose uptake. In addition, adiposity leads to increased secretion of proinflammatory cytokines that inhibit insulin action which leads to reduced glucose uptake and systemic inflammation. Simultaneously, release of molecules that enhance insulin sensitivity such as adiponectin is reduced in obese individuals[10]. Consequently, excessive weight is the strongest indicator of an individual´s risk of developing T2D; incidence increases progressively with body mass index (BMI) and being obese (BMI $\geq$30 kg/m^2) is associated with a seven-fold increased risk compared to being normal weight (BMI <25)[11]. The association with T2D is linear, every unit increase in BMI has been estimated to increase the relative risk by 18%[12]. Abdominal obesity is particularly detrimental as visceral fat is a stronger determinant of insulin resistance than subcutaneous fat, and therefore there is a strong association between waist circumference,

waist-to-hip ratio and waist-to-height ratio and the risk of T2D[13]. Importantly, it has been estimated that 70-82% of all T2D patients are attributable to overweight and obesity[14]. Support for a causal relationship between adiposity and T2D comes also from Mendelian randomization studies which show associations with both BMI and waist circumference[15]. The process by which overweight promotes diabetes starts early, data from the Swedish AMORIS study show that patients with T2D display higher BMI levels than non-diabetic counterparts already twenty years prior to diagnosis[16]. Data from the Stockholm Diabetes Prevention Program also indicate that the risk of T2D increases with duration and not only degree of overweight[17]. Furthermore, overweight is especially harmful in individuals with family history of diabetes, the combination of these risk factors confers a 17 to 25-fold increased relative risk of T2D[14].

PHYSICAL ACTIVITY AND SEDENTARINESS

Physical activity is associated with a reduced risk of T2D[18]; high versus low total physical activity is associated with an approximately 25% reduced relative risk. These associations are believed to reflect beneficial effects of physical activity on body weight. In addition, physical activity has been shown to have direct effects on insulin sensitivity[19] and glycaemic control[20]. In line with this, epidemiological studies show that the association between physical activity and T2D is attenuated but remains after adjustment for BMI[21]. In contrast, sedentary time22 and hours of TV viewing are positively associated with incidence of T2D; after adjustment for overall physical activity, every additional hour of TV viewing per day is associated with a 9% increased relative risk of T2D in a recent meta-analysis[23]. Globally, it has been estimated that a quarter of the adult population do not reach the WHO recommendation of at least 150 min of moderate intensity physical activity per week[24] and there is nothing to suggest that levels of physical activity are increasing. On the contrary, a large Swedish study based on accelerometer data from 354,277 individuals showed a decline in cardiorespiratory fitness (VO2max) in the adult working population between 1995 and 2017, and also that the proportion of adults with low cardiorespiratory fitness (<32 VO2max) increased from 27% to 46%[25].

TOBACCO

Smoking is associated with a 39% increased relative risk of T2D and the risk increases in a dose-dependent manner by number of cigarettes smoked[26]. The association has been attributed to negative effects of nicotine on insulin resistance[27], but increased systemic inflammation[28], and adverse effects on pancreatic tissue and beta cell function[29] may also contribute to the excess risk. Snus use is also associated with increased risk of T2D[30] which is compatible with a negative effect of nicotine on insulin sensitivity. Globally, WHO has estimated that 20% of the population over the age of 15 smoke, but the proportion of smokers is falling in most parts of the world[31]. Smoking prevalence is declining in the Swedish population, according to the Public Health Agency[32], 7% of the adult population (similar in men and women) reported smoking in 2018, compared to 14% in 2006. Prevalence of snus use has been more stable and in 2018, 18% of men and 4% of women in Sweden reported daily use.

LOW BIRTH WEIGHT

There is a well-documented link between low birth weight and T2D hypothesized to reflect intrauterine exposure to malnutrition, leading to insulin resistance and/or reduced development of pancreatic beta cells[33]. The association appears to be linear and a 20% reduced relative risk has been estimated per 1 kg increase in birth weight. The underlying mechanism is not entirely clear but according to the ‘thrifty phenotype hypothesis’

introduced in 1992[34], poor nutrition of the foetus may lead to metabolic disturbances and a phenotype adapted to saving energy. Such a phenotype will, in the context of energy excess and rapid post-natal growth, have an increased risk of later obesity and T2D. In support of this hypothesis, it has been shown that the combination of low birth weight and adult overweight will lead to a very high risk of T2D[35]. One Mendelian randomization study addressed the association between low birth weight and T2D and found support for a causal effect[15].

PSYCHOSOCIAL FACTORS

It has also been suggested that psychological and psychosocial factors may increase the risk of T2D. The most consistent findings are seen for major depression, a recent meta-analysis show a 48% increased relative risk[15]. The underlying mechanism may involve cortisol, which is elevated in individuals with depression[36], and positively associated with insulin resistance[37]. The association may also, at least in part, be mediated by weight gain, poor diet, sleep deprivation, sedentariness and smoking which tend to cluster with depression[38]. On top of that, use of anti-depressants is associated with weight gain, which may further increase the diabetes risk[39]. Besides associations with depression, excess risk of T2D has also been reported in relation to stress[40], experience of adverse life events[41] and sleep disturbances, but these findings are less consistent.

SOCIO-ECONOMIC STATUS AND OCCUPATION

The risk of T2D is not evenly distributed in the population, an excess risk is found in individuals with low socio-economic status irrespective of whether it is measured by education, income or occupation[15]. The excess risk is mainly attributed to adverse lifestyle factors, which are also unevenly distributed in the population, and among those primarily obesity[42]. Data on the incidence of T2D across different occupational groups is sparse but a recent Swedish study based on data from the entire population born 1937 to 1979 explored this topic in detail[43]. The analyses revealed that the risk of T2D is highest in cleaners, professional drivers and manufacturing workers and their risk is three-fold higher than in low risk occupations such as university teachers and physiotherapists. The excess risk coincides with vast differences in the prevalence of risk factors for T2D across these occupational groups including overweight, smoking and low physical fitness.

AUTOIMMUNE DIABETES

OVERWEIGHT AND OBESITY

Excess weight has been linked to the risk of autoimmune diabetes; according to a meta-analysis based on nine epidemiological studies, obesity is associated with a two-fold increased relative risk of T1D in children (BMI assessed between ages 1 and 12 years)[44]. Support for a causal link between adiposity and T1D comes from a Mendelian randomization study[45]. This is particularly serious since prevalence of childhood obesity is increasing globally, according to WHO, there has been a ten-fold increase in the last four decades and one out of five children is overweight or obese[46]. In addition, paternal and maternal pre-pregnancy obesity was associated with increased risk of T1D in analyses of two Scandinavian cohorts[3]. LADA has also been linked to excessive weight, data from two Scandinavian studies indicate a three- to six-fold increased risk in obese individuals[14]. Insulin resistance that increases the insulin demand may mediate the effect of overweight on T1D and LADA. Through this mechanism, excess weight may stress the beta cells and

lead to accelerated beta cell apoptosis and promote onset of diabetes by accelerating an ongoing autoimmune process[47].

PHYSICAL ACTIVITY

Physical activity has been linked to a reduced risk of LADA[48]. The potential association may reflect beneficial effects of physical activity on insulin sensitivity. Whether physical activity may prevent or postpone onset of T1D remains to be investigated.

TOBACCO

As opposed to findings in T2D, several studies have linked parental smoking to a reduced risk of T1D in the offspring[49-50], including a recent study on maternal smoking during pregnancy based on data from three different cohorts[51]. A beneficial influence of smoking on autoimmune diabetes may be due to immune suppressive effects of nicotine[52]. Findings in relation to LADA are contradictory; smoking was associated with an increased risk in a Swedish study[53] and a reduced risk in a Norwegian study[54]. Considering that smoking may have negative effects on insulin sensitivity but positive effects on autoimmunity, these seemingly contradictory results may simply reflect that the net effect of these mechanisms in terms of LADA risk differs depending on population characteristics.

LOW BIRTH WEIGHT

In contrast to findings in T2D, high rather than low birth weight is associated with a slightly increased risk of T1D; a meta-analysis based on 29 epidemiological studies found a 10% increased risk in children with birth weight over 4 kg[55], after adjustment for potential confounders including maternal diabetes. It is not clear whether this reflects a causal association, alternative explanations behind this link include effects of maternal ethnicity, maternal overweight or nutrition. Only one previous study has investigated birth weight in relation to LADA and similar to findings in T2D, an excess risk of LADA was seen in individuals with low birth weight[35]. Also, in accordance with T2D studies, the combination of low birth weight and adult overweight conferred a particularly high risk of LADA indicating a similar underlying mechanism, possibly linked to foetal nutrition and a thrifty phenotype prone to obesity and diabetes[34].

PSYCHOSOCIAL FACTORS

The risk of T1D in children has also been linked to psychological stress, especially experience of serious life events. In a Swedish study, an increased risk of T1D was seen in children experiencing divorce, accidents and death in the family[56] and in a Danish registry-based study, death of a family member conferred an increased risk of T1D[57]. The associations have primarily been attributed to negative effects of stress on insulin resistance, but stress has also been suggested to affect immune response through increased cortisol levels[5]. In contrast to findings in childhood T1D, no association between a wide range of serious life events and the risk of LADA was seen in a recent Swedish study[58].

INFECTIONS

Viral infections have long been suspected as environmental triggers of T1D in children, with support coming from epidemiological, in vitro and animal studies[59]. The strongest evidence is seen for enteroviruses, a meta-analysis based on 26 epidemiological studies found a 10-fold increased relative risk of T1D in children exposed to such viruses[60]. The risk of T1D has also been linked to exposure to herpes, rota, rubella and mumps viruses[59]. More recently, respiratory infections, gastroenteritis and influenza have also been linked to

T1D[61-63]. Maternal virus infections, primarily enterovirus, is also associated with increased risk of T1D in the offspring[64]. Interestingly, a recent study from the U.S. found a 33% reduced relative risk of T1D in children who received rotavirus vaccination[65]. It has been hypothesized that virus infections can lead to a persistent low-grade infection in susceptible individuals. This may trigger an inflammatory response and subsequent autoimmunity[59]. Such an effect could potentially increase the risk of LADA, but this hypothesis remains to be explored.

ANTIBIOTICS

Exposure to antibiotics have been hypothesized to increase the risk of T1D in children by influencing the composition of the gut microbiota[66]. Broad-spectrum antibiotics have been linked to excess risk of T1D in children delivered by caesarean section[67], and children with frequent exposure to antibiotics had increased risk of T1D in two Scandinavian studies[68,69]. Results have not been consistent; two other Scandinavian studies did not find an association[70,71]. Antibiotics have not been investigated in relation to LADA.

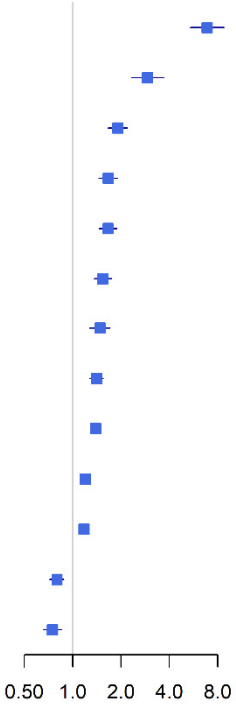
CONCLUSIONS

TYPE 2 DIABETES

Unhealthy lifestyle factors play a key role in the promotion of T2D. A Cochrane review evaluating the effect of diet and physical activity in the prevention of T2D shows that the combination of increased physical activity and diet modification reduces the relative risk by 43% in people with pre-diabetes[72]. Data from epidemiological studies support that the preventive potential of T2D is substantial: A recent meta-analysis based on 14 studies showed that individuals with the healthiest lifestyle (using information on BMI, smoking, alcohol, physical activity and diet) had 75% lower risk of developing T2D than individuals with the unhealthiest lifestyle[73]. Furthermore, a Chinese study based on > 400,000 individuals found that a healthy BMI, waist-hip ratio and diet together with non-smoking could prevent approximately 73% of all cases of T2D[74]. Importantly, data from both randomized clinical trials and epidemiological studies support that lifestyle modification substantially reduces the risk of T2D also in individuals with genetic susceptibility to diabetes[75] or family history of diabetes[75]. Among lifestyle factors, retaining a healthy weight is by far the most important factor. Estimation of population attributable risks indicate that 70-82% of all T2D cases are attributable to overweight[14]. An overview of lifestyle factors linked to T2D with strong evidence is given in Figure 6.

Figure 6. Relative risk of type 2 diabetes in relation to the lifestyle factors with the strongest evidence.

Lifestyle factor	Relative risk (95% CI)
BMI (obese vs.normal)	6.88 (5.39-8.78)
BMI (overweight vs. normal)	2.93 (2.33-3.68)
Sedentary time (high vs. low)	1.91 (1.66-2.19)
Waist-to-height ratio (per 1 SD increase)	1.67 (1.46-1.90)
Waist circumference (per 1 SD increase)	1.66 (1.47-1.88)
Waist-to-hip ratio (per 1 SD increase)	1.54 (1.36-1.75)
Major depressive disorders	1.48 (1.28-1.74)
Education (low vs. high)	1.41 (1.28-1.55)
Smoking (current vs. never)	1.39 (1.33-1.44)
Television watching (per 2 hours/day increase)	1.20 (1.14-1.27)
BMI (per 1 kg/m2 increase)	1.18 (1.15-1.20)
Birth weight (per 1 kg increase)	0.80 (0.72-0.88)
Leisure time physical activity (high vs. low)	0.75 (0.66-0.85)

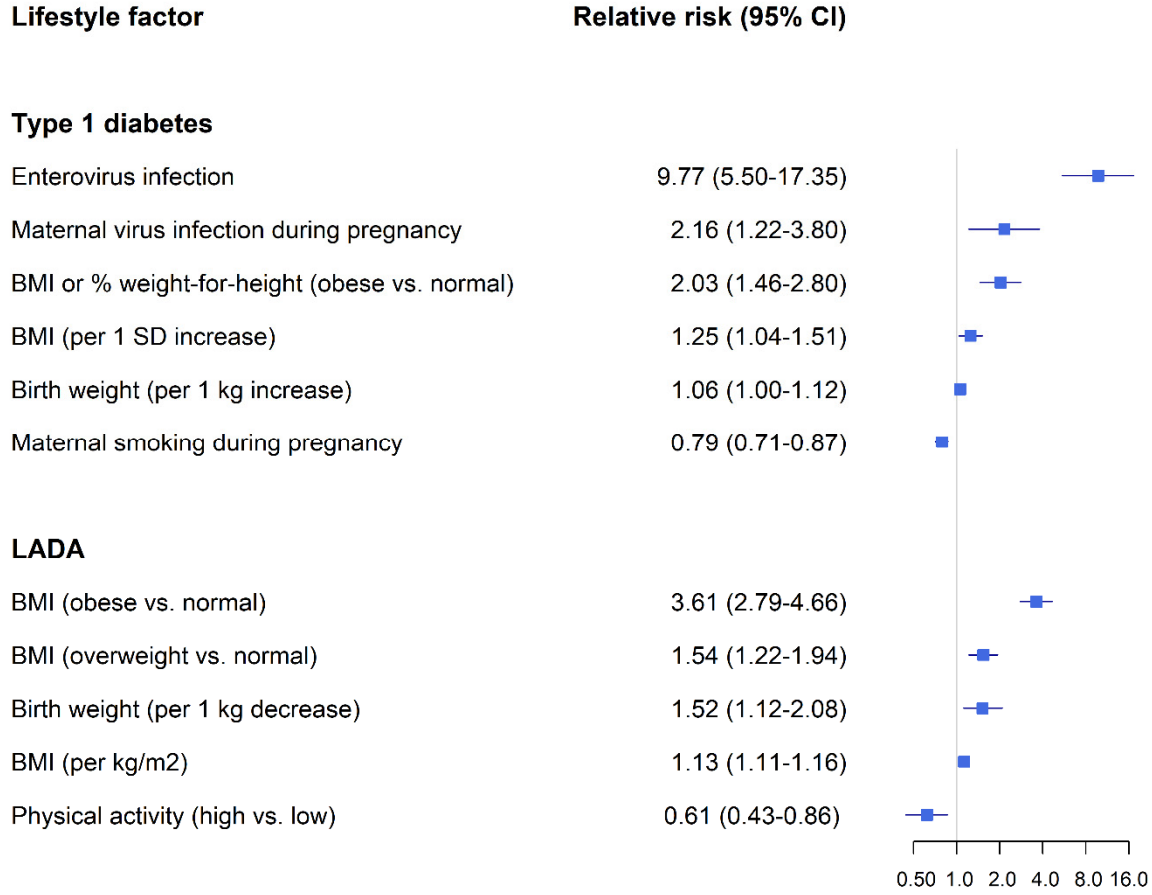


All relative risk estimates come from the umbrella review by Bellou et al[15] except for BMI per kg/m^2 that was extracted from Hartemink et al[1].

AUTOIMMUNE DIABETES

What triggers autoimmunity besides genetic factors is not clear. Associations between T1D and several potential risk factors have been reported but many have proved difficult to replicate and intervention studies have so far been unsuccessful in preventing T1D in children[4]. The strongest evidence is seen for virus infections, especially enterovirus infections, which are associated both with the occurrence of autoantibodies and T1D. Overweight is associated with an increased risk of T1D in children in epidemiological studies and this link is supported by findings of a Mendelian randomization study. Regarding LADA, results of the limited number of studies conducted to date indicate that factors known to be associated with insulin resistance and T2D like overweight, low birth weight and physical inactivity also increase the risk of LADA[7]. This suggests that insulin resistance may play a key role in the development of autoimmune diabetes in both children and adults. Estimation of population attributable risk based on Scandinavian studies indicates that overweight accounts for 31-56 % of all individuals with LADA[14]. An overview of factors linked to T1D and LADA with strong evidence is given in Figure 7. Taken together, available data suggest that overweight increases the risk of both T2D and autoimmune diabetes, most likely by promoting insulin resistance. This emphasises the importance of reducing overweight and obesity in the population in order to prevent diabetes.

Figure 7. Relative risk of type 1 diabetes and LADA in relation to the lifestyle factors with the strongest evidence.



For T1D, relative risk estimates come from Verbeeten et al.[44] (BMI), Hidayat et al.[49] (maternal smoking), Cardwell et al.[55] (birth weight), Allen et al.[64] (maternal virus infection), Yeung et al.[60] (entero virus). For LADA, estimates were taken from Hjort et al.[35] (birth weight), Rasouli et al.[53,54] (smoking), Hjort et al.[14] (BMI), Hjort et al.[48] (physical activity).

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DIET

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INTRODUCTION

Dietary habits and diet quality are of great importance in the development of T2D. Landmark intervention trials among high-risk individuals indicate nearly 60% risk reduction of T2D among individuals receiving intensive lifestyle modifications of dietary and physical activity habits compared to those receiving standard or no treatment[1,2]. A Cochrane systematic review of 12 randomized controlled trials (RCT) confirms the effectiveness of dietary and physical activity modifications in T2D development[3]. For autoimmune forms of diabetes, the role of diet is less clear; several dietary factors have been suggested to play a role in the aetiology, but the evidence is limited[4,5]. Since the body of evidence related to dietary factors is considerably larger for T2D compared to autoimmune diabetes, together with T2D being the predominant subtype in the population, the major part of this chapter focuses on T2D. The limited evidence regarding diet and autoimmune diabetes is summarized in a separate section. Overweight is the single most important risk factor for T2D. A high-quality diet helps maintaining a healthy bodyweight, which in turn is a key factor in prevention of T2D. However, on top of this, separate types of foods or nutrients may have additional beneficial, or adverse, effects on T2D risk through direct effects on insulin sensitivity or insulin secretion. Most of the studies referred to below have included measures of adiposity (most commonly BMI) in the statistical models, thus implying direct associations beyond any potential effects on adiposity.

This chapter is primarily based on recent, comprehensive review articles[4-9] complemented with important primary studies. Most of the reported findings arise from prospective cohort studies where diet has been assessed some time, often several years, prior to onset of diabetes. RCTs and Mendelian randomization studies are also considered where relevant. Studies of cross-sectional design, where diet and diabetes status are assessed at the same time point, are not considered since such studies cannot determine the temporality, i.e. whether the reported diet preceded the onset of diabetes and hence, causality cannot be inferred. Furthermore, findings from case-control studies must be interpreted with caution since such studies may be prone to recall bias, i.e. that there are systematic differences in how well cases and controls recall their dietary intake. However, in some instances a case-control study is the most efficient and feasible study design.

TYPE 2 DIABETES

FRUIT AND VEGETABLES

The overall association between both fruit and vegetable intake and T2D is modest; the risk decreases by 2% for each additional 100 g serving per day according to a meta-analysis of 13 (fruit) and 11 (vegetables) prospective cohort studies. However, a 10% decreased risk was observed for intakes up to 200-300 grams of fruit per day[7]. Furthermore, high fruit intake is also associated with lower risk of developing overweight and obesity (summary relative risk [RR] in a meta-analysis of four studies: 0.88, 95% CI 0.80-0.96)[18], implying a subsequent reduction in T2D risk given that excess body fat is a strong risk factor for T2D. For vegetable intake, a 9% decreased risk of T2D has been observed for daily intakes up to 300 grams[7]. Fruits and vegetables are rich in dietary fibers and are important sources of

micronutrients (e.g., vitamin C and magnesium), polyphenols, and carotenoids, which may decrease the risk of T2D through reduced oxidative stress and beneficial effects on glucose metabolism[19,20].

GRAINS AND GLYCEMIC LOAD

Consumption of whole grain have consistently been associated with a decreased risk of T2D; RR per one daily serving was 0.87 (95% CI 0.82-0.93) based on 12 prospective studies[6]. The reduced risk seems to be dose-dependent up to intakes of about 50 grams per day, but no additional beneficial effects for greater intakes[7]. Beneficial effects on glucose metabolism is supported also by results from RCTs[21]. Whether refined grains are associated with T2D seems less clear as no association was observed when highest versus lowest intakes were compared in a meta-analysis of 15 prospective studies, but an increased risk was found for intakes of 200-400 grams per day[7]. In support of an association, an increased risk of T2D has been observed for adherence to diets high in glycaemic load, i.e. diets including high intake of foods rich in refined grains and other carbohydrates that induce rapid rise in blood glucose levels[22].

NUTS AND LEGUMES

Nuts contain several compounds with favourable effects on glucose homeostasis, inflammation, and oxidative stress, such as dietary fiber, unsaturated fatty acids, magnesium, and polyphenols[23]. In addition, nuts are an important part of the Mediterranean diet, which has demonstrated protective effects on T2D in both RCTs and epidemiological studies (see the Dietary Pattern section below). Legumes are rich in dietary fibers and important micronutrients including folate, magnesium, and potassium. However, consumption of neither nuts nor legumes were associated with risk of T2D in meta-analyses of eight (nuts) and 12 (legumes) prospective studies[6].

DAIRY PRODUCTS

Total dairy product intake was inversely associated with T2D in a meta-analysis of 21 prospective cohort studies, where the summary RR for highest versus lowest category of intake was 0.91 (95% CI 0.85-0.97)[7]. In a dose-response analysis, the relative risk decreased by 6% up to intakes of 400-600 grams/day but with no additional risk reduction for higher levels of intake. However, a large prospective study with participants from eight European countries did not find an association between total dairy intake and T2D[24]. Results from a Mendelian randomization study based on data from the same cohort suggested that milk intake was not associated with T2D, but it was not possible to assess any other dairy products due to the instrumental variable used[25]. Fermented dairy products such as yoghurt and cheese have been suggested to exert beneficial effects on gut microbiota. Yoghurt may be the type of dairy product most commonly associated with lower risk of T2D, whereas an association is less evident for consumption of cheese and other fermented dairy products[6]. Consumption of low-fat dairy products has been suggested to be inversely associated with T2D[26] although controversies exist[6,27].

FISH, OMEGA-3 FATTY ACIDS, AND VITAMIN D

Overall, dietary fish intake does not seem to be associated with T2D incidence in prospective epidemiological studies[7]. There are geographical discrepancies in the results and increased relative risks have been reported in studies from North America, decreased relative risks in Asian and Australian studies, and no overall association in studies from Europe[28]. These differences may partly be explained by differential preparation methods or level of contamination in different species[29]. Fish, especially fatty fish such as salmon and

herring, are high in certain long-chain omega-3 fatty acids (PUFA; polyunsaturated fatty acids) including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Serum levels of omega-3 PUFA have been associated with lower risk of T2D, with the strongest association seen for DHA30. Inverse associations for fatty fish intake have been suggested based on prospective data from European and Asian populations[31,32], although not supported by all[33]. Findings from a recent Swedish study indicate that persistent organic pollutants (POPs) in fish may be masking a beneficial effect of fatty fish intake on T2D risk34. EPA and DHA have anti-inflammatory and immunomodulatory properties[35]. However, a recent Mendelian randomization study found no support for a protective effect of long-chain omega-3 fatty acids on T2D risk[36]. Fish is also an important source of naturally occurring vitamin D, which may reduce inflammation and exert beneficial effects on the immune system[37]. Higher circulating levels of vitamin D have been associated with decreased relative risk of T2D in numerous epidemiological studies[38] and supported by a recent Mendelian randomization study[39], but the role of vitamin D remains controversial since supplementation of vitamin D has not indicated any beneficial effects in RCTs[40].

EGGS

Egg consumption does not contribute to T2D risk according to a meta-analysis of 13 prospective studies[6]. Earlier studies have reported increased relative risks[41], but more recent work have found that these are generally limited to U.S. populations whereas studies from non-U.S. populations report no associations[7,42]. It is likely that the U.S. findings are explained by other factors related to egg consumption such as meat intake[43].

UNPROCESSED AND PROCESSED RED MEAT

Red meat such as beef, pork, and lamb, could be consumed as unprocessed meat, e.g. steaks or minced meat, or as processed meat products, e.g. ham and sausages. There is considerable evidence of an increased risk of T2D in relation to processed red meat consumption. In a meta-analysis of prospective studies, the summary RR was 1.27 (95% CI 1.20-1.35) when comparing highest versus lowest categories of intake, and RR per 50 g daily serving was 1.37 (95% CI 1.22-1.55). The risk associated with unprocessed red meat is lower with 17% increased relative risk (RR 1.17, 95% CI 1.08-1.26) per additional 100 g/day[7]. Consumption of red meat has been associated with elevated fasting glucose and fasting insulin levels[44]. The association with T2D may partly be mediated by weight gain[45]. There are several compounds in red meat that have been hypothesized to affect diabetes risk, including nitrates, nitrites and nitrosamines, advanced glycation end products (AGEs), sodium, and heme-iron[46], many of which are more abundant in processed red meat products compared to unprocessed meat.

SWEETENED BEVERAGES

There is convincing evidence indicating that consumption of sugar-sweetened beverages increases the risk of T2D. The relationship follows a dose-response pattern7 with summary RR of 1.26 (95% CI 1.12-1.31) for each additional daily serving of sugar-sweetened beverage in a meta-analysis of 14 prospective studies[6]. The increased risk is likely explained by a combination of factors including excess energy intake leading to increased adiposity and overweight, and direct adverse effects of the high sugar intake on glucose metabolism such as increased insulin resistance[47,48]. Artificial sweeteners, e.g. aspartame and acesulfame K, or other non-nutritive sweeteners, such as stevia, are used in some beverages as non- or low-caloric alternatives to sugar. Whether intake of these beverages affect the risk of T2D is controversial; positive associations have been suggested[6] but are potentially explained by BMI or by other dietary or lifestyle factors that co-occur with

artificially sweetened beverage consumption[49-51]. There is some mechanistic support of a role of artificially sweetened beverages and T2D risk as consumption has been suggested to distort satiety signalling resulting in enhanced appetite[52] as well as cause alterations in gut microbiota leading to deteriorated glucose tolerance[53,54]. However, consumption of two daily cans (á 330 mL) of an artificially sweetened beverage for 12 weeks showed no effects on plasma glucose and insulin levels or total energy when compared to unsweetened, noncaloric beverage in an RCT among 60 normal weight and overweight men[55]. Any potential effect of these beverages may, however, differ depending on type of sweetener used, as indicated by results from a 12-week RCT comparing the effects of high consumption of four different low-calorie sweeteners on body weight[56].

COFFEE AND TEA

Coffee consumption has quite consistently been associated with decreased risk of T2D; a meta-analysis of 30 studies found that the risk decreased by 6% for each additional daily cup of coffee. In a comparison of highest (median: 5 cups/day) to lowest (median: 0 cups/day) category of intake, the summary RR was 0.71 (95% CI 0.67-0.76)[57]. However, a potential protective effect may not be attributed to caffeine since a reduced risk has been observed for both caffeinated and decaffeinated coffee[58]. Furthermore, no support for a role of caffeine in T2D development has been found in Mendelian randomization studies[59]. Coffee is a blend of many compounds and the one most extensively studied, besides caffeine, in relation to T2D is chlorogenic acid; a polyphenol that may have favourable effects on insulin and glucose homeostasis. RCTs of coffee intake have yielded mixed findings; increased levels of adiponectin, a glucose regulatory hormone that may increase insulin sensitivity, has been reported[60], whereas others did not find effects on insulin sensitivity but reported decreases in fat mass[61].

Tea consumption was weakly associated with a reduced relative risk of T2D in a meta-analysis of 13 prospective studies[6]. In region-specific analyses, the inverse association displayed a dose-response pattern only in European studies whereas another meta-analysis of 12 studies reported an inverse association limited to Asian studies[62], which highlights the need for further studies on the role of tea on T2D risk in different populations and for different types of tea.

ALCOHOL

Consumption of alcoholic beverages is associated with T2D risk in a non-linear fashion: The lowest risks have been observed for light and moderate intakes, which were associated with 18-25% reduced relative risk (RR 0.82, 95% CI 0.71-0.94 [low] and 0.75, 95% CI 0.67-0.83 [moderate]) compared to no alcohol consumption in a meta-analysis of 26 studies[6]. Although the quality of evidence is weaker for different types of alcoholic beverages, the inverse association is primarily found for wine consumption, whereas moderate consumption of spirits is not associated with protective effects[6]. Suggested mechanisms for a protective effect of alcohol include improved insulin sensitivity[63] and decreased inflammation[64]. A meta-analysis of intervention studies failed to show improvements in insulin sensitivity in relation to alcohol intake overall (beneficial effects limited to women only) but observed improvements in fasting insulin and HbA1c[65]. Heavy alcohol consumption is not associated with T2D in epidemiological studies[6]. It is important to point out that the magnitude of the potentially beneficial effects of light and moderate alcohol intake is dependent on the choice of reference group, which varies between studies; some include both never-drinkers and former drinkers, some include only never-drinkers, and some studies define the comparison group as those with lowest intake (excluding never- and former-drinkers). For instance, in a meta-analysis of studies comparing current alcohol consumers to never-drinkers only, there were no indications of beneficial effect[66].

Taken together, many studies suggest beneficial effects of alcohol consumption on T2D risk, but some of these may potentially overestimate the magnitude of the protective effect. Importantly, although alcohol may confer some protection from T2D at light to moderate levels of consumption, alcohol abuse is identified as one of the leading risk factors for the global burden of all diseases. Thus, unlike healthy foods, alcohol consumption is not to be recommended as means of reducing T2D risk.

DIETARY PATTERN

No food item is consumed in isolation, which is why it is of interest to study dietary patterns. Adherence to various healthy dietary patterns has been associated with lower incidence of T2D[6]. The term 'healthy dietary pattern' could be considered both vague and heterogeneous. However, there are a of number of relatively well-defined dietary patterns that have been used in research of diabetes and other cardiometabolic diseases. One of the most renowned is the Mediterranean diet, which has been linked to reduced T2D risk in both an RCT setting[10] and in numerous epidemiological studies[6]. The Mediterranean diet promotes high intakes of nuts, vegetables, fruits, fish and seafood, olive oil or high monounsaturated fatty acid (MUFA) to saturated fatty acid (SFA) ratio, moderate alcohol consumption, and generally limited intakes of red meat, and (high fat) dairy products[10,11]. Higher adherence to a Mediterranean diet was associated with 15% decreased relative risk of T2D compared to lower adherence in a meta-analysis of nine prospective studies (summary RR 0.85, 95% CI 0.76-0.95)[6]. Beneficial effects of the Mediterranean diet have been attributed to improved cardiovascular health and reductions in fasting glucose, fasting insulin, insulin resistance, and inflammatory markers[12].

Another healthy dietary pattern associated with lower risk of T2D is the DASH diet (Dietary Approaches to Stop Hypertension), which is a diet rich in fruit and vegetables, low-fat dairy products, whole grain, nuts, fish, and poultry, while limited in sweets, sugar-sweetened beverages, red meat, sodium, and saturated fats[13,14]. The DASH diet was, as its name implies, originally developed to prevent high blood pressure but also seems to have beneficial effects on T2D risk[6].

In 2011, the first RCT assessing the potential effects of a healthy Nordic diet was published[15]. The diet included high intakes of high-fiber plant foods, whole grains, fruits, berries, vegetables, rapeseed oil, nuts, fish, and low-fat dairy products but limited intakes of salt, added sugars and saturated fats. The trial was designed to explore changes in cardiometabolic factors among individuals with hypercholesterolemia and indeed found the Nordic diet to improve blood lipid profiles after six weeks. The intervention group also showed improved insulin sensitivity, which was primarily related to the weight loss that occurred despite the diet being ad libitum (no caloric restrictions). A recent meta-analysis of RCTs assessing the effect of the Nordic diet on blood glucose control found reductions in serum insulin levels and insulin resistance, although no effects were found for other markers of blood glucose control such as fasting blood glucose[16]. Adherence to 'unhealthy dietary patterns' is associated with an increased risk of T2D[6]. One such example is the so-called Western diet, which is characterized by high consumption of red meat, fried products, high fat dairy products, refined grains, and sweets[17].

DIETARY SUPPLEMENTS

Most people in the Swedish population get enough vitamins and minerals through their regular dietary intake and a recent review of RCTs concluded that overall, dietary supplementation of vitamins and minerals does not seem to be important in the prevention of T2D[67]. One of the micronutrients for which the recommended intake may be difficult to reach for some people is vitamin D. Vitamin D has been hypothesized to influence T2D

risk, but this is not supported by results from RCTs; no effect of vitamin D supplementation has been found on glucose homeostasis, insulin resistance, or prevention of T2D in trials with follow-up between 4 weeks and 7 years[40,68]. Magnesium intake is associated with decreased risk of T2D and it is the micronutrient for which the quality of evidence is considered highest (moderate quality of evidence) in the umbrella review by Neuenschwander et al[6]. There is some evidence suggesting that magnesium supplementation may exert beneficial effects on glucose metabolism in high risk individuals through improved plasma glucose levels and possibly also reduced insulin resistance[69]. The beneficial effects seem to be present also among individuals with magnesium levels within the normal range[70]. However, the most recent Swedish national dietary survey found that the intake of magnesium through foods (mainly bread, dairy products, fruits, and vegetables) was adequate for most people[71]. The potential role of supplementation of omega-3 fatty acids has been investigated in RCTs, but a recent meta-analysis of these concluded that increasing intakes of long-chain omega-3 fatty acids or total omega-3 fatty probably has little or no effect on T2D prevention[72].

AUTOIMMUNE DIABETES

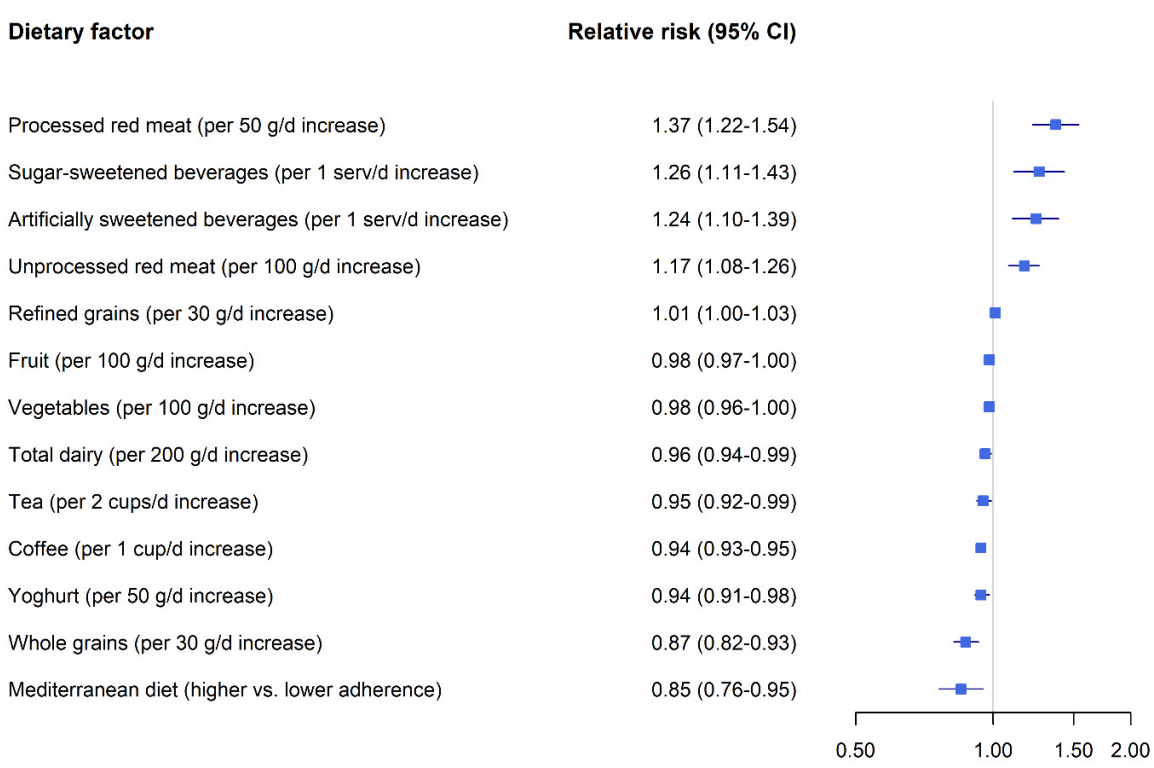
Several dietary factors have been implicated in the development of islet autoimmunity and T1D in children, but results have been inconsistent and no associations have been firmly established[8,9]. Cow's milk is among the most studied dietary factors and a high intake in childhood has been associated with increased risk of childhood T1D[8]. However, the potential role of cow's milk in the development of autoimmunity and T1D remains unclear; an RCT in genetically susceptible children showed no protective effect of early exposure to an extensively hydrolysed baby formula (with no intact proteins) compared to a conventional cow's milk-based formula[73,74]. Gluten intake has also been hypothesized to increase the risk, but this remains inconclusive since studies have provided mixed findings for both prenatal exposure and exposure in childhood[8]. Other dietary factors that have been associated with increased relative risk of childhood T1D include high intake of sugar[75], and of red meat, nitrate, and nitrite[76-78]. However, confirmations in other studies are needed, preferably based on prospectively collected dietary data.

Protective effects of omega-3 fatty acids, particularly those of marine origin, on autoimmune diabetes have been hypothesized due to their anti-inflammatory properties. Decreased relative risk of developing autoantibodies in relation to omega-3 fatty acid intake or serum concentrations have been reported[8], but findings are inconclusive[9]. Vitamin D has immunomodulatory properties and may thereby have protective effects but neither maternal nor childhood intake seem to be associated with T1D. Some studies of circulating 25-hydroxyvitamin D, which reflects the total vitamin D from diet and sun exposure, have suggested that higher levels may be associated with decreased risk whereas others have found no association[8]. Long duration of breastfeeding has been hypothesized to be protective, but this is not supported by large cohort studies[8]. The timing, both regarding age and cessation of breastfeeding, and for infant introduction to solid foods or specific foods, e.g. gluten/cereal products[79,80], has been hypothesized to play a role in T1D development but so far, such data is inconclusive.

Studies of adult onset T1D in relation to dietary factors are lacking. Studies of LADA (latent autoimmune diabetes in adults), a form of autoimmune diabetes that also shares the feature of insulin resistance with T2D, are limited but the reported findings seem to be coherent with its hybrid nature. In line with some findings on childhood T1D, fatty fish intake has been associated with a reduced relative risk of LADA[81] and an increased relative risk has been observed for processed red meat intake[82]. Furthermore, and in contrary to T2D, an increased relative risk of LADA has been observed in relation to coffee

consumption but only among those at increased genetic risk of autoimmune diabetes[83,84]. In similarity with T2D, a reduced relative risk of LADA has been reported with moderate alcohol consumption[85,86], and an increased relative risk has been reported for high intakes of sugar-sweetened beverages[87,88]. The research on dietary risk factors for LADA is still in its infancy; The presented findings are mainly based on retrospectively collected dietary data from one Swedish case-control study. Hence, it is important to replicate these findings in other populations, preferably with prospective data on dietary intake. The development of diabetes is most likely a result of complex interactions involving both lifestyle/environmental and genetic factors. Furthermore, the degree of autoimmunity as well as number and type(s) of autoantibodies vary within the autoimmune diabetes spectrum. Along those lines, several studies on LADA have found that the associations differ by degree of autoimmunity[82,85], highlighting the heterogeneity in the group of patients with adult onset of autoimmune diabetes and the complex interplay with genetic factors.

Figure 8. Relative risk of type 2 diabetes in relation to foods and beverages with the strongest evidence, adapted from the umbrella review by Neuenschwander et al[6].



CONCLUSIONS

Diet plays an important role in the development of T2D, and adherence to a healthy diet, such as the Mediterranean, may reduce the risk. Among individual food groups, whole grain and habitual coffee consumption have consistently been associated with lower risk of T2D, whereas sugar-sweetened beverages and processed red meat consumption have emerged as risk factors. The dietary factors for which the associational evidence with T2D is strongest are presented in Figure 8. Despite the numerous studies conducted, a recent umbrella review [6] concluded that there is a need for additional, high quality studies to identify dietary factors that may be used in prevention of T2D. National surveys show that intakes of fruit, vegetables, whole grain, dietary fiber, and fish are generally too low in the Swedish population, while the consumption of sugar-sweetened beverages is high. Thus,

there is room for improvement and higher adherence to the guidelines could potentially reduce T2D incidence. Importantly, evidence from studies evaluating dietary patterns as well as evaluations of single food groups in relation to T2D risk are largely in concordance with the Nordic Nutrition Recommendations[89] and the Swedish Food Agency dietary guidelines[90].

Studies published to date suggest that diet plays a role also in the development of T1D and LADA, i.e. autoimmune forms of diabetes. But so far, no dietary factors have been established in the aetiology of T1D although candidate factors exist. Regarding LADA, the number of studies is very limited but those few conducted indicate that some dietary risk factors may be shared with T2D whereas others may be more related to autoimmunity. This is important since it means that the risk of LADA may be partly modifiable and potentially reduced by adhering to a healthy diet.

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ENVIRONMENTAL CHEMICALS

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INTRODUCTION

The general population is continuously exposed to chemicals in the environment every day throughout the lifetime. Diet and drinking water are major sources for many chemical exposures, but exposure also occurs via air, contaminated soil, household dust, and consumer products, such as electronics, cosmetics, textiles, food packaging material and toys. Over the last decades, there has been an increasing concern that some of these chemicals may interfere with the normal function of the endocrine system, so called endocrine disruptors (EDs). An ED is an exogenous chemical, or mixture of chemicals, that can interfere with the normal function of the hormone system and cause adverse health effects. They may for example activate or block hormone receptors or interfere with hormone synthesis, transport or metabolism. Endogenous hormones act at very low concentrations and an increasing body of evidence from animal studies indicates that very low doses of EDs, sometimes within the range of human exposure levels, may lead to adverse effects. EDs have been pointed out as potential contributing factors to the development of several health conditions and chronic diseases, such as reproductive dysfunction, neurodevelopmental and metabolic disorders, obesity, insulin resistance, and T2D[1,2]. Especially exposure during foetal development or early childhood are of concern because of detrimental developmental effects. A previous review of epidemiological and experimental studies evaluated the evidence for involvement of EDs in the development of diabetes, based on data published until early 2014[3]. In that review, moderate human and animal evidence was found for a connection between diabetes and exposure to p,p´-dichlorodiphenyldichloroethylene (DDE), a metabolite of the chlorinated pesticide dichlorodiphenyltrichloroethane (DDT). Human evidence was also found for an association with exposure to polychlorinated biphenyls (PCBs), however, the animal evidence was considered poorer in this case. For other chemicals, including bisphenols, phthalates and fluorinated compounds, the evidence was concluded to be scarce and especially lacking prospective human studies.

In this chapter, the intention is to summarize what is known about some common environmental chemicals and their contribution to diabetes risk based on an updated literature search. Chemicals were selected for review based on their relevance in terms of widespread human exposure and reported associations with T2D, although literature on T1D was also reviewed. We focus on persistent chlorinated, brominated and fluorinated organic pollutants, as well as bisphenols and phthalates (Table 2). While the manufacture and use of some of the persistent organic pollutants (POPs) in focus here have been banned or restricted, they are still present in the environment and food chain leading to exposure in the population. In contrast, the non-persistent bisphenols and phthalates are quickly metabolized in biological systems and do not bioaccumulate. Although these chemicals do not build up in the human body, their use in consumer products is widespread, leading to continuous exposure in the population. This has been observed in biomonitoring studies from different countries, where measurable levels of phthalate and bisphenol metabolites are repeatedly reported in large portions of the study populations[4].

Table 2. Overview of persistent and non-persistent chemicals reviewed in this report.

USE AND SOURCES OF HUMAN EXPOSURE	TOXICOLOGICAL CHARACTERISTICS AND HEALTH EFFEECTS
PERSISTENT ORGANIC POLLUTANTS (POPs)	
Dioxins make up a group of 210 chemicals that are by-products of industrial processes. They accumulate in the food chain specifically in animal fat. The main sources of human exposure are fish, meat and dairy products. In new-borns, breast milk is an important source of exposure	Dioxins cause adverse effects on reproduction and development at very low doses. The also cause adverse effects on the endocrine system, liver, immune system and neurodevelopment in animal studies. Dioxins are known agonists of the Ah-receptor and perturb the normal functions of the endocrine system.
PCBs are banned but have been widely used in industrial processes, construction materials and products. There are 209 different PCBs. Some PCBs have similar structure and effects as dioxins and are known as "dioxin-like" PCBs. PCBs contaminate soil, air and water and bioaccumulate in the food chain. The main sources of human exposure are fish, meat, and dairy. In new-borns, breast milk is an important source of exposure.	Dioxin-like PCBs show the same toxicity and health effects as dioxins. Also, the non-dioxin like PCBs cause adverse effects on the endocrine system, liver, immune system and neurodevelopment in animal studies.
Chlorinated pesticides are used for destruction of insects, weeds or microorganisms. Organochlorine pesticides have high persistence in the environment and humans are exposed mainly via food, e.g. meat, fish and dairy. The chlorinated pesticides include the fungicide hexachlorobenzene, and the insecticides DDT and its persistent metabolite DDE. DDT has been used in control of malaria but is now banned in many countries.	Wide range of toxic effects. DDE binds to the androgen receptor and has anti-androgenic properties.
PFAS include >4,500 compounds, with PFOS and PFOA as the most studied. PFAS have been widely used since the 1950's in industrial and consumer applications (food packaging, water-repellent fabrics, waxes, fire-fighting foams, shampoos, cosmetics, insecticides). Their extremely persistent characteristics have led to ban of some PFAS. Human exposure is primarily via drinking water (often caused by fire-fighting foam contamination), food and leakage from food packaging.	Different PFAS have been shown to cause adverse effects on the liver, metabolism, thyroid and immune system in animal studies. Exposure to PFAS in the human population is associated with increased cholesterol in blood in adults, lower birth weight and effects on the immune system in children of exposed mothers, and cancer.
Brominated compounds Polybrominated diphenyl ethers (PBDE) have been commonly used as flame retardants in plastics and textiles. They are easily released from products such as furniture and electronics. Human exposure is mainly from food, such as fish, shellfish and meat, and household dust. Several of the most hazardous PBDEs have been banned but persist in the environment.	PBDEs have been shown to cause adverse effects on the liver, reproductive organs, thyroid and immune system in animal studies. They also seem to affect reproduction and neurobehavioral development. In humans, associations have been observed between PBDE-exposure and effects on the thyroid hormones.
NON-PERSISTENT CHEMICALS	
Bisphenols are commonly used in plastics and epoxy resins, for example in toys, construction materials, electronics and as coating in food cans. They are also used in thermal printing papers. The most common is BPA. The main source of human exposure is via food that has been in contact with materials containing bisphenols, household dust and cashier receipts.	Many bisphenols have been shown to have endocrine activity in cell studies and to disturb the endocrine system in animal studies. BPA is an ED with estrogenic properties and adverse effects on reproduction and development in animal studies. Effects of BPA on CVD and neurobehavioral development has been reported in human studies.
Phthalates are used as plastic and rubber softeners in toys, flooring and medical tubing. They are also used in paints and adhesives. Human exposure mainly occurs orally, e.g. by putting toys in the mouth, or via air, as phthalates are very volatile.	Several phthalates are identified as EDs under EU regulation. They have primarily anti-androgenic properties and cause adverse effects on reproduction and development.

PERSISTENT ORGANIC POLLUTANTS

Persistent organic pollutants (POPs) are chemicals that are persistent in the environment and have the potential for long-range transport and the ability to bio-magnify and bio-accumulate in ecosystems. They also have significant negative effects on human health and the environment. The chlorinated POPs, which include dioxins, polychlorinated biphenyls (PCBs) and organochlorine (OC) pesticides, are among the most widely dispersed and most concerning POPs. The dioxins and PCBs comprise large numbers of individual compounds, which are grouped into the categories polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) on the one hand, and dioxin-like (DL) and non-dioxin-like PCBs on the other hand. Dioxins are mainly by-products of industrial processes but can also result from natural processes, such as volcanic eruptions and forest fires. PCBs are man-made synthetic chemical mixtures, widely used in electrical equipment, liquid ink solvents and especially plasticizers. The OC pesticides were produced to be toxic to living organisms, used to protect crops against unwanted insects, weeds or microorganisms and include individual compounds such as the fungicide hexachlorobenzene, and the insecticide DDT and its persistent metabolite p,p′- DDE. In addition to the chlorinated POPs, there are also brominated and fluorinated POPs, such as the brominated flame-retardants (BFRs), and the perfluoroalkyl and polyfluoroalkyl substances (PFAS). BFRs and PFAS are industrial chemicals in current production and frequently used in numerous common consumer products. More than 4,500 PFAS are currently on the market. There are 28 POPs listed by the Stockholm Convention[5] which means that they are destined for elimination, restriction, or reduction because of their toxicological properties in biota, their persistence and bioaccumulation potential in the environment and living organisms, and their wide global distribution. Several of these listed chemicals are organochlorine pesticides (e.g. DDT, chlordane, dieldrin and aldrin). Out of the brominated and fluorinated compounds, only a few have been listed (e.g. perfluorooctane sulphonate (PFOS), perfluorooctanoic acid (PFOA), a handful of polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD).

EXPOSURE

Chlorinated POPs are highly persistent and lipophilic and accumulate in the food chain. As a result, there is a pronounced age-dependent body burden increase in humans[6] and wildlife. Despite regulatory activities through the Stockholm convention and other national and international activities to minimize environmental emissions and human exposures – a process that started in the 1980's in most countries –, chlorinated-POPs continue to be detected in human adipose tissue, blood and breast milk worldwide[6,7]. Once these fat-soluble hydrophobic molecules enter the body, they are primarily stored in adipose tissue and slowly released into the circulation to be eliminated over several years[8]. Sources for current exposure are mainly fatty food of animal origin such as fatty fish, meat and dairy products[9,10]. Since chlorinated POPs are hydrophobic, they generally do not occur in drinking water or food of plant origin at levels of health concern. Large segments of the population are being exposed to background dioxins and PCBs levels that are exceeding the tolerable weekly intake (TWI) recommended by the European Food Safety Authority (EFSA)[11]. Occupational and accidental by-stander exposure may still occur in certain areas of the world. Humans are currently exposed to PFAS in daily life, mainly through drinking water[12] and diet, with fish and seafood as suggested important sources[13]. PFAS also appear in an array of everyday items, such as textiles, furniture, clothing, polishing and cleaning agents and in food packaging and cookware, leading to contamination of food[14,15]. In the recent EFSA evaluation, small or non-existing safety margins were identified for both PFOS and PFOA. As a result, EFSA[16] launched a preliminary TWI that was markedly decreased for PFOS and PFOA and a considerable proportion of the European population

exceeds this TWI. BFRs have been used in a variety of materials, such as furniture, electronics, and construction materials, as flame retardants.

DIOXINS, PCBS AND CHLORINATED PESTICIDES

EPIDEMIOLOGICAL STUDIES

Plasma measurements of dioxins, PCBs and chlorinated pesticides have been associated with T2D and insulin resistance in population-based studies, largely supported by cross-sectional studies and accidental, occupational and geographical (subjects living near a contaminated area) exposure studies[17]. As an example, in total 41 cross-sectional and eight prospective studies published through early 2014 were compiled in a meta-analysis[18]. The pooled relative risks estimates for T2D were, based on comparison of the highest concentration category with the lowest, 1.91 (95% CI, 1.44-2.54) for dioxins, 2.39 (95% CI, 1.86-3.08) for total PCBs, and 2.30 (95% CI, 1.81-2.93) for chlorinated pesticides. Results from prospective studies were, however, only available for PCBs and for the chlorinated pesticides, showing a pooled RR of 1.63 (95% CI, 1.15-2.33) and 2.43 (95% CI, 1.39-4.25), respectively. All these prospective studies adjusted their analyses for BMI and were, with few exceptions, based on self-reported T2D diagnosis (Table 3-4). After this meta-analysis, two nested case-control studies have been published[19,20]. In the American Nurses' Health Study, the ORs were 1.55 (95% CI, 1.13, 2.13) for DDE and 1.95 (95% CI, 1.42, 2.69) for the sum of DL-PCBs, comparing highest tertile with lowest[20]. They also reported the results for hexachlorobenzene HCB; OR, 1.67 (95% CI, 1.24, 2.23). In this study, the OR estimates were dependent on whether the authors adjusted the models for baseline BMI – and only DL-PCBs remained clearly associated with T2D incidence after this adjustment (OR, 1.78; 95% CI, 1.14-2.76). The researcher also observed that not only baseline BMI but also pre-baseline weight change affected the associations. In fact, there were interactions between the chlorinated POPs and weight change before baseline and incidence of T2D. Thus, they observed stronger associations among those who had been weight stable as compared to those who gained weight before baseline corresponding to OR 2.41 (95% CI, 1.22-4.77) for the DL-PCBs. The results from this study clearly highlight the complex link between blood concentrations of the chlorinated POPs, adiposity and incidence of T2D (see section below). The second nested case-control study was performed in a Swedish population-based prospective cohort and included repeated measurements of the chlorinated POPs before and after T2D diagnosis – a diagnosis validated by specialists based on the WHO recommendations including the absence of autoantibodies in blood. The researcher observed around 50% increased ORs per one standard deviation increase in the different chlorinated POPs; ORs 1.42 (95% CI, 0.99-2.06) for the sum of non-DL-PCBs and 1.44 (95% CI, 0.99- 2.10) for the sum of DL-PCBs, 1.55 (95% CI, 1.01-2.38) for HCB, and 1.46 (95% CI, 0.97-2.18) for DDE[19]. These models were adjusted for BMI and the results were independent of whether the concentrations of the chlorinated POPs were expressed by their wet-weights or were standardized to the lipid content of the blood plasma[19]. Importantly, while the DDE concentrations in the American study of nurses[20] were similar to that in the Swedish study, the exposure to DL-PCBs (n=2; PCB118 and PCB156) and HCB was higher in the Swedish study[19].

Given the long half-life of chlorinated POPs, it is generally considered that blood concentrations are a good reflection of very long-term exposures. Nevertheless, a bias may arise in cross-sectional and case-control studies, where the concentrations are measured at the time of, or after, the T2D onset. There is a possibility that T2D might alter the metabolism of the chlorinated POPs, slowing down their excretion from the body and/or increased lipolysis, which releases them from the storage in adipose tissue[21], both mechanisms leading to increased serum concentrations in T2D in cross-sectional studies[19].

The potential overestimation of the association with T2D by the cross-sectional design was explored in the aforementioned Swedish study[19], where the odds of T2D was assessed both prospectively and cross-sectionally in the same individuals accounting for factors related changes in concentrations. An attenuation of the ORs was observed moving from the cross-sectional to the prospective assessments, evidencing this speculated reverse causality. In this case the subjects with T2D were successfully intervened on regarding individual factors such as weight and blood lipids as a result of the diagnosis. However, despite the evidence suggesting the existence of a reverse pathway (T2D causing elevated chlorinated POPs in blood), the magnitude of the reverse effect does not seem to be very large[18,19,22].

Table 3. Prospective studies on PCBs (mainly focusing on the dioxin-like (DL) PCBs) measured in blood in relation to type 2 diabetes.

Type of study	Type of PCBs	Exposure categorization comparisons	No of cases / BMI-adjustment	Multivariable-adjusted RR/OR (95% CI)
Meta-analysis of eight cohort studies[18].	A mix of PCBs both DL- and non-DL-PCBs	4th quartile vs. 1st PCB-poisoned victims vs. ref pop 4th quartile vs. 1st to 3rd 5th quintile vs. 1st 3rd tertile vs. 1st	Adjusted for BMI	Pooled 1.63 (95% 1.15-2.33)
Nurses' Health Study; Nested case-control study[20].	DL-PCBs	3rd tertile vs. 1st	793 case-control pairs. With and without BMI adjustment	1.95 (95% 1.42-2.69) without BMI; 2.60 (95% 1.81-3.72) adjusted for weight change; 1.78 (95% 1.14-2.76) adjusted for weight change and BMI
Västerbotten Intervention Programme; Nested case-control study[19].	DL-PCBs	Per 1 SD increment	129 case-control pairs. With and without BMI	1.34 (95% 1.00-1.79) without BMI; 1.44 (95% 0.99-2.10) with BMI.

The average exposure biomarker of the DL-PCBs (two were in common: PCB118 and PCB 156) indicated higher exposure at baseline in the Swedish study as compared to the US-cohort of nurses.

Adiposity is important to consider in studies assessing the association between biomarkers of chlorinated POPs and T2D, because higher body fat is linked to a slower elimination of these substances. This means that historical BMI, a very strong risk factor for T2D, affects the actual POP concentration, especially in a situation when the exposure is decreasing (non-steady state). On the other hand, in the Nurses' Health Study, weight gain before blood collection was consistently associated with lower concentrations of all groups of chlorinated, possibly due to dilution by the expanded adipose tissue compartment. Another complicating factor is that both BMI and plasma lipid concentrations could potentially lie in the causal pathway between the chlorinated POPs and T2D, acting as mediators, and in this case adjusting for BMI will not provide the results of the total effect. But since both BMI and plasma lipid are correlated with the exposure—elevated lipid concentrations tend to carry proportionally higher concentrations of lipid-soluble contaminants – and with the outcome, they might also act as confounders for the associations with T2D. There are also

studies (cross-sectional) suggesting that accumulated chlorinated POPs in adipose tissue may play a more critical role in the pathogenesis of T2D than the adipose tissue itself[23], but this is difficult to verify. Despite all these methodological constraints, the best evidence of a link between chlorinated POPs and T2D seems to exists for DDE and the dioxin-like PCBs[3,19,20]. Those studies evaluating both insulin resistance and secretion have reported that blood concentrations of the chlorinated POPs were more strongly associated with decreased insulin secretion than with increased insulin resistance[24-27]. This could be because the overproduction of insulin by pancreatic beta cells during insulin resistance can mask the direct effect of these substances on beta cell function[25].

Table 4. Prospective studies on organochlorine pesticides (mainly focusing on p,p'-dichlorodiphenyl-dichloroethylene; DDE) measured in blood in relation to type 2 diabetes.

Type of study	Type of pesticides	Exposure categorization	No of cases/BMI-adjustment	Multivariable-adjusted RR/OR (95% CI)
Meta-analysis of five cohort studies through early 2014[18].	Mix of pesticides mainly DDE	4th quartile vs 1st to 3rd; 3rd tertile vs 1st. 4th quartile vs 1st. 5th quintile vs 1st	Adjusted for BMI	Pooled 2.43 (95% 1.39-4.25)
Nurses' Health Study; Nested case-control study[20].	DDE	3rd tertile vs. 1st	793 case-control pairs. With/ without BMI-adjustment	1.55 (95% 1.13-2.13) without BMI-adjustment; 1.66 (95% 1.17- 2.36) adjusted for weight change; 0.93 (95%.59-1.46) adjusted for weight change and BMI
Västerbotten Intervention Programme; Nested case-control study[19].	DDE	Per 1 SD increment	129 case-control pairs. With/without BMI-adjustment	1.50 (95% 1.12-2.00) without BMI; 1.46 (95% 0.97-2.18) with BMI adjustment

The average exposure biomarker DDE showed very similar concentrations in the Swedish study as in the U.S. cohort of nurses.

EXPERIMENTAL STUDIES AND POTENTIAL MECHANISMS

In animal studies, dioxins, PCBs and chlorinated pesticides have been shown to alter glucose homeostasis, including the induction of hyperglycaemia and glucose intolerance[28], and insulin resistance[29,30]. Available experimental data indicate that these substances can act as direct oxidative and inflammatory agents, increasing the production of reactive oxygen species (ROS) and activating inflammatory pathways, and thereby disrupting glucose homeostasis and increasing the risk of insulin resistance and ultimately diabetes[31]. These inflammatory and oxidative effects may be induced by impairment of mitochondrial function, since mitochondria are a target of environmental toxicants[32]. Chlorinated pesticides have been shown to impair mitochondrial function in hepatocytes and aggravate disorders of fatty acid metabolism, especially DDT[33,34]. An in vitro cell study demonstrated that chlorinated pesticides can directly reduce insulin secretion at very low doses[25]. In vitro studies show that low doses of dioxin reduce glucose uptake in the adipose tissue, pancreas, and liver[35] and cause autophagy in beta cells[36] and death of beta cells[37], due to an increase in pro-inflammation cytokines. Additional studies have demonstrated that dioxin can modulate the insulin signalling cascade at the level of the insulin receptor 38. PCB treatment of beta cells resulted in an increase in intracellular calcium levels and an

activation of Ca2+/calmodulin-dependent kinase II (CaMK2). Because glucose-stimulated insulin secretion is a calcium-dependent process, disruption of this signalling pathway is a likely target for PCB-mediated beta cell disruption[39]. The DDT metabolite DDE has also been shown to affect beta cell function, by downregulating the expression of glycolysis-associated proteins[40]. Dioxins and dioxin-like PCB congeners exert their toxicity mainly via activation of the aryl hydrocarbon receptor (AhR). It should be noted, however, that there are differences in sensitivity of the AhR between humans and rodents, which may limit conclusions for human health. In vitro[41-44] and animal[45-48] evidence reveals, however, that dioxin-like PCBs induce chronic inflammation, through different AhR-mediated pathways such as via expression of several inflammatory markers[41,43] or increasing cellular oxidative stress[45].

Many of these substances are known to be able to interfere with hormone signalling pathways. For example, PCBs include mixtures of congeners with estrogenic and antiestrogenic effects[49,50] and DDT is known to have oestrogen agonist activity[51], but its metabolite DDE has antiandrogenic properties[52]. There are also interactions between the AhR and oestrogen receptor signalling pathways, suggesting that dioxins could have indirect effects on some oestrogen-mediated endpoints as well[53]. The non-dioxin-like PCBs do not activate AhR, but instead bind to and activate the constitutive androstane receptor and/or the pregnane X receptor[54,55]. Both of these nuclear receptors are also implicated in the intermediary metabolism of physiological molecules such as hormones, vitamins, fatty acids, triglycerides, and cholesterol[56,57]. In the aforementioned 1999–2002 NHANES cross-sectional study[23], the magnitude of association between chlorinated POPs and T2D was much stronger with trans-nonachlor, oxychlordane, p,p′-DDE, and PCB153, which do not have dioxin activity, than with the PCDDs, which do have dioxin-like activity. In fact, the chlorinated POPs' toxic equivalency factors (TEFs), which measure the ability of a given dioxin-like contaminant to bind to the AhR, were not related to the strengths of the associations between these substances and T2D in that study.

PFAS AND BROMINATED COMPOUNDS

EPIDEMIOLOGICAL STUDIES

The epidemiological evidence on PFAS exposure and T2D is limited and inconsistent, and only three of the existing studies are prospective[58-60]. There are some reports showing null[58,60,61] or inverse associations[62], but also positive associations[59,61,63], such as the recent prospective nested case-control U.S. study (Nurses' Health Study II)[59]. However, the recent prospective nested case-control study performed in Sweden[64] yielded overall inverse associations between individual PFAS and incidence of T2D, although mostly statistically non-significant. Moreover, PFAS were associated with improved trajectories of insulin resistance during 10 years of follow-up in the diabetes-free individuals[64]. The explanation for the overall contradicting results is unclear, and it is puzzling that different studies of adequate quality across the world generate contrasting results, even at similar levels of exposure. We can speculate that the diet and possibly lifestyle, which differ among populations, could be a common cause of both the PFAS exposure and the development of T2D, being able, consequently, to bias the findings. For instance, foods contaminated by food packaging material[65] such as popcorn[59] could be an important source of PFAS exposure in some populations, while the consumption of fish could be the dominating source in other. If this is the case, the potential beneficial effects of fish consumption or the detrimental effects of fast food consumption on T2D could hide or override any effects of PFAS. Altogether, human epidemiological studies published to date provide insufficient support for an association of PFAS with T2D, obesity and metabolic syndrome. In contrast, EFSA considers the support for causal associations between exposure to PFOS and PFOA

and increased serum levels of cholesterol to be strong16. The human evidence regarding bromated POPs is scarce and currently lends no support of an association with T2D[3,17].

EXPERIMENTAL STUDIES AND POTENTIAL MECHANISMS

Some animal data support a potential beneficial effect of PFAS in T2D pathology[66-68]. PFAS are activators of the PPARs (peroxisome proliferator-activated receptors)[69], which play a critical role as regulators of lipid and glucose metabolism[70,71]. Some hypolipidemic and antidiabetic drugs targeting PPAR, such as fibrates and thiazolidinediones, have been widely used[72,73]. On the other hand, PFAS, especially PFOA and PFOS, induce ROS production, likely as a consequence of inhibition of the mitochondrial respiratory chain[74-76]. It has also been shown that livers from rats treated with PFOS presented augmented ROS levels and diminished antioxidant defence (decreased superoxide dismutase (SOD) and catalase activities[77]. Therefore, whether these latter compounds improve or disrupt glucose homeostasis is not clear.

AUTOIMMUNE DIABETES

Currently, there is no support of any associations for PCBs, pesticides or PFAS and autoimmune diabetes[78]. In contrast to epidemiological data, exposure to the non-dioxin-like PCB-153 was found to reduce the incidence of T1D in an experimental study using the non-obese diabetic (NOD) mouse model[79], and another experimental study found that high doses of the DDT metabolite p,p'- DDE increased diabetes incidence and severity in NOD mice[80]. Similarly, life-long exposure to perfluoroundecanoic acid (PFUnDA) was shown in one study using the NOD mouse model to result in detrimental effects on the pancreatic islets and the immune system at the highest doses, while lower doses seemed to have a protective effect[81].

BISPHENOLS

Bisphenols are chemicals that are used in a variety of industrial applications and production of different materials[82]. Bisphenol A (BPA) is the most commonly used bisphenol and is produced in very large volumes globally. Bisphenols are used for the manufacture of polycarbonate plastics and epoxy resins and as antioxidants and UV-stabilizers in a wide range of industrial applications and in consumer products[82]. They are also used as developing agents in thermal paper, such as receipts and tickets. The toxicity of BPA has been extensively studied in animals and humans and it is one of the few chemicals that has been identified and regulated as an ED under the European chemical's legislation REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals). BPA can bind to and activate oestrogen receptors in the cell nucleus, as well as on the cell surface and causes reproductive toxicity in animal studies in the form of reduced fertility and effects on the development of offspring. Recent studies indicate that it may also interact with androgen receptors and the thyroid hormone receptor. The toxicity of other bisphenols, such as Bisphenol F (BPF), Bisphenol S (BPS) and Bisphenol AF (BPAF), which are increasingly used to replace BPA, is much less investigated but based on the data available and similarities in molecular structure it is likely that many bisphenols exhibit the same type of toxicity as BPA 82,83. BPA is banned from use in baby bottles throughout the EU since 2011 and the use in thermal paper was banned from January 2020. Sweden also has national bans in food packaging for children up to three years of age and against the use of BPA in the relining of water pipes. Use of the other bisphenols are not yet regulated.

EXPOSURE

Polycarbonate plastics and epoxy materials have a widespread use in many different consumer products and applications, such as food and water containers, lining of food cans, dental filling materials, building materials, and electronics, and exposure to bisphenols is prevalent in the general population[83]. Bisphenols are not very volatile, and the main route of exposure in humans is via ingestion, for example via food that has been in contact with polycarbonate plastics or epoxy materials. Bisphenols are also commonly found in household dust 84, which provides a significant source of exposure especially in small children. Exposure to bisphenol (commonly BPA or BPS) from thermal papers (receipts or tickets) may also be significant 82,83. Bisphenol is applied to the surface of the paper and not bound into the material, meaning that it may readily be transferred onto the skin by touching the paper. However, BPA has been found to not be absorbed via skin to a large degree and the most significant exposure from thermal paper is likely from putting hands in the mouth or transfer of the chemical from the hands onto food. Another likely scenario is that small children may put paper receipts into their mouths, which would result in a very high short-term exposure relative to the background bisphenol exposure. BPA has also been found in breastmilk and it may cross the placenta leading to exposure of the developing foetus via the mother's blood.

EPIDEMIOLOGICAL STUDIES

In cross-sectional assessments, subjects with T2D generally show higher concentration of BPA in urine. In prospective assessments no significant associations were observed with T2D[85] or were reported only in sub-groups, such as the younger of two cohorts included in a case-control study nested in two US-cohorts – the Nurses' Health Studies[86]. In another prospective cohort study, BPA showed no significant associations with the incidence of T2D or with 4-year change of fasting or 2h plasma glucose levels. The authors did, however, observe BPA to be significantly associated with a 4-year increase in fasting glucose in participants with a higher genetic risk score of diabetes[87]. The very short half-life of BPA in the body is a challenge in epidemiological studies, questioning the relevance of a single exposure measurement. In a recent case-cohort study from France, BPA and BPS were measured twice in >700 participants (baseline and at 3 years) during totally 9 years of follow-up of incident diabetes[88], which is a step toward refining the exposure assessment. In this study incident diabetes was defined as either treatment with glucose-lowering agents, or elevated fasting plasma glucose or glycated haemoglobin at any of the three health examinations after inclusion and multivariable-adjusted models were adjusted for BMI. BPA (mean of the two measurements, but not the baseline measurement alone) was associated with increased risk of T2D, but there was no clear dose-response. Participants in the second, third, and fourth quartile of mean BPA concentrations in urine had close to a doubling of the incidence of T2D, with hazard ratios (HRs) 2.56 (95% CI: 1.16, 5.65), 2.35 (95% CI: 1.07, 5.15), and 1.56 (95% CI: 0.68, 3.55), respectively. For BPS, the presence, as compared to not detected in urine at one or both time points were associated with incident diabetes, with HR 2.81 (95% CI: 1.74, 4.53). The results demonstrated a nonlinear relationship between exposure to BPA and diabetes incidence. The nonmonotonic association could be due to chance but is also consistent with the nonmonotonic dose-response relationships described for BPA in the literature, hypothesized to be related to cytotoxicity, receptor regulation or the competition with endogenous hormones.

EXPERIMENTAL STUDIES AND POTENTIAL MECHANISMS

Development of T2D or associated metabolic disturbances after exposure to BPA has been extensively investigated in experimental studies. Several recent reviews exist that summarise in vitro and in vivo data and suggest plausible mechanisms implicating BPA in the development of T2D[3,89-91]. In vivo studies in rats and mice generally show effects on insulin synthesis and secretion, as well as impaired glucose homeostasis and glucose intolerance. The data indicate that BPA exposure affects the endocrine pancreas and that different mechanisms may be at play, depending on the timing of exposure[89]. Exposure during foetal development seems to interfere with cell differentiation in the pancreas, affecting beta cell proliferation and apoptosis and leading to increases in pancreatic beta cell mass. A potential mechanism initiated by altered oestrogen signalling in foetal life leading to modifications of beta cell mass and an excess of insulin signalling during early life and impaired glucose tolerance during adulthood has been suggested[92]. Adult exposure to BPA has been reported to enhance oxidative stress in the pancreas, which may provide a mechanism for the observed effects on insulin and glucose homeostasis. Data from an in vitro study in the pancreatic beta cell line INS-1E, showed that BPA reduces pancreatic beta cell function, however, relatively high doses were tested in this study[93]. Another potential mechanism may be via epigenetic dysregulation of genes involved in glucose and lipid metabolism, which has been reported in recent rodent studies after developmental and adult exposure to BPA[90]. However, further studies are needed to elucidate the plausibility of epigenetic changes as a mechanism for BPA-induced T2D development. BPA and other compounds acting via activation of oestrogen receptors have been shown to cause obesity in animal studies[94], providing another possible mechanism for some bisphenols contributing to metabolic dysfunction and T2D.

AUTOIMMUNE DIABETES

In experimental studies in the NOD mouse model, exposures to BPA and BPS have been shown to alter immune responses and accelerated development of T1D[95-99]. These effects were observed both in studies where exposure started in utero and in mice only exposed as adults. Effects were primarily observed in female mice.

PHTHALATES

Phthalates is a large group (over a hundred registered under REACH) of chemicals that are mainly used as plasticisers in plastic and rubber materials. They can be found in products such as flooring, wallpapers, cables, foil and plastic-coated fabrics, paints and adhesives, toys, shoes, and plastic tubes. Phthalates are generally very volatile and are continuously released from materials into the environment. Several phthalates are of concern for human health, mainly due to being reproductive toxicants, and having endocrine disrupting properties acting as anti-androgens[100,101]. Five phthalates, namely dicyclohexyl phthalate (DCHP), diisobutyl phthalate (DIBP), benzyl butyl phthalate (BBP), bis(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP) have been classified as EDs under REACH, meaning that there are restrictions to how they can be used in different materials and products. BBP, DEHP and DBP are completely banned in all toys and childcare products.

EXPOSURE

Phthalates are readily metabolised in the body and do not accumulate. However, because of the widespread use, human exposure to these substances is continuous. The general population is primarily exposed to phthalates via inhalation and from food and household dust. Small children may also be exposed from putting toys or other products in the mouth.

However, as stated above, the most problematic phthalates have been banned from use in toys. Intermittent high exposure to phthalates may occur in patients receiving medical treatments, such as transfusions. This has especially been reported for infants treated in neonatal wards[102].

EPIDEMIOLOGICAL STUDIES

A recent systematic review of the epidemiological literature aimed at evaluating the evidence of any metabolic effects associated with phthalate exposure[103]. Only one prospective study was deemed as being of adequate quality and subsequently used to evaluate the incidence of T2D – a case-control study nested in two U.S. cohorts (the Nurses' Health Study and the Nurses' Health Study II)[86] while more studies were included in the evaluation of insulin resistance. The results for the nested case-control study was dependent on the cohort. In the younger women (Nurses' Health Study II), phthalate exposure was significantly associated with T2D while there was no association among the older women (Nurses' Health Study). In the younger cohort, the OR was 2.14 (95% CI, 1.19-3.85), comparing highest quartile of total phthalate exposure (sum of eight phthalates) with lowest, adjusted for BMI. Similar results were observed for DEHP metabolites and butyl phthalates[86]. Altogether, for DEHP, DBP, DIBP the summary evidence for an association with diabetes risk was considered moderate in the systematic review[103], supported by coherence across outcomes and plausible mechanisms from animal and in vitro studies. For DINP, BBP, DEP, however, the evidence was considered slight[103].

EXPERIMENTAL STUDIES AND POTENTIAL MECHANISMS

Phthalates are known to interact with PPARs, which are receptors involved in mechanisms for adipogenesis, lipid metabolism, and metabolic homeostasis 104. Data from in vitro studies in the pancreatic beta cell line INS-1E and from animal studies indicate that exposure to phthalates may also reduce pancreatic beta cell function, potentially by increasing ROS generation and dysregulating antioxidant defence mechanisms[93,105,106]. Varying results have been reported for the effects of different phthalates on glucose metabolism, as well as obesity in animal studies[107]. This is likely due to differences between studies in terms of design and reliability, but also because different phthalates exhibit different mechanisms, effects or potency. DEHP is one of the most studied phthalates, and for which there has been high concern regarding adverse health effects. Exposure to DEHP in adult rats has been reported to decrease serum insulin levels and to interfere with insulin signalling in adipose tissue[106]. Reduction in beta cell mass, beta cell dysfunction and effects on glucose homeostasis have been observed in offspring to female rats exposed to DEHP during gestation and lactation[108]. Epigenetic changes have also been suggested as a mechanism for DEHP-induced disturbances in insulin signalling and glucose homeostasis[109,110].

AUTOIMMUNE DIABETES

In contrast to BPA and BPS, the phthalates DEHP, DBP, BBP and DiBP have not been found to accelerate development of T1D in the NOD mouse model[96].

CONCLUSIONS

Despite research gaps and some critical issues not fully addressed in most original articles, we judge the evidence adequate to conclude that exposure to dioxins, PCBs and chlorinated pesticides is associated with increased risk of T2D, independently of obesity. Furthermore, a growing body of animal and cell-based experimental studies support the effects of these persistent substances on various aspects of insulin synthesis, release, and cellular action. Currently, it is difficult to disentangle which of them that may contribute to most of the associations observed since these exposures are highly correlated. Yet the evidence seemed most consistent for the DL-PCBs and DDE because of more available data from prospective studies. For the PFAS there is limited evidence and no conclusion can be drawn.

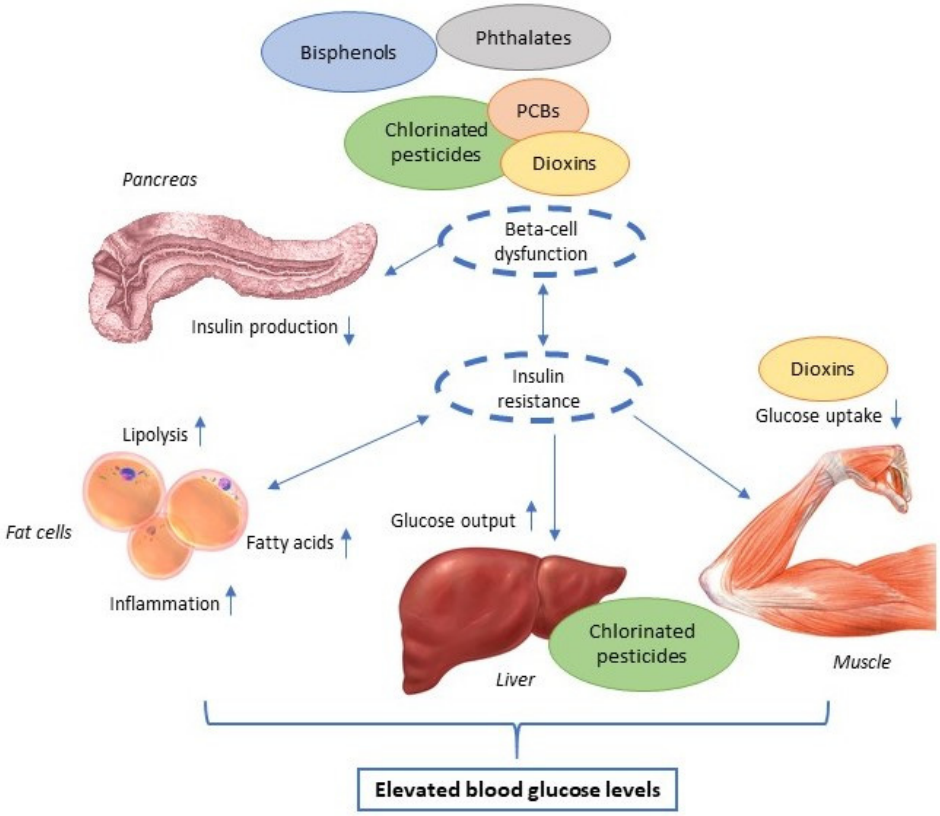
For the bisphenols and the phthalates evidence from epidemiological studies is limited, and the short half-life of these compounds complicates the epidemiological assessments. Although the evidence was summarized as moderate for some of the phthalates and T2D in a recent systematic review, we deemed the epidemiological evidence for both phthalates and bisphenols as limited because of too few prospective studies. Nevertheless, a quite extensive body of experimental evidence is available indicating that bisphenols may interfere with glucose homeostasis and insulin signalling and several plausible mechanisms have been suggested. However, mechanisms likely differ depending on whether exposure occurs during early development or in adulthood. The animal data on phthalates also indicate a potential for involvement in obesity development and altered insulin signalling and glucose metabolism.

Overall, the reviewed epidemiological and toxicological data provide some insight into potential mechanisms by which environmental chemicals could contribute to the development of diabetes (Figure 9). One potential mechanism that is well supported by empirical evidence as well as biological plausibility is mitochondrial dysfunction and consequent oxidative stress caused by increased ROS production[111]. Excessive ROS can react with lipids, nucleic acids and proteins, causing oxidative damage in tissues and cells[112]. ROS are pro-inflammatory agents. Inflammatory and oxidative damage to beta cells is a major cause of beta cell dysfunction and eventual beta cell death, which shuts down the capacity of the pancreas to produce and secrete the glucose-lowering hormone insulin. Adipose tissue and the liver are other major targets of inflammation and oxidative stress and are involved in the complex sequence of events underlying insulin resistance, impaired insulin secretion, and the ultimate development of T2D. Changes of the metabolism of sugars and lipids in the liver as well as of the mechanisms of insulin-sensing promote systemic metabolic adaptations that lead to immune cell activation and amplification of inflammation[31]. To keep ROS levels under control and avoid their potentially detrimental effects, mitochondria have evolved an antioxidant defence[113]. When antioxidant defences fail to cope with excessive ROS production, cells undergo oxidative stress, which has been associated with insulin resistance and T2D[114-116]. Disruptions of signalling pathways modulating insulin biosynthesis and secretion, or glucose and lipid metabolism may also provide an explanation to how environmental chemicals could promote T2D. A variety of hormones including oestrogens, androgen, thyroid hormone, and glucocorticoids are involved in the homeostasis of glucose and lipid metabolism[117]. Several of the POPs, specifically the PCB, PFAS and PBDEs, have been shown to interfere with thyroid hormone signalling, which could potentially lead to perturbations of cortisol pathways and insulin resistance. The PFAS and phthalates can interact with and activate PPAR receptors, leading to subsequent changes in gene expression regulating glucose and lipid metabolism. There are also reports linking exposure to bisphenols and phthalates to epigenetic alterations, e.g. aberrant DNA methylation, histone demethylation and

deacetylation, and impaired miRNAs, which are connected to the regulation of glucose homeostasis.

For autoimmune diabetes, both epidemiological and experimental data are scarce. There are a few in vivo experimental studies available, primarily using the NOD mouse model, which indicate that the POPs and bisphenols may play a role in accelerating T1D development. However, no associations with T1D have been established in epidemiological data of the POPs and the epidemiological data on the bisphenols is still too unreliable to draw any conclusions.

Figure 9. The hypothesized involvement of chemicals in the pathogenesis of type 2 diabetes.



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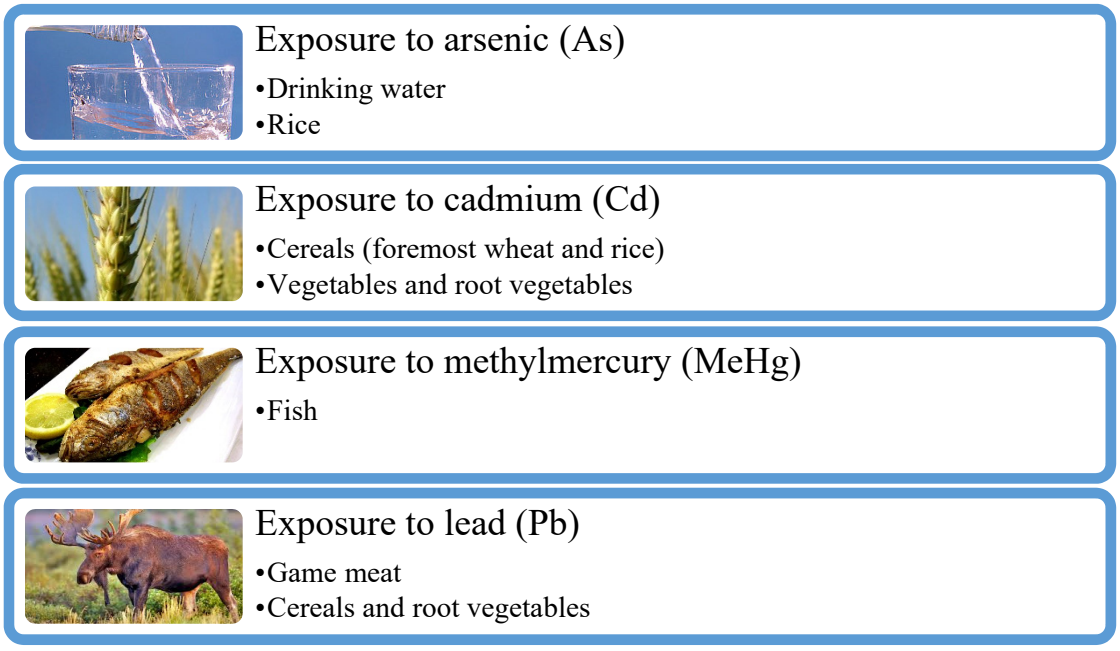
METALS

MARIA KIPPLER

INTRODUCTION

The present chapter focuses on the most widely studied toxic metals, namely arsenic, cadmium, lead and the organic form of mercury (hereafter referred to as methylmercury). Metals constitute a special class of chemicals, as they are persistent, often cooccurring in food and drinking water (Figure 10), and they share many toxicological properties, such as induction of oxidative stress and inflammation, which are suggested key events in the development of T2D[1-13]. For some of the metals, several review articles have been published, including both epidemiological and experimental studies assessing the link between exposure to metals and T2D. For ethical reasons, no RCTs have been performed. Thus, this chapter will primarily summarize information from existing reviews and meta-analyses. Individual studies have only been referred to if they describe more recent prospective data, or if they include a more detailed evaluation of existing data. The role of metals in the development of T1D is much less studied and no studies have been found on metal exposure and LADA. The few available studies on metals and T1D are summarized at the end of the present chapter.

Figure 10. The main dietary sources of exposure to the metals discussed in this chapter.



ARSENIC

EXPOSURE

Arsenic is a semi-metal and a well-known toxicant and carcinogen in its inorganic form. Arsenic occurs naturally in bedrock at varying concentrations world-wide, resulting in a wide range of concentrations in ground water. In some areas, arsenic has also been emitted

from industrial activities such as mining and smelters, glassmaking, and wood preservation. The general population is exposed to inorganic arsenic mainly via drinking water and certain types of food, such as rice. People may also be exposed to organic forms of arsenic via fish and other seafood, but these forms are much less toxic[4, 5]. Elevated concentrations of inorganic arsenic in ground water used for drinking water are commonly occurring in Bangladesh, India, Taiwan, and in certain areas in South America, China and the US. In Sweden, moderately elevated concentrations of inorganic arsenic in private wells have been detected in certain areas of Västerbotten, Bergslagen and in the eastern parts of central Sweden (www.sgu.se). The EU standard for drinking water is 10 µg/L, however, the responsibility for testing of arsenic in private wells lies with the property owner. The Swedish Food Agency has estimated that about one third of the inorganic arsenic that we are exposed to originates from rice and rice-based products. This has resulted in several dietary recommendations; i) adults should not eat rice or rice-based products every day, ii) children should not eat rice or rice-based products more than four times per week, and iii) small children (<6 years of age) should not consume rice cakes or rice-based beverages (www.slv.se). In order to reduce the intake of inorganic arsenic further, people are recommended to cook rice in excess water, which is then discarded. Also, polished rice is preferred over whole grain rice, as the arsenic is primarily found in the outer layers of the rice grain[6]. Unfortunately, also several essential elements, like zinc, are mainly located in the husk.

Once inorganic arsenic (arsenate and arsenite) is absorbed in the body, it is methylated into methylarsonic acid (MMA) and dimethylarsinic acid (DMA) in the liver and thereafter excreted via the kidneys together with a small fraction of inorganic arsenic[7]. Arsenic retained in tissues is mainly in the form of trivalent inorganic arsenic and MMA. Generally, the relative proportion of arsenic metabolites in urine is around 10-30% inorganic arsenic, 10-20% MMA and 60-80% DMA, but with large interindividual and intrapopulation variations[7].

EPIDEMIOLOGICAL STUDIES

In 2011, the National Toxicology Program (NTP) has concluded that existing epidemiological data provide limited to sufficient evidence for an association between arsenic and T2D in populations with relatively high arsenic exposure via drinking water (≥150 µg arsenic/L), while at lower exposure levels, they considered the evidence to be insufficient[8]. Since that report, several prospective studies at low exposure levels have been conducted in the U.S. and in Denmark[9-12]. In the Danish cohort (n=57,053), individual time-weighted average arsenic concentrations in drinking water (mostly below 3 µg/L, 95th percentile 2.1 µg/L, maximum 25 µg/L), estimated based on the residential address and water arsenic from the Geological Survey database, was associated with incidence of T2D[13]. Similarly, in a case-cohort study in Colorado (n=488), the estimated lifetime exposure to measured inorganic arsenic concentrations in drinking water (71% below 20 µg/L) was associated with T2D incidence[9]. In a study among American Indians in Arizona (150 T2D cases and 150 controls), total urinary arsenic (range 6.6-123 µg/L; interquartile range (IQR): 15.3–29.4 µg/L) was associated with increased incidence of T2D[10]. However, in a large cohort study of individuals in Arizona, Oklahoma and North and South Dakota (Strong Heart Study, n=1694), total urinary arsenic (IQR 6.1-17.7 g/L) was not associated with the incidence of T2D[11]. On the other hand, in a more recent study, including family members from the Strong Heart Study (n=1,838 American Indians), low-level arsenic exposure based on sum of urinary inorganic arsenic metabolites (IQR 2.9-7.2 µg/g creatinine, range 1-35 µg/g) was associated with the incidence of T2D[12]. Thus, the evidence is conflicting. It should be emphasized that the arsenic exposure in most of these prospective studies was very low, corresponding to the "background exposure" through

water and/or food in most populations. The interindividual and day-to-day variations are probably large, considering the small concentration ranges reported.

In 2014 a meta-analysis was conducted, including 17 studies (3 case-control, 3 cohort and 11 cross-sectional studies) published between 1990 to 2013 with arsenic exposure from the low-to-high dose range[14]. Twelve studies had assessed arsenic in drinking water (known to be essentially inorganic), the majority via estimation and only a few via individual measurements, and seven studies had measured the total arsenic concentration in urine. For arsenic in water (highest *versus* lowest category) and T2D the summary RR was 1.23 (95% CI 1.12 to 1.36) after removal of three studies with high heterogeneity. The corresponding summary RR for total urinary arsenic was 1.28 (95% CI 1.14 to 1.44). In subgroup analysis by study design, the positive association was independent of study design for both arsenic in water (both cohort and cross-sectional) and urine (case-control and cross-sectional). Finally, based on three cross-sectional and one case-control study with varying arsenic concentrations in drinking water[15-18], a dose-response analysis indicated that by every 100 µg/L increment in inorganic arsenic in water T2D prevalence increased by 13% (RR: 1.13; 95% CI: 1.00 to 1.27). However, there was an indication of a threshold around 150-250 µg/L. Importantly, a major problem is that the meta-analysis is dominated by cross-sectional studies, making the evaluation of causal relationships highly uncertain.

In relation to arsenic metabolism, there is evidence of an impact on the association of arsenic exposure with T2D, although the role of this relationship is not clearly understood. For other outcomes such as cancer, skin lesions and cardiovascular disease, higher MMA% and lower DMA% in urine have generally been associated with increased disease incidence without considering the overall exposure [19, 20]. For T2D, the opposite pattern has been observed; i.e. that lower MMA% and higher DMA% was associated with an increased risk of T2D[11, 21, 22]. Most of these studies were conducted in highly exposed populations in Bangladesh and Mexico (>100 µg/L in drinking water), with the exception of one study conducted in the U.S[11]. However, there may be residual confounding in these studies, as the urinary DMA% has been found to increase with increasing BMI[23, 24], and high BMI is a risk factor for T2D. Further research is needed to clarify if arsenic metabolism may modify potential associations between arsenic exposure and T2D.

Taken together, based on epidemiological data there is enough evidence of an association between inorganic arsenic exposure and T2D in highly exposed populations (≥150 µg arsenic/L drinking water), whereas evidence remain inconclusive for populations with low-to-moderate exposure. There is a need for more large-scale prospective studies at all exposure levels, using valid individual exposure biomarkers such as urinary arsenic species, with reliable diagnosis of T2D and information about well-established risk factors. Also, as emphasized above, further studies are needed to clarify the role of arsenic metabolism on T2D incidence.

POTENTIAL MECHANISMS

In NTP´s evaluation in 2011, experimental animal data was considered inconclusive, although it was noted that more recent studies on diabetes-relevant endpoints appear to support epidemiological data linking arsenic exposure and T2D. It was also concluded that animal data indicate several pathways by which arsenic may affect pancreatic beta cell function and insulin sensitivity. However, they also emphasized that animal studies need to better reflect human exposure scenarios in terms of internal dose, and that well characterised endpoints such as blood glucose and insulin levels should be studied, in combination with modification by adiposity.

In a recent review of the experimental literature[25], including both *in vivo* and *in vitro* studies, it was suggested that arsenic exposure affects whole-body glucose homeostasis,

insulin-stimulated glucose uptake, glucose-stimulated insulin secretion, hepatic glucose metabolism, as well as adipose and pancreatic beta cell dysfunction. Also, by searching the publicly available Comparative Toxicogenomics Database, 16 genes were identified which were all associated with sodium arsenite, insulin resistance and T2D[25]. The genes were found to encode proteins involved in for example glucose homeostasis, oxidative stress, inflammation, lipid metabolism, energy balance, lipid metabolism and adipogenesis, suggesting dysregulation of arsenic in various metabolic tissues. However, in summary there is still a need for optimal study design for *in vivo* and *in vitro* studies in order to accurately reflect human arsenic exposure. Key issues that need to be considered are doses, species differences in arsenic metabolism and kinetics, duration of exposure, and routes of exposure.

As concluded in a recent review[1], epidemiological studies of the association between inorganic arsenic and obesity are so far inconclusive and limited. For example, in a case-control study from northern Chile, cumulative arsenic exposure was associated with increased odds of T2D, and the corresponding odds were greater in individuals with excess BMI[26]. In a study from National Health and Nutrition Examination Survey (NHANES) in the U.S, urinary arsenic was not associated with BMI or hip-to-waist ratio in pregnant or breastfeeding women[27]. The inconclusive results may partly be related to age, timing of the exposure, the exposure assessment, and the levels of exposure.

CADMIUM

EXPOSURE

Cadmium occurs naturally in the ground but has also been emitted into the environment via for example mining and smelting, industrial emissions, and use of fertilizers leading to a widespread dispersion in the environment and contamination of soil, including arable land, in many areas of the world[28]. Cadmium has a high soil-to-plant transfer rate. Accordingly, commonly consumed food of plant origin such as cereals (primarily wheat and rice), vegetables and root vegetables are the major source of cadmium exposure. Some food items, such as offal (kidney and liver), shellfish, wild mushrooms, and certain seeds and cacao, may contain elevated levels, but as the consumption of these types of food is usually low, they contribute much less to the exposure. Fortunately, only a few percent of the ingested cadmium is actually absorbed in the gastrointestinal tract, although interindividual differences exist, depending on age, iron status, fiber intake and pregnancy[29-31]. Tobacco smoking is another important source of cadmium exposure. Over a lifetime it has been estimated that regular tobacco smoking contributes to a similar amount of cadmium as the dietary exposure[32]. The European Food and Safety Authority established a tolerable weekly intake (TWI) of 2.5 µg cadmium/kg body weight, in order to protect against renal tubular damage which is currently considered as the critical adverse effect of cadmium exposure. The Swedish Food Agency has estimated that the median intake of cadmium from food in adults is about 1 µg/kg body weight per week, although some individuals may exceed the TWI. As cadmium exposure originates from important staple foods it is highly important to reduce the cadmium content in such food.

Besides kidney damage, long-term low-level cadmium exposure has been associated with various other adverse health outcomes such as bone toxicity, cancer, cardiovascular disease and mortality[33, 34]. Also, early-life exposure has been associated with child growth and cognitive development[35, 36]. Cadmium has also been suggested to have endocrine disrupting properties[37], which raises concern about the involvement of cadmium in the development of T2D.

EPIDEMIOLOGICAL STUDIES

Multiple epidemiological studies have assessed the association between cadmium exposure and T2D, however, most of the studies are of cross-sectional design and only two prospective studies have been identified (both conducted in Sweden). One prospective study was conducted in southern Sweden, including 4,585 individuals aged 46-67 years without history of diabetes[38]. During a mean follow-up of 15 years, 622 individuals (299 men and 323 women) were diagnosed with diabetes. Blood cadmium concentration (range 0.01 to 5.07 µg/L) at baseline was not associated with the incidence of T2D (HR 1.11; 95 CI 0.82-1.40, comparing extreme quartiles). The second prospective study was conducted in Gothenburg and it included 68 cases with incident T2D, 58 with impaired glucose tolerance and 118 with normal glucose tolerance[39]. Neither blood nor urinary cadmium was associated with the prevalence or incidence of T2D or impaired glucose tolerance. Also, cadmium exposure at baseline was not associated with insulin production, blood glucose, or HbA1c levels, or with changes in HbA1c during follow-up. In addition, results are inconclusive from cross-sectional studies of cadmium exposure, assessed either via measurements in urine or blood, with T2D conducted in North America, Australia and Asia[40].

Despite few prospective studies, several meta-analyses have been conducted since 2017[40-43]. In the latest meta-analysis by Guo and co-workers[40], including 13 studies (the two prospective studies from Sweden, two cross-sectional studies from the U.S, one from Australia, and eight from Asia), cadmium exposure was associated with a summary OR of 1.27 (95% CI: 1.07 to 1.52) for T2D when comparing the highest versus lowest exposure category. In sub-group analysis by exposure biomarker, both urinary and blood cadmium was associated with increased odds of T2D (OR: 1.31; 95% CI: 1.02 to 1.69 and OR: 1.29; 95% CI: 0.94 to 1.75), although the association with blood cadmium was not significant. In a dose-response analysis, including six cross-sectional studies[44-49], every 1 µg/g creatinine increase in urinary cadmium was associated with 16% increased prevalence of T2D (OR: 1.16; 95% CI 1.04 to 1.27). The analysis also indicated a positive association between urinary cadmium concentrations >2.43 µg/g creatinine and T2D.

Many of the epidemiological studies conducted so far have several limitations, some of which may explain the inconsistent results. Foremost, all studies, except two[38, 39], were of cross-sectional design. Also, some of these studies were small, with sample sizes ranging from 124 to 551 individuals, resulting in low power with imprecise estimates and wide confidence intervals. Secondly, the associations between urinary cadmium and T2D were slightly more pronounced than those of blood cadmium[40, 41, 43], which may be problematic due to the cross-sectional design as *i*) urinary cadmium, which reflects the amount accumulated in the kidney, increases with increasing age (half-life 10-30 years) and elevated concentrations are associated with renal damage[33] and ii) diabetes is also an established risk factor of renal damage, making it hard to establish a causal relationship. Finally, for many of the studies there was a lack of information concerning the type of diabetes. However, as almost all studies included only adult subjects (>18 years of age) or subjects older than 30 years of age, it can be assumed that most of the cases had T2D. In summary, there is need of more large-scale prospective studies exploring a link between low-level exposure to cadmium and T2D.

POTENTIAL MECHANISMS

In contrast to observational studies on cadmium and diabetes, the results of experimental studies are more uniform. In both short-term and long-term *in vivo* cadmium exposure

models it has been indicated that cadmium has some type of diabetogenic effect[50]. Although the cellular mechanisms have not yet been fully elucidated, they may be separated into three potential categories: increased gluconeogenesis, altered glucose transport and disruption of pancreatic islet function[50]. To date, the latter category has been widely studied, however, it should not be excluded that all three categories may be involved and act synergistically. The theory of cadmium-related pancreatic islet dysfunction has emerged for several reasons: Human pancreatic islet samples have been shown to contain cadmium in varying concentrations (range 7 to 72 nmol/g protein)[51]. Also, exposing mouse beta cells to environmentally relevant cadmium doses (0.1 to 1 µmol/L) has resulted in a dose- and time-dependent accumulation of cadmium, which, in turn, resulted in an inhibition of glucose stimulated insulin secretion[51]. Similarly, in several animal studies cadmium exposure has resulted in decreased insulin concentrations in serum[52-54]. Several possible mechanisms have been suggested behind this pancreatic islet dysfunction including alterations in i) energy metabolism, ii) oxidative stress, iii) Ca channel function, and iv) cell-cell adhesion[50].

To date, the results from epidemiological studies concerning cadmium exposure and obesity are conflicting, ranging from negative, positive or no association. For example, in a cross-sectional study in the U.S. using NHANES 1999-2002 data, urinary cadmium concentrations were inversely associated with BMI and waist circumference[55]. On the contrary, in a small-scale cross-sectional study of women in Australia urinary cadmium was positively associated with waist circumference[56]. In a large Korean study, no association was observed between blood cadmium and percentage of body fat[57]. These contrasting results may at least partly be due to differences in levels of cadmium exposure. Thus, more large scales studies are needed to determine the role of cadmium exposure in obesity.

MERCURY

EXPOSURE

In 2013, the Minamata Convention on Mercury was globally adopted, and it entered into force in 2017, aiming to protect human health and the environment from anthropogenic emissions and releases of mercury and mercury compounds[58]. Mercury is released into the environment mainly as mercury vapour, which is thereafter oxidised and precipitated to soil and water as inorganic mercury (ionic form). In anaerobic sediments, primarily in aquatic and marshland environments, inorganic mercury can be biotransformed into methylmercury by microorganisms. This is highly problematic as methylmercury biomagnifies in the food chain, resulting in high concentrations in large predatory fish. Thus, the general population is primarily exposed to mercury in the form of methylmercury via consumption of fish, especially freshwater fish from contaminated lakes and large predatory ocean fish. More than 80% of the ingested methylmercury is absorbed in the gastrointestinal tract with small interindividual differences[59]. Once absorbed methylmercury can cross both the placenta and the blood-brain barrier. Accordingly, elevated exposure to methylmercury has been associated with damage of the central nervous system (CNS), especially during development. In blood, methylmercury is mainly localized in the erythrocytes and the concentrations may be used for exposure assessment (also whole blood). As methylmercury binds to sulfhydryl groups it can also be measured in hair or possibly nails.

To reduce the exposure to methylmercury as much as possible, the Swedish Food Agency has established dietary recommendations concerning fish consumption. Women that are pregnant, lactating or planning to get pregnant are advised not to eat fish species that may contain methylmercury more than 2-3 times per year, and the general population is advised not to eat certain self-caught fresh water fish (perch, pike, pike perch, and burbot) more

than once per week. EFSA has established a TWI for methylmercury of 1.3 µg/kg body weight, and the U.S. National Research Council has established an even lower TWI of 0.7 µg/kg bodyweight. According to the Swedish Food Agency few pregnant women exceed this level (<4%). Also, Swedish temporal trend studies suggest that the concentrations are annually decreasing[60].

EPIDEMIOLOGICAL STUDIES

Several studies, many of cross-sectional design, have assessed the association of methylmercury exposure, measured in either whole blood, hair or toenails, with T2D, but the results are inconclusive[61]. In a large prospective study of 3,875 young American adults aged 20-32 years, toenail mercury was positively associated with the incidence of T2D (HR: 1.65, 95% CI 1.07-2.56; comparing extreme quartiles)[62]. However, in two other U.S. cohorts of 9,267 middle-aged and elderly men and women, toenail mercury was not associated with T2D incidence in neither women (HR: 0.86; 95% CI 0.66–1.11) nor men (HR: 0.69; 95% CI 0.42–1.15), and a decreased risk was observed when both sexes were combined (HR: 0.77; 95% CI 0.61–0.98), comparing extreme quintiles[63]. In sub-group analyses, toenail mercury was inversely associated with T2D among subjects with low intake of omega-3 fatty acids and among subjects who were overweight or obese, but whether this reflects benefits of fish consumption or something else requires further studies. Finally, in a prospective study of 2,212 Finnish men aged 42-60 years, toenail mercury was not associated with T2D (HR: 0.91; 95% CI: 0.67–1.24; comparing extreme quartiles)[64].

In summary, more large-scale prospective studies in populations with varying exposure to methylmercury via fish are needed in order to determine a potential link with T2D. Studies also need to explore potential confounding by beneficial nutrients in fish containing methylmercury.

POTENTIAL MECHANISMS

Several experimental studies have indicated a role of methylmercury in the development and aggravation of metabolic syndrome, as reviewed by Tinkov and co-workers[65]. Experimental studies, both *in vivo* and *in vitro*, have also indicated that methylmercury exposure affects pancreatic beta cell development and function, which can result in insulin resistance and hyperglycemia[66]. The following mechanisms of methylmercury-related pancreatic beta cell dysfunction have been suggested *i*) binding to sulfhydryl groups on proteins, breakage of disulphide bounds, disruption of protein structure and function, leading to protein degradation and endoplasmic reticulum stress, which in turn has been linked to development of metabolic syndrome, *ii*) increased production of reactive oxygen species and oxidative stress resulting in mitochondrial dysfunction and decreased ATP synthesis, which in turn may affect membrane potential and ion channels that are required for insulin secretion, and *iii*) suppression of JNK signalling pathway resulting in decreased PDX-1 activity, which is important for beta cell development[66].

The evidence from epidemiological studies exploring the link between methylmercury exposure and obesity is limited and inconclusive. In a cross-sectional study of 2,114 Korean adults, blood mercury concentrations were associated with BMI and waist circumference, as well as with several other markers of metabolic syndrome such as diastolic blood pressure, total cholesterol and triglycerides[67]. On the contrary, in a study of U.S. women aged ≥20 years participating in NHANES, blood mercury concentrations were inversely associated with BMI, and when comparing normal and overweight women blood mercury was on average 22% lower among those who were overweight[68].

EXPOSURE

Lead has been widely used in both industrial and consumer products (e.g. coins, pipes, additive in gasoline, alloys, solders, colour pigment) and is still used in some products such as car batteries, plastic, ammunition and in some solders of electronic products. Lead is often present in brass components in taps and tube fittings, which may leach into the drinking water. Therefore, it is recommended to flush the water for a short while before collecting water for consumption. Lead has also been shown to leach during cooking or storage of acidic food in old antic brass containers or in lead-glazed ceramics. The latter are not for sale in Europe. In Sweden and in other countries consumption of meat from game, shot by leaded ammunition, has resulted in increased lead exposure[69]. Also, certain shellfish and offal may contain elevated concentrations of lead. Nevertheless, as lead is absorbed by various plants and deposited on leafy green vegetables, the main exposure often originates from vegetables and cereals which are frequently consumed[70].

In connection with the ban of leaded gasoline, the lead concentrations in blood have decreased in Sweden and in other countries[69]. According to the Swedish environmental health-based surveillance, blood lead concentrations in children in southern Sweden have steadily decreased between 1978 and 2007 (geometric mean decreased from 60 to 13 µg/L)[71] and in 2017 the average concentration had decreased to 7 µg/L (https://ki.se/imm/tidsserier-och-data). EFSA has identified several critical effects that are associated with low-level lead exposure: developmental neurotoxicity in young children, and cardiovascular effects and nephrotoxicity in adults. EFSA has estimated a so called refence point of 12 µg lead/L, based on a benchmark dose level, in blood for developmental neurotoxicity, 15 µg lead/L in blood for chronic kidney disease, and 36 µg lead/L in blood for systolic blood pressure[70]. The lead-related effects on the cardiovascular system raise concern about the potential involvement of lead in T2D development.

EPIDEMIOLOGICAL STUDIES

Several studies have explored the link between lead exposure and metabolic syndrome and related disorders[2], and the majority of the studies have reported positive associations. On the other hand, very few epidemiological studies have been conducted on lead exposure and T2D, and all are of cross-sectional design. In a study from the Korean National Health and Nutrition Examination Survey (KNHANES) in 2009-2010, including 3,184 individuals aged 30 years or older, blood lead concentrations were not associated with the prevalence of T2D [OR: 0.75; 95% CI 0.52-1.08 comparing the lowest (geometric mean blood lead 14.3 µg/L) and the highest quartiles (geometric mean blood lead 40.8 µg/L)][72]. In addition, there was no association of blood lead with either HOMA-IR, HOMA-Beta cell function or fasting insulin. In a study in the Canadian Health and Measure Survey 2007-2011, including 7,176 individuals aged 20-79 years, blood lead concentrations were not associated with fasting glucose levels ≥1.10 µg/L or glycated haemoglobin (HbA1c ≥5.7%)[73]. Most of the individuals (85%) had a blood lead concentration below 25 µg/L. In summary, there is a need of more prospective studies assessing the link between lead exposure and T2D.

POTENTIAL MECHANISMS

There are still relatively few experimental animal studies on the link between lead exposure and diabetes-related outcomes. According to a review[74], several studies in rats in the 1970s to 80s have suggested that elevated lead exposure can induce hepatic glucose production, resulting in elevated blood glucose levels. A more recent experimental study, using both *in*

vitro and *in vivo* models, indicated that lead exposure disrupted insulin secretory function of islets through activating GSK-3β and ER stress[75]. Also, in the *in vivo* studies on rats exposed to lead via drinking water there was an increased activity of gluconeogenic enzymes (PEPCK and G6P), in combination with increased levels of blood glucose and glucose intolerance. The suggested lead-related molecular mechanisms involved in the pathogenies of T2D includes induction of oxidative stress and altering of intracellular signalling pathways (for example Ca signalling and protein kinase C activity)[74].

In experimental studies on obese rats, exposure to lead via drinking water induced fasting hyperglycaemia and glucose intolerance[76]. The epidemiological literature on lead exposure and obesity is limited. In a Chinese cross-sectional study of 5,348 adults, blood lead was positively associated with BMI and fasting blood glucose in women, but not in men[77]. Interestingly, early-life lead exposure appears to be associated with later life overweight or obesity, but the few studies conducted are inconclusive. In a prospective birth cohort study in the U.S, including 1442 mother-child dyads, maternal erythrocyte lead concentrations during pregnancy, comparing concentrations ≥50 µg/L to <20 µg/L, were associated with an increased risk of overweight or obesity (OR: 1.65; 95% CI 1.18-2.32) during childhood[78]. On the contrary, in a smaller prospective study of 248 mother-child dyads in Mexico, maternal bone lead concentrations (reflecting cumulative exposure) were associated with lower BMI z-scores, waist circumference, sum of skinfolds and body fat percentage at 8-16 years, while there were no associations with childhood exposure[79]. Thus, more experimental and epidemiological studies are needed assessing if obesity may serve as a mediator in the potential link between lead exposure and T2D.

AUTOIMMUNE DIABETES

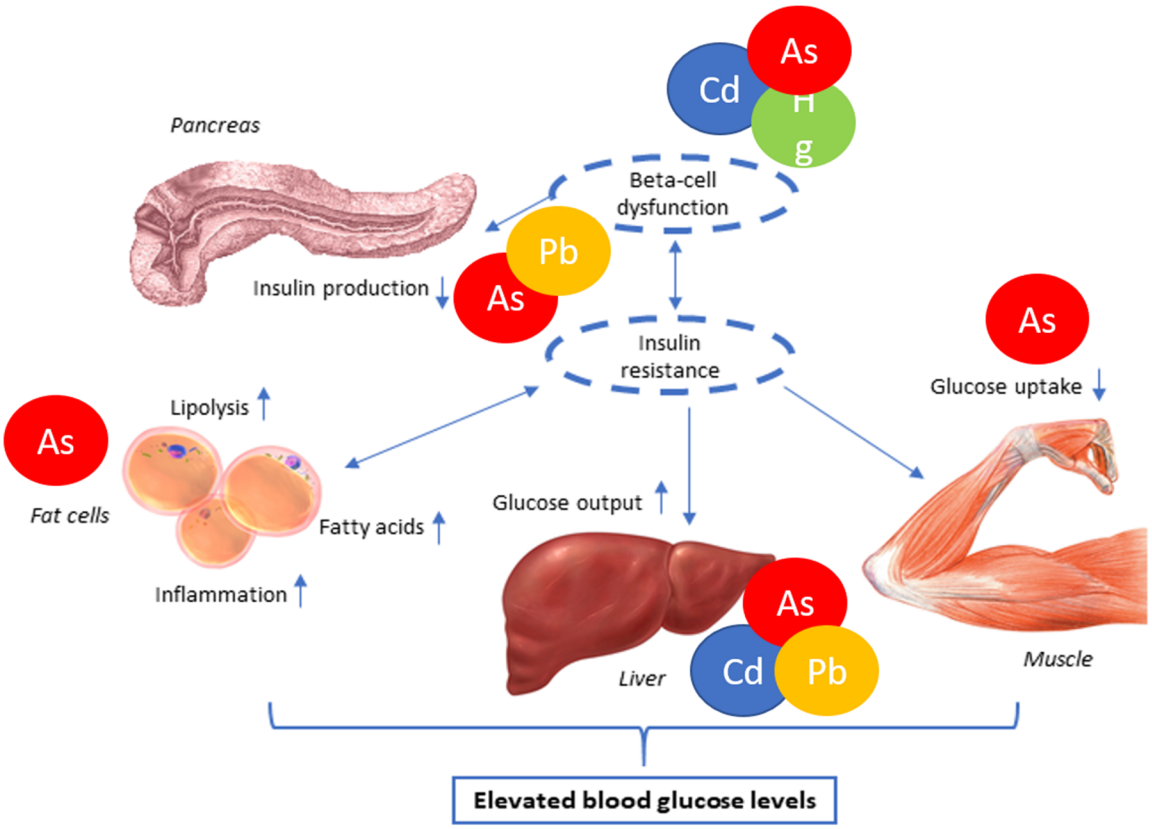
As indicated above, exposure to many metals has been associated with pancreatic beta cell dysfunction, developmental immunotoxicity[80, 81] and early-life epigenetic changes[82, 83], and therefore, its plausible that they may play a role in the development of T1D. Nevertheless, epidemiological studies assessing the link between early-life metal exposure and T1D are scarce. To date, one cross-sectional study in the U.S, an ecological study in Canada, and a nested case-control study in Sweden have been identified[84, 85]. In the U.S. study of 688 individuals <22 years of age (429 cases of T1D, 85 cases of T2D, and 174 controls), the total sum of plasma arsenic was not associated with T1D[85]. However, the different arsenic metabolites in plasma were associated with T1D; comparing the interquartile range of the percentage of inorganic arsenic, MMA%, and DMA% the odds ratios were 0.68 (95% CI 0.50-0.91), 1.33 (1.02-1.74), and 1.28 (1.01-1.63), respectively. Arsenic metabolites in plasma were not associated with T2D. This pattern with T1D is not the same as has previously been observed in relation T2D in adults in other studies, i.e. lower MMA% and higher DMA%[11, 21, 22], which warrants further studies. The main drawbacks of this study are the cross-sectional design and the measurements of the very low concentrations of arsenic in plasma (IQR 0.064-0.11 µg/L in controls, 0.064-0.11 µg/L in T1D cases, 0.062-0.099 µg/L in T2D cases). The correlation between arsenic in whole blood and urine is often good, but less is known about the correlation between arsenic in plasma and urine. In a population-based Canadian study of children in the age span of 0-14 years, a community-based analysis indicated a significant association between concentrations of arsenic in drinking water and incidence of T1D[84], although it should be noted that there were also several other contaminants in drinking water that were associated with T1D. In the nested case-control study in Sweden, including 20 children who developed T1D and 40 age- and sex-matched controls, cord blood concentrations of arsenic, cadmium, mercury or lead were not significantly different between cases and controls[86]. However, there was a significant difference in the concentration of aluminium in cord blood. These results should be

interpreted with caution due to the small sample size and the fact that for all metals many samples were below the limit of detection.

CONCLUSIONS

To date, there is sufficient epidemiological evidence of an association between inorganic arsenic exposure and T2D in highly exposed populations (≥150 µg arsenic/L drinking water), while the evidence remains inconclusive for populations with low-to-moderate exposure. For cadmium, the epidemiological evidence is limited. The studies conducted so far have several limitations, foremost the cross-sectional design and use of imprecise exposure markers, and the few prospective studies that have been conducted did not find any evidence of an association with T2D. A similar scenario applies to methylmercury, where most of the studies are of cross-sectional design and the results from the few available prospective studies are inconclusive. For lead, the epidemiological data are very limited, and thus, no conclusions can be drawn on the link with T2D. For all metals, there is limited experimental data supporting a link with diabetes-related outcomes (see overview Figure 11) and several potential modes of action have been suggested. Whether exposure to metals may play a role in development of autoimmune diabetes remains to be elucidated.

Figure 11. The hypothesized involvement of metals in the pathogenesis of type 2 diabetes



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AIR POLLUTION AND NOISE

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INTRODUCTION

Air pollution and noise rank as the top two environmental causes of ill health in Europe.[1] Cardiovascular diseases dominate among adverse health effects caused by long-term exposure to ambient air pollution, while sleep disturbances and annoyance are most prominent for noise. There is growing evidence that both air pollution and noise may be of importance for development of T2D. However, many important aspects are not well understood, such as which air pollution components are of importance or the role of different transportation noise sources. Furthermore, the evidence is very limited on interactions between air pollution and noise as well as on population attributable risks. Given the comparatively high prevalence of T2D and the important role as risk factor for common serious diseases, identification and management of major environmental causes has a preventive potential of substantial public health relevance.

This chapter initially describes exposure to air pollution and noise, including time trends. In order to illustrate the public health impact, population attributable risks (PAR) are also highlighted for some common health effects other than T2D based on population exposure estimates as well as epidemiological data on exposure-response relationships. The PAR estimates do not include T2D because of insufficient evidence. The next two sections summarize the literature on associations between air pollution or noise and diabetes, respectively, primarily based on epidemiological data. First, evidence on T2D is covered, which is most abundant, then data on T1D, which are very limited. One section on potential mechanisms is included, partly based on experimental data. This section also contains a discussion of the evidence regarding air pollution or noise exposure and overweight. Hyperglycaemia and obesity are key features of the metabolic syndrome, an important risk factor for T2D and cardiovascular disease, and may share some important etiological pathways in relation to air pollution and noise. Finally, a section with conclusions is included.

EXPOSURE

Air pollution consists of a complex mixture of different particles and gases. Major sources include road traffic, residential heating and long-range transport, often transnational. Exposure to increased levels of air pollution is widespread, particularly in urban areas. For example, it has been estimated that in 2016 almost 75% of the urban population in Europe was exposed to fine particles ($PM_{2.5}$) exceeding the WHO guidelines[2]. In an international comparison, air pollution levels are low in Sweden and have generally decreased in recent decades[3]. However, particulate levels can be elevated in some areas during certain parts of the year due to the use of studded tyres and wood for residential heating, leading to exceedances of air quality standards. Air pollution is the most important environmental factor from a public health point of view and in 2012 it was estimated that 289 000 deaths in Europe were attributed to ambient air pollution exposure, primarily from ischemic heart disease and stroke, using $PM_{2.5}$ as exposure indicator[4]. In view of new evidence on adverse effects of air pollution, especially at levels below current guidelines, WHO is currently revising the air pollution guidelines.

Traffic noise is an increasing environmental exposure, primarily as a consequence of continuous urbanization and growth of the transport sector. In 2012 approximately 100 million people in Europe were estimated to be exposed to noise levels from road traffic exceeding 55 dB L_{den}, which is the European Environment Agency indicator level and has been linked to harmful health effects[5]. Corresponding exposure to railway and aircraft noise affected 19 and 4.1 million, respectively. In Sweden close to two million people (20%) are exposed to traffic noise exceeding 55 dB L_{Aeq} 24h[3]. WHO has estimated that at least one million healthy years of life are lost every year from traffic-related environmental noise in Western Europe, mainly due to sleep disturbance and annoyance, but cardiovascular disease also contributes[6]. The burden of disease from noise is the second highest in Europe among all environmental exposures, after air pollution, and in 2018 WHO proposed more strict environmental noise guidelines[6].

AIR POLLUTION

Long-term exposure to air pollution can induce adverse health effects in children and adults well below current air quality guidelines[7]. The dominating effects from a public health point of view occur in the cardiovascular system and respirable particles, especially $PM_{2.5}$, provide the most consistent evidence. An important mechanism behind adverse health effects is induction of systemic inflammation[8,9]. Other health effects related to air pollution exposure include lower respiratory tract diseases in children as well as chronic obstructive pulmonary disease and lung cancer in adults. These outcomes primarily result from local damage induced by various air pollution components.

Many studies from different parts of the world have investigated associations between exposure to ambient air pollution and occurrence of T2D, mostly published during the last decade. They are of longitudinal or cross-sectional design and come from North America,[10-25] Europe[26-35] and Asia[36-43]. A majority of the studies found an increased incidence, prevalence or mortality in relation to estimated exposure to different air pollution components. The studies generally used NO_2, $PM_{2.5}$ and/or PM_{10} as indicators of air pollution but no clear picture emerged of associations with specific components. Some of the studies found stronger associations in certain subgroups but this evidence is not consistent. Interactions have been indicated between air pollution exposure and genes involved in insulin resistance[44] and IL-6 metabolism[45] in relation to the risk of T2D, suggesting sensitive subgroups of the population as well as relevant etiological pathways. No recent meta-analysis is available covering most of the studies mentioned above but excess relative risks were generally in the order of 5% to 20% per 5 $\mu g/m^3$ for $PM_{2.5}$, the air pollution component for which most evidence is available. Based on exposure-response functions in the study by Bowe et al.[22] it was estimated that ambient $PM_{2.5}$ contributed to about 3.2 million incident cases of diabetes globally.

In view of the lack of a recent combined analysis and assessment of the evidence on air pollution and diabetes in adults, a meta-analysis has been performed for this report of the 10 cohort studies on $PM_{2.5}$ exposure and incidence of T2D. Only longitudinal studies on incidence of T2D are included, since such studies provide the strongest evidence for assessment of causality. Another prerequisite for inclusion is that the studies contain individual data on lifestyle variables, which may be important confounders. Thus, "administrative" cohorts solely formed from registry information are excluded in this meta-analysis. The results are summarized in Figure 12, showing relative risks (or similar measures of association) for each study as well as overall, based on a random effects model. To facilitate comparisons the risk estimates have been recalculated to an increment of 5 $\mu g/m^3$, as other increments were often used in the different studies. There is an overall excess relative risk of 6% (95% CI 4% to 9%), with no strong evidence of heterogeneity

between the studies. Using the modified GRADE criteria proposed by van Kempen et al.[46] the evidence is classified as having a "high degree of certainty" (Table 5). This results from the initial classification of cohort studies as providing evidence with a "high degree of certainty" and one quality characteristic leading to downgrading and another to upgrading of the evidence.

Several studies have reported on associations between ambient air pollution exposure and blood glucose levels, insulin resistance or beta cell function, predominantly in adults.[18,36,47-60] Most of the studies were of cross-sectional design. A recent systematic review concluded that 1 µg/m^3 in NO_2 exposure was related to a 1.25% change in the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and a 0.60% change in insulin.[61] For 1 µg/m^3 of PM_{10} corresponding increases were 2.77% and 2.75%, respectively. There were no significant associations between $PM_{2.5}$ and insulin resistance biomarkers. No relevant review is available of the epidemiological evidence on air pollution exposure and blood glucose or HbA1c levels. However, in most studies levels of fasting blood glucose or HbA1c appeared to be related to estimated NO_2 and/or $PM_{2.5}$ exposure, supporting the evidence on air pollution and T2D.

One case-control study[62] and one ecological study[63] focused on air pollution exposure and T1D. Although some associations were reported the evidence is too limited to allow firm conclusions.

Most studies on air pollution and T2D did not adjust for noise exposure, although the two exposures are highly correlated when road traffic is the main source. Two studies showed that the associations between air pollution exposure and T2D disappeared when noise exposure was entered into the model, while the association with noise remained, suggesting that noise exposure was more relevant as a causal factor[20,32]. Very limited evidence suggested no strong interactions between exposure to air pollution and noise for induction of T2D,[32,64] however, these analyses were hampered by a low statistical power, primarily because of strongly correlated exposures.

Figure 12. Relative risk (RR) for type 2 diabetes in relation to an increment of 5 µg/m^3 of $PM_{2.5}$ in different studies and overall.

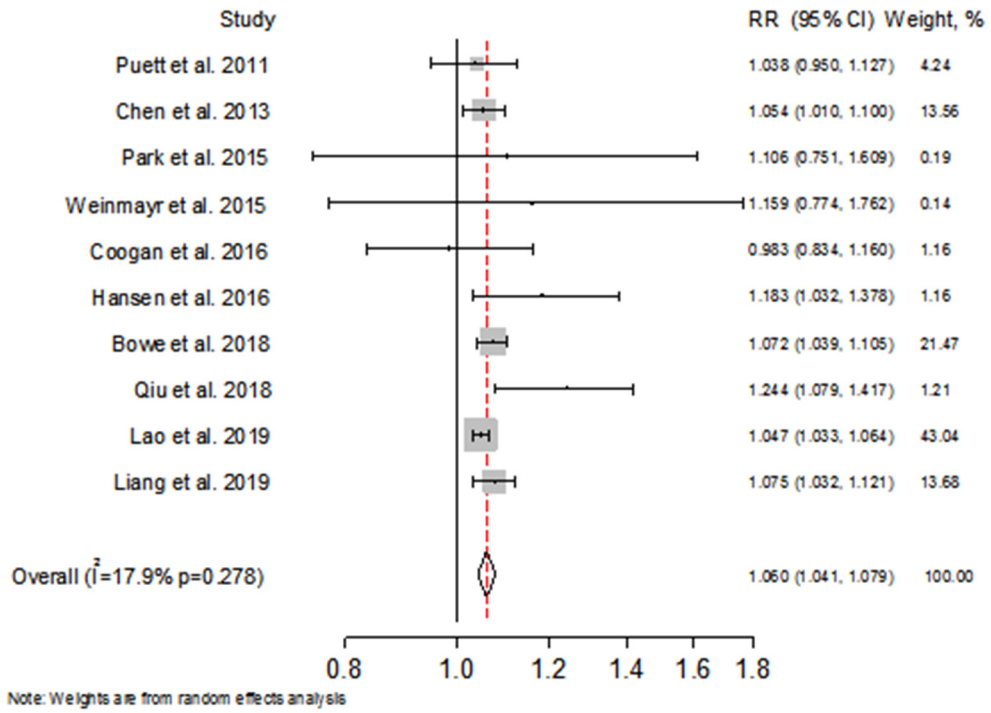

Table 5. Assessment of quality of evidence on exposure to $PM_{2.5}$ and incidence of type 2 diabetes based on a modification of GRADE*

Characteristic	Up/downgrading	Comment
Limitations of study design	Downgrading	Uncertain outcome assessment, no noise data**
Inconsistency	No	Low heterogeneity in risk estimates between studies
Indirectness	No	Relevant study populations
Imprecision	No	Confidence intervals do not include RR <0.75 or >1.25
Publication bias	No	No evidence of publication bias
Exposure-response gradient	Upgrading	All studies suggest positive RRs
Magnitude of effect	No	RR lower than 1.5
Plausible confounding	No	Confounding contributing to positive RR cannot be excluded

**Adapted from van Kempen et al[46]. **For a comprehensive capture of most cases of incident T2D a combination of questionnaire, prescription registry and patient registry (both outpatient and hospital based) information is needed. This was generally not the case in the included studies. Furthermore, noise exposure was not considered in the analysis although it may me an important confounder when local traffic is a major source of air pollution.*

NOISE

A recent systematic review evaluated the evidence on environmental noise exposure and cardiovascular diseases as well as metabolic diseases, primarily overweight/obesity and T2D.[65] It concluded that there is high quality evidence for a link between exposure to road traffic noise and incidence of ischemic heart disease. A large number of studies showed associations between road traffic noise exposure and hypertension, but the overall quality of the evidence was rated as very low, primarily because it was based on studies with cross-sectional design. For other cardiovascular outcomes and/or traffic noise sources the evidence was more limited and not enough for interpretation of causal relationships, although increased risks related to noise exposure were often observed. Studies published after those included in the systematic review provide a mixed picture,[66-70] however, mostly reporting associations between transportation noise exposure and cardiovascular disease.

The WHO review considered the evidence on traffic noise and T2D to be of moderate quality, however, primarily studies published until 2014 were included[65]. Only a few cohort studies have assessed the relation between long-term environmental noise exposure and T2D. In general, positive associations were found,[20,32,64,71] but the evidence is not completely consistent[72]. Most studies focused on road traffic noise, however, suggestive associations have been observed for aircraft noise,[32] but not for railway noise[32,73] or wind turbine noise.[74] A recent meta-analysis estimated a 17% increase in the relative risk for T2D per 5 dB of exposure to aircraft noise[75]. The corresponding excess relative risk for road traffic noise was 7%, suggesting a stronger relation for aircraft noise, similar to the situation for annoyance[6]. It appears that night-time road traffic noise exposure results in increased HbA1c levels[76]. A 10 dB difference in exposure was associated with a 0.02% increase in mean Hb1Ac, with a stronger effect in diabetics and subjects with a certain genetic risk variant for diabetes, also implicated in melatonin profile dysregulation. Strong interactions have been observed between different transportation noise sources in relation to obesity[77] and between traffic noise and different types environmental stressors for

myocardial infarction[78] and body weight[79]. Unfortunately, no such studies are available for noise and T2D.

There appear to be no studies on environmental noise exposure and T1D.

POTENTIAL MECHANISMS

Possible mechanisms for air pollution effects on T2D, as well as on cardiovascular disease, include systemic inflammation and endothelial dysfunction, contributing to alterations in visceral adipose tissue metabolism and insulin transduction[80,81]. The role of specific air pollution components for induction of T2D is unclear[31]. Etiological mechanisms may be similar for noise induced cardiovascular and metabolic effects. For example, short sleep duration is associated with overweight, and insomnia constitutes a risk factor for hypertension and T2D[82,83]. In addition, chronic stress and prolonged elevation of cortisol levels may promote central fat deposition[84] and work related stress is associated with T2D[85] as well as cardiovascular disease[86]. Increased saliva cortisol levels have been observed in subjects excessively exposed to noise near European airports[87]. Night-time transportation noise exposure can induce impaired glucose tolerance and insulin sensitivity[88].

Animal experiments provide further insight into the potential etiological mechanisms. Particulate air pollution, such as $PM_{2.5}$, can induce pulmonary oxidative stress causing vascular insulin resistance,[89] impaired glucose metabolism[90] and other relevant metabolic disorders[91]. Noise exposure may also increase weight gain and insulin resistance[92,93].

High blood glucose and central obesity are two of the key components of the metabolic syndrome, which is an important risk factor for both T2D and cardiovascular disease. The etiologic mechanisms may be similar, and it is of interest to assess the evidence on air pollution and noise in relation to the risk of overweight and obesity. A recent systematic review concluded that the evidence regarding the impact of air pollution on body weight status remains mixed[94]. For transportation noise most studies show associations[65,77,79,95]. In some studies the associations were particularly evident for central obesity.

CONCLUSIONS

Air pollution and traffic noise can induce serious adverse health effects, primarily in the cardiovascular system. Increasing evidence also points to a role of these exposures for development of metabolic diseases, such as T2D and overweight. In particular, epidemiological studies published during the last decade from different parts of the world indicate that exposure to ambient air pollution can increase the risk of T2D. Supporting evidence comes from studies of blood glucose levels, insulin resistance and beta cell function, as well as from experimental studies, illustrating relevant etiologic pathways.

There are fewer epidemiological studies on environmental noise exposure and T2D, but most of them reported positive associations, primarily for road traffic and aircraft noise. Plausible etiological mechanisms have been indicated, such as noise induced sleep disturbances and stress reactions. Furthermore, supporting experimental evidence has been provided.

Major risk factors for T2D relate to lifestyle and include sedentary living, excessive calorie intake, tobacco and alcohol. When exposure is widespread, such as for ambient air pollution and transportation noise, environmental factors may also be of public health importance, even if individual excess risks are low. Furthermore, environmental exposures may be more easily influenced by preventive measures than lifestyle factors, e. g. by legislation and technological developments. Public awareness is crucial for successful and

sustainable prevention. In view of the comparatively high prevalence of T2D and the important role as risk factor for common serious diseases, identification and management of major environmental causes has a preventive potential of substantial public health relevance.

Planning authorities in urban areas all over the world experience challenges related to environment and health. For example, there is an increasing number of conflicts in development of infrastructure (housing, roads etc) because of noise from traffic. In Sweden, authorities have recently relaxed noise guidelines to facilitate urban planning and development, despite the growing evidence on serious adverse health effects from environmental noise exposure. This will probably lead to increasing exposure to both air pollution and noise from road traffic. It is crucial that new research findings are taken into consideration in planning processes and legislation to facilitate a health sustainable urban development.

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URBAN GREENNESS

MARE LÖHMUS SUNDSTRÖM

INTRODUCTION

This chapter aims to give an overview of the literature on the association of urban greenness (≈urban vegetation) exposure and T2D risk. Initially, a brief summary is provided about the known health effects of urban greenness and the most common ways of its exposure estimation. Thereafter the theoretical framework of possible biological links connecting urban greenness and T2D is discussed. This is followed by a critical synthesis of the existing literature on the greenness-T2D relationship. The chapter ends with a discussion around the main findings.

From the beginning of the third millennium there has been an explosion in the interest of studying the link between exposure to urban nature and human health[1,2]. Several studies indicate that exposure to natural settings in urban context can have a range of positive outcomes for human health and wellbeing[3-11]. Recent overviews on the topic have concluded that increased exposure to urban vegetation is associated, among others, with reduced general mortality, ameliorated mental health, increased physical activity, and improved birth outcomes[1-3]. In addition, living in green neighbourhoods and/or studying in schools surrounded by abundant vegetation is believed to benefit both cognitive and motor development in children and adolescents[12-15]. It is, however, important to emphasise that some studies also find no associations or report non-beneficial effects of urban nature exposure on human health outcomes[16,17-23]. In the international context, accessibility to urban green is often related to income inequalities[24]. Several literature reviews regarding inequities in urban park access have reported a reoccurring pattern connecting ethnic minorities and lower socioeconomic status to fewer hectares of parkland per neighbourhood, fewer hectares of parkland per person, and to parks with lower quality, maintenance, and safety[25-27].

EXPOSURE

Epidemiological studies focusing on the human health/nature relationship often use different terms when referring to urban nature, the most common ones of which are: urban green space, urban green structure, urban green infrastructure, urban green, and urban greenness[11]. Confusingly, the content of each of these terms may also vary across publications. “Green space”, for example, can either refer to a defined area such as a park, or a forest, or be used as a quantitative term summarizing the “amount” of all photosynthesising organisms (from trees to algae in the duck pond) within a given area[3]. In the present chapter, we mainly use the term “urban greenness”, and define it as the latter – i.e. the quantitative summarizing term.

Two types of indicators, proximity and cumulative, are commonly used in epidemiological research to assess an individual’s exposure to greenness[28]. Proximity indicators most often refer to the geographical distance between a person’s residential address and a “green area”[27]. The definition of a “green area” may vary between studies but is most often defined by criteria such as the area size, surface material and the percentage of tree coverage. Cumulative indicators, on the other hand, estimate the quantity of greenness within the area of interest – most commonly the area surrounding a research subject’s place of residence. Often, the quantity of greenness is assessed by estimating the percentage of land covered by

total or a certain type of vegetation from land-use/ land-cover maps or from photographic area images. The most commonly used cumulative indicator is the Normalized Difference Vegetation Index (NDVI) which is derived from satellite data and is based on land surface reflection of visible red and near-infrared parts of the spectrum[11,28].

FINDINGS

Twenty-two articles investigating the relationship between greenness exposure and diabetes or diabetes-related biomarkers were assessed for review. Six of the studies had prospective cohort design[116-121] (Table 6), 14 were cross-sectional[122-135] and two ecological[136,137] (Table 7). This report is focused on prospective studies, and therefore only those are mentioned below. However, the overview over the cross-sectional studies can be found in table 7. Due to large methodological differences between publications regarding the presentation and analysis of data, a meta-analysis was not possible based on the prospective studies. The majority of the reports used some kind of cumulative greenness indicator, derived either from land-use maps (i.e. Urban Atlas) or from satellite data (i.e. NDVI)[117-121]. All six prospective studies found at least one significant inverse association between greenness exposure and a diabetes-related outcome (i.e. increased greenness availability was associated with lower risk of diabetes). However, as several of the studies presented results from more than one analysis, and/or used more than one way to measure greenness exposure, also non-significant negative associations[119] and no associations[116,118,119] were reported. All studies adjusted their main models for individual and/or area-based socio-economic factor (i.e. household income, education or similar). Four studies had included a physical activity variable[117,118,120,121], one a dietary variable[121] and three an obesity indicator (i.e. BMI)[117,118,120] either in the main model or in the sensitivity, mediation or interaction analyses. In two studies, central obesity measures were treated as health outcomes[116,121] and not as confounders or mediators. One study adjusted for air pollution levels in their main model[118] and one included air pollution as a co-exposure in the mediation analysis[121].

Three of the assessed prospective studies had T2D incidence as the main health outcome[116,117,119]. Dalton et al[117] reported that older adults living in the neighbourhood with highest greenness quartile had a 19% lower hazard ratio of diabetes development (HR 0.81; 95% CI 0.65, 0.99) compared to the individuals in the lowest quartile. The effect of greenness was not found to be mediated by physical activity. Lower odds (OR 0.988; 95% CI 0.981, 0.994) for diabetes incidence were found to be associated with a 1% increase in the tree canopy coverage, but not with a similar increase in the total cumulative greenness estimate (estimated from land use maps) in an Australian cohort (aged ≥45 years at the baseline)[119]. Paquet et al[116] related the size of neighbourhood's public open spaces (including parks, forests, sport fields and more) to decreased diabetes incidence (RR 0.75; 95% CI 0.69, 0.83); however, the greenness-diabetes relationship was not the main focus in this study. Studies addressing other diabetes-related outcomes showed similar trends. Lin et al. found an inverse association between fasting plasma glucose levels and neighbourhood greenness (NDVI) in a Taiwanese cohort (aged 43±13 years at the baseline)[120]. A German study, including data from two birth cohorts, demonstrated that an increase in NDVI values by two SD decreased the insulin resistance (IR) (Homeostasis Model Assessment (HOMA)-IR) in 15-year old adolescents by -7.4% (95% CI -13.3, -1.1)[118]. However, when the authors adjusted the model for NO_2, the association between HOMA-IR and NDVI disappeared[118], suggesting that the insulin resistance/greenness association in this case was, at least partly, attributable to confounding by air pollution exposure. De Keijzer et al.[121] defined metabolic syndrome in the participants (aged 45-69 at baseline) in a Spanish cohort, based on measurements of plasma glucose concentrations and possible diabetes treatment, but also on waist circumference and blood pressure measurements, and serum

triglyceride and HDL cholesterol levels. They showed that an interquartile range (IQR) increase in residential NDVI was associated with 13% (95% CI 1%, 23 %) lower HR of metabolic syndrome. Additional mediation analyses showed a possible effect of physical activity and air pollution. Two previous studies have provided results from meta-analyses concerning the association between greenness exposure and T2D risk[29,138]. Den Braver et al.[29] reported a non-significant negative relationship between greenness exposure and T2D (RR 0.90, 0.79, 1.03) and Twohig-Bennett et al.[138] found a significantly reduced risk of T2D in relation to greenness (OR 0.72, 0.61, 0.85). Both studies, however, based their analyses on mainly cross-sectional studies.

MECHANISMS

Key risk factors for T2D include lack of physical activity, unhealthy diet and overweight[29]. In general, socioeconomic factors, such as education and income, influence an individual's activity and dietary habits, but also a person's choice of the place to live[30-32]. Although many theories exist, greenness is generally thought to affect health by mitigating the effect of harmful exposures (such as heat, noise and air pollution), relieving mental and physiological stress, and promoting health-beneficial human activities such as exercise and socializing[2,33]. Figure 13 illustrates the possible pathways through which the urban greenness may affect T2D risk. These pathways are discussed shortly below.

URBAN GREENNESS MITIGATES HARMFUL ENVIRONMENTAL EXPOSURES

Air pollution is an important public health concern that is affecting respiratory, cardiovascular and metabolic health[34-42], as well as contributing to glucose metabolism dysregulation and development of diabetes[43,44]. In addition, a growing number of studies indicate that exposure to traffic noise, is associated with increased risk for various cardiovascular and metabolic diseases[45-50] including T2D[51-53]. Both reduced noise annoyance[54-60] and a possible acoustic noise reduction e.g.[61,62] have been linked to increased neighbourhood greenness. Urban vegetation, especially trees, have been suggested to be able to improve air quality by removing pollutants[63-65]; however, the efficiency of this process at different locations and by different species is still unclear[66].

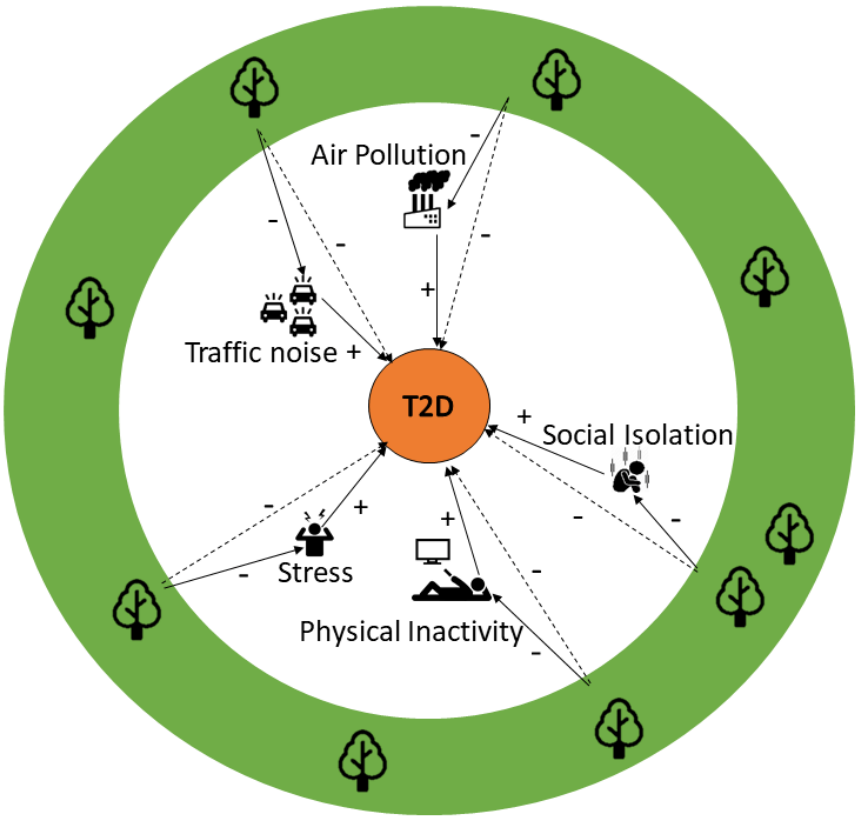
URBAN GREENNESS PROMOTES HEALTHY HUMAN BEHAVIOURS

Social relationships have a well-known protective health effect[67,68] while social isolation is a predictor of increased morbidity and mortality[69-71]. Furthermore, structural and functional characteristics of the social networks are reported to be associated with T2D development[72-74]. Increasing the quantity and quality of urban greenness is thought to foster social interactions and promote a sense of community, among adults and children[75-78], whereas a shortage of greenness in the neighbourhood is associated with feeling lonely and lacking social support[79,80]. Physical activity has a well-established positive impact on health[3,81,82] and significantly reduces the risk of developing T2D[83-85]. Abundant vegetation and bodies of water may provide an inviting setting and thus increase the motivation and time spent on recreational walking, and other physical activities[2,86-98], particularly among certain groups, such as dog owners[99]. Physical activity in natural environments has been reported to increase human well-being more than physical activity in built environments[100,101].

URBAN GREENNESS RELIEVES MENTAL AND PHYSIOLOGICAL STRESS AND PROMOTES IMMUNE FUNCTION

Green environments have a relaxing, stress-reducing effect, which allows people to recover from demanding situations[3]. Urban greenness may thus affect human health and wellbeing via complex psycho-endocrine mechanisms that regulate the function of hypothalamic pituitary adrenal (HPA) axis[11]. HPA axis controls, among other functions, the secretion of the glucocorticoid cortisol, and strives to keep it within the physiologically optimal range, necessary for accomplishing various physiological functions crucial for survival. In chronically stressed individuals, dishabituation of HPA axis triggers increased release of glucocorticoids and catecholamines. This process is associated with a wide range of disease outcomes and immune system malfunction[71,102-105]. Increased cortisol secretion (and thus chronic stress) also affects glucose metabolism by promoting gluconeogenesis in liver, suppressing glucose uptake in adipocytes and in skeletal muscles, facilitating lipolysis in adipocytes, suppressing insulin secretion, and inducing insulin resistance and inflammation[104]. These processes may in certain conditions trigger maladaptive neuroendocrine events underlying development of T2D[104]. Several studies have provided evidence for the potential role of urban greenness in buffering or reducing stress[106-114 115] however, the complexity and sensitivity of the stress regulation physiology is often a methodological complication.

Figure 13. Conceptual pathways through which urban greenness is believed to affect the development of type 2 diabetes.



Arrows beginning in the green circle depict the directional ("+"- increasing, "-"-decreasing) effect of urban greenness on the T2D risk factors, shown in the middle circle. (Dotted lines show the sum effect of each pathway on the T2D risk).

Table 6. Prospective cohort studies included this review. All studies estimated the greenness adjacent to place of residence (buffer sizes reflect the circular area around study participants' place of residents within of which the greenness exposure was measured)

Reference	Country	Main greenness exposure estimate	Outcome	Outcome assessment	Adjustments	Results
Paquet et al. 2014[116]	Australia	Other greenness estimate	T2D incidence	Registers/records/blood tests	Socioeconomic status	RR 0.75 (95% CI 0.69, 0.83) per 1 IQR increase in the size of public open spaces (1 km buffer). RR 1.01 (95% CI 0.90, 1.13) per 1 IQR increase in greenness of the public open spaces (1 km buffer).
Dalton et al. 2016[117]	UK	Cumulative greenness	T2D incidence	Self-reported	BMI, PA, socioeconomic status	HR 0.81 (95% CI 0.65, 0.99) highest versus lowest IQR of green land cover (800m buffer).
Thiering et al. 2016 [118]	Germany	Cumulative greenness	IR/fasting glucose level	Registers/records blood tests	BMI, PA, socioeconomic status, air pollution	Change in insulin resistance per 2-SD increase in NDVI (1 km buffer): -7.4 (95% CI -13.3, -1.1). Change in insulin resistance per 2-SD increase in NDVI (500m buffer): -5.5 (95% CI -11.3, 0.8). Change in IR per 2-SD increase in NDVI when adjusted for NO_2 (500m, resp. 1 km buffer): -0.7 (95% CI -7.6, 6.8), resp. -2.7 (95% CI -9.9, 5.1)
Astell-Burt et al. 2019[119]	Australia	Cumulative greenness Cumulative tree canopy cover	T2D incidence	Self-reported	Socioeconomic status	OR 0.998 (95% CI 0.992, 1.003) per 1% increase of green land cover (1.6 km buffer), OR 0.988 (95% CI 0.98, 0.99) per 1% increase of tree canopy cover (1.6 km buffer).
Lin et al 2019[120]	China	Cumulative greenness	IR/fasting glucose level	Registers/records blood tests	BMI, PA, socioeconomic status	Change in fasting plasma glycose levels per 0.1 increase of NDVI (500m, resp. 1 km buffer), (CI 95%): -0.79 (-1.10, -0.49), resp. -0.71 (-1.01, -0.40)
de Keijzer et al. 2019[121]	UK	Cumulative greenness	IR/fasting glucose level Metabolic syndrome	Registers/records blood tests	Socioeconomic status, diet. In sensitivity analyses PA and air pollution.	HR 0.87 (95% CI 0.79, 0.99) for metabolic syndrome per 1 IQR increase in NDVI (500m buffer). HR 0.90 (95% CI 0.77, 1.01) for metabolic syndrome per 1 IQR increase in NDVI (1 km buffer).

CI – confidence interval; IQR – inter-quartile range; HR-Hazard Ratio; RR- Relative risk; PA-Physical activity; IR-Insulin resistance

Table 7. Cross-sectional and ecological studies included this review. All studies estimated the greenness adjacent to place of residence.

Reference	Country	Design	Exposure estimate	Outcome	Outcome assessment	Adjustments	Association*
Bodicoat et al. [122]	UK	Cross-sectional	Cumulative greenness	T2D prevalence	Registers/records/ blood tests	BMI, PA	Significant negative
Astell-Burt et al.[123]	Australia	Cross-sectional	Cumulative greenness	T2D prevalence	Self-reported	PA, diet	Significant negative
Maas et al.[124]	Netherlands	Cross-sectional	Cumulative greenness	T2D prevalence	Registers/records/ blood tests		Significant negative
Ulmer et al[125]	USA	Cross-sectional	Cumulative tree canopy cover	T2D prevalence	Self-reported	BMI	Non-significant negative
Klompmaker et al.[126]	Netherlands	Cross-sectional	Cumulative greenness	T2D prevalence	Self-reported	BMI, PA, air pollution, noise	Significant negative
Ihlebæk et al.[127]	Norway	Cross-sectional	Cumulative greenness	T2D prevalence	Self-reported	PA	Null association Significant positive
Müller et al.[128]	Germany	Cross-sectional	Cumulative greenness, Proximity to green area	T2D prevalence	Self-reported	BMI	Significant negative
Yang et al.[129]	China	Cross-sectional	Cumulative greenness	T2D prevalence IR/ glucose markers	Registers/records/ blood tests	PA, air pollution	Significant negative
Dadvand et al.[130]	Iran	Cross-sectional	Time spent in green areas	IR/ glucose markers	Registers/records/ blood tests	Diet	Significant negative
Fan et al.[131]	China	Cross-sectional	Cumulative greenness	IR/ glucose markers	Registers/records/ blood tests	BMI, diet	Significant negative Null association
Yang et al.[132]	China	Cross-sectional	Cumulative greenness	Metabolic syndrome	Registers/records/ blood tests	PA, air pollution	Significant negative
Plans et al.[133]	Spain	Cross-sectional	Cumulative greenness	T2D prevalence	Self-reported		Null association
Tamosiunas et al. [134]	Lithuania	Cross-sectional	User or non-user of parks	T2D prevalence IR/ glucose markers	Registers/records/ blood tests/self-report		Significant negative
Brown et al.[135]	USA	Cross-sectional	Cumulative greenness	T2D prevalence	Registers/records/ blood tests		Significant negative
Groenewegen et al.[136]	Netherlands	Ecological	Cumulative greenness	T2D prevalence	Registers/records/ blood tests	Air pollution	Null association
Ngom et al. 2016[137]	Canada	Ecological	Proximity to green area	T2D prevalence	Registers/records/ blood tests		Significant negative Null association

*PA-Physical activity; IR-Insulin resistance. *non-significant; P value >0.05 or 95% CI including 1.0.*

CONCLUSIONS

Most of the assessed studies reported that increased neighbourhood greenness is associated with decreased T2D risk. However, the link between greenness exposure and T2D remains vague, mostly, because of the large methodological differences between the studies that make it difficult to summarize and quantify the possible effect that urban greenness exerts on diabetes incidence in meta-analyses. Furthermore, the pathophysiological processes mediating a potential relationship are still unknown. The shortage of prospective studies on the topic, compared to the abundance of cross-sectional ones, is apparent.

According to previous literature, lack of physical activity, unhealthy diet, and high BMI play a key role in T2D development. In addition, various urban environmental exposures, such as air pollution and noise have been suggested to affect the T2D risk[29,43,44,53,83-85], however, in the present report only the air pollution was found to be conclusively associated with T2D. Socioeconomic factors, such as income and education, strongly influence an individual's activities and dietary habits, but also the possibility to choose housing location and quality[30-32]. Thus, when exploring the greenness-diabetes risk relationship, relevant co-exposures should be included in the statistical analyses. All assessed studies adjusted for some socioeconomic variable in their analysis and most of the publications included data about physical activity levels and/or obesity indicators. However, only two prospective studies investigated the influence of air pollution levels[118,121] on the greenness/T2D relationship.

Even if the effect of air pollution and noise on diabetes risk is relatively small compared to some socioeconomic and lifestyle factors, the role of these environmental exposures should not be forgotten when the greenness and T2D association is addressed, as the quantity of greenness and pollution exposures may not be independent of each other[33]. Urban vegetation has been suggested to attenuate air pollution and noise levels and greener areas in general tend to hold fewer pollution sources (i.e. roads, industries)[33]. A couple of the publications, assessed in this chapter did report possible mediation or confounding by air pollution in the greenness-diabetes relationship[118,121], however most of the studies did not adjust their models for the levels of environmental pollution. Residential greenness and air pollution/noise also seem to entail antagonistic health effects regarding the risk of T2D[33,44,139] and thus attenuate each other's impact in multi-exposure models[118,126].

Whether greenness is associated with incidence of autoimmune diabetes has not been investigated.

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CONCLUSIONS

TYPE 2 DIABETES

Lifestyle factors play a key role in the development of T2D. It has been shown that as many as three-quarters of all cases can be attributed to overweight, sedentariness, unhealthy diet and smoking, with excess weight being by far the most important risk factor. Diet is important since it influences weight, however, a direct link between individual dietary factors and T2D is also seen: Intake of whole grains and coffee is associated with a reduced risk, while sugar-sweetened beverages and processed meats such as sausage and bacon increase the risk.

Both experimental animal studies and epidemiological studies indicate that exposure to chemicals that are included in the group of PCBs, especially the DL-PCBs, and chlorinated pesticides, such as DDT and its metabolite DDE, increase the risk of T2D. Short-lived chemicals such as bisphenol A and phthalates have in cell and animal studies been shown to influence mechanisms of importance for glucose tolerance. However, there are too few epidemiological studies to conclude that these chemicals increase T2D risk in humans.

We are exposed to metals such as arsenic, cadmium, methylmercury and lead through food and/or drinking water. Data from experimental animal studies suggest that this could increase the risk of T2D. However, the epidemiological studies are few, contradictory and often methodologically weak. The most consistent finding is an increased risk related to high exposure to arsenic in drinking water, however, this applies to higher levels than those occurring in Sweden.

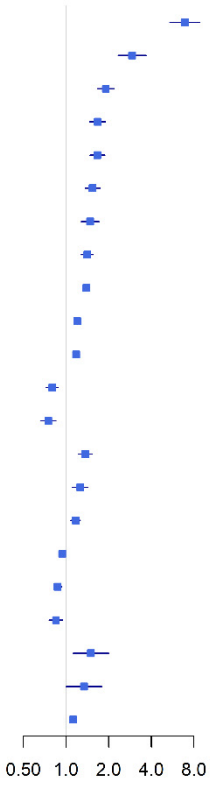
Epidemiological studies provide support that exposure to air pollution, especially fine particles, could increase the risk of T2D. Mechanistic studies show that these particles can lead to systemic inflammation, which can affect insulin sensitivity. Whether exposure to noise also increases the risk of T2D is not clear, although a few epidemiological studies point in this direction.

Living in greener neighbourhoods could potentially reduce the risk of T2D by stimulating physical activity and reducing stress. Some support for the hypothesis is provided by epidemiological studies, but the knowledge base is currently very limited.

The figure below (Figure 14) shows relative risks for lifestyle and environmental factors that, with strong support in the scientific literature, can be linked to the risk of T2D. The results primarily come from the most recent and relevant meta-analyses. The relative risks cannot easily be compared since they partly depend on the units used for the different risk factors, but the figure gives an overview of the state of knowledge. It is important to note that the importance of an individual factor for public health depends both on the risk associated with the exposure factor and the distribution of exposure in the population. As a result, a factor such as air pollution which is associated with a relatively small excess in risk, can still have a significant impact on public health if exposure is widespread. For T2D, being overweight is the dominant risk factor as it carries both high relative risk and is a common occurrence in the population. Obesity is also linked to an increased risk of autoimmune diabetes. Preventing obesity is thus a key public health measure to reduce diabetes.

Figure 14. Relative risk of type 2 diabetes in relation to the lifestyle and environmental factors with the strongest evidence.

Risk factor	Relative risk (95% CI)
BMI (obese vs.normal)	6.88 (5.39-8.78)
BMI (overweight vs. normal)	2.93 (2.33-3.68)
Sedentary time (high vs. low)	1.91 (1.66-2.19)
Waist-to-height ratio (per 1 SD increase)	1.67 (1.46-1.90)
Waist circumference (per 1 SD increase)	1.66 (1.47-1.88)
Waist-to-hip ratio (per 1 SD increase)	1.54 (1.36-1.75)
Major depressive disorders	1.48 (1.28-1.74)
Education (low vs. high)	1.41 (1.28-1.55)
Smoking (current vs. never)	1.39 (1.33-1.44)
Television watching (per 2 hours/day increase)	1.20 (1.14-1.27)
BMI (per 1 kg/m2 increase)	1.18 (1.15-1.20)
Birth weight (per 1 kg increase)	0.80 (0.72-0.88)
Leisure time physical activity (high vs. low)	0.75 (0.66-0.85)
Processed red meat (per 50 g/day increase)	1.37 (1.22-1.54)
Sugar-sweetened beverages (per 1 serving/day increase)	1.26 (1.11-1.43)
Unprocessed red meat (per 100 g/day increase)	1.17 (1.08-1.26)
Total coffee (per 1 cup/day increase)	0.94 (0.93-0.95)
Whole grain (per 30 g/day increase)	0.87 (0.82-0.93)
Mediterranean diet (high vs. low adherence)	0.85 (0.76-0.95)
DDE* (per 1 SD increase)	1.46 (0.97-2.18)
DL-PCB* (per 1 SD increase)	1.34 (1.00-1.79)
Air pollution-PM2.5** (per 10 µg/m3 increase)	1.12 (1.08-1.16)



**DL-PCBs- dioxin-like PCB. DDE- Dichlorodiphenyldichloroethylene, a metabolite of DDT. RR for DL-PCB and DDE are based on data from a Swedish study as there are no meta-analysis available.*
***The concentration of $PM_{2.5}$ in Swedish cities is close to 10 µg/m^3.*

AUTOIMMUNE DIABETES

For autoimmune forms of diabetes such as T1D in children and LADA, there is strong evidence that obesity increases the risks, and furthermore, that certain viral infections increase the risk of T1D. Several other lifestyle and dietary factors have been linked to the risk of autoimmune diabetes in children or adults, but there is not enough evidence to draw any definite conclusions. Regarding environmental factors such as chemicals, metals, air pollution, noise and proximity to urban greenness, their potential role in the development of autoimmune diabetes is largely unexplored.

RESEARCH NEEDS

LIFESTYLE AND DIET

- There is a need to continue exploration of the potential influence of lifestyle and dietary factors on the development and promotion of autoimmunity leading to T1D and autoimmune diabetes in adults.
- Interaction between lifestyle/dietary factors and genetic susceptibility needs to be investigated in relation to both T2D and autoimmune diabetes. Such information may help in identifying individuals that are susceptible to risk factors and for whom lifestyle intervention may be particularly beneficial.
- More high-quality studies are needed of the relationship between diet and T2D, including innovative study designs and novel methods to increase the possibilities of inferring causality, e.g. Mendelian randomization studies. There is also a need for intervention studies on the influence of diet on incidence of T2D as well as underlying mechanisms, e.g. effects on insulin sensitivity and beta cell function.
- Contemporary research indicates that T2D is a heterogeneous disease encompassing subgroups with different pathophysiology. By studying lifestyle and dietary factors in relation to these different subgroups it may be possible to identify lifestyle risk factors that are concealed in analyses of heterogenous patient groups.

CHEMICALS

- Conclusions regarding the contribution to T2D risk from exposure to ***POPs*** are primarily hampered by difficulties in distinguishing between potential contributions from different compounds together with covarying risk factors. Research is needed to further investigate how the interplay between BMI, exposure and persistence of chemicals could affect the risk of developing T2D.
- Currently, conclusions about to what extent exposure to non-persistent environmental chemicals, such as bisphenols and phthalates, could contribute to T2D risk are hampered by limitations in the exposure assessment of these short-lived chemicals. High quality prospective studies with repeated measurement of the exposure would provide more confidence in conclusions.
- Better understanding of mechanisms for the association between exposure to both persistent and non-persistent environmental chemicals and T2D would overcome some of the uncertainties caused by confounding and increase confidence in conclusions. Potential mechanisms by which environmental chemicals could contribute to the risk of diabetes need to be further elucidated, e.g. by further mechanistic studies in vitro and development of adverse outcome pathways.

METALS

- For all metals there is a need for high quality prospective studies at low-to-moderate exposure levels, using well-established individual exposure biomarkers, reliable diagnosis of T2D and including information about well-established risk factors. For arsenic it is highly important to consider interactions with the metabolism of arsenic.

- For all metals there is a need for research that can disentangle the potential interplay between exposure, BMI/obesity, and the development of T2D.
- Future experimental studies investigating the influence of metals on diabetes risk should use doses that are of relevance to human exposure, and the actual internal dose should always be assessed. For arsenic, it is also highly important to consider that the metabolism varies between humans and different animal species.
- Potential mechanisms by which metals can cause or contribute to T2D needs to be clarified.

AIR POLLUTION AND NOISE

- Evidence on air pollution effects on T2D risk is mostly available for $PM_{2.5}$. More research is needed on the role of other air pollution components as well as of emissions from certain sources, such as local combustion and road dust on T2D risk.
- More studies are needed on the association between exposure to different transportation noise sources and T2D. Preferably the studies should involve assessment of sleep disturbances and stress reactions to shed light on etiological mechanisms.
- Interactions between air pollution and noise from road traffic in relation to T2D development should be investigated as both these exposures have been associated with increased risks and they often occur together.
- Population attributable risks for T2D related to air pollution and noise need to be estimated, which necessitates accurate assessment of population exposures.

GREENESS

- There is a need for prospective studies to clarify whether urban greenness may reduce the risk of T2D.
- Future studies on the association between urban greenness and diabetes risk need to consider both quantitative and qualitative aspects of greenness, the influence of potential confounders such as overweight/obesity and air pollution and use a stringent definition of the outcome.

GENERAL

- To minimize risks of selection bias, the epidemiological studies on environmental exposures and T2D need to have a high quality of the ascertainment of disease occurrence in the study bases. This has often not been the case and is particularly difficult because many cases of T2D remain undiagnosed.
- Common to all environmental exposures is that very few studies have investigated their role for development of immunological types of diabetes, such as T1D and LADA. This needs to be addressed both in high quality longitudinal epidemiological as well as in experimental studies, where etiological mechanisms can better be elucidated.

ABBREVIATIONS

AhR	Aryl hydrocarbon receptor
BFRs	Brominated flame-retardants
BMI	Body Mass Index
BPA	Bisphenol A
BPS	Bisphenol S
CI	Confidence interval
CHD	Coronary heart disease
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DHA	Docosahexaenoic acid
DL	Dioxin-like
DMA	Dimethylarsinic acid
ED	Endocrine disruptor
EFSA	European Food Safety Authority
EPA	Eicosapentaenoic acid
HbA1c	Glycated haemoglobin
HCB	Hexachlorobenzene
HOMA	Homeostasis Model Assessment
HR	Hazard Ratio
IQR	Inter quartile range
IR	Insulin resistance
KNHANES	Korean National Health and Nutrition Examination Survey
LADA	Latent autoimmune diabetes in adults
MUFA	Monounsaturated fatty acid
NDVI	Normalized Difference Vegetation Index
NHANES	National Health and Nutrition Examination Survey
NO_2	Nitrogen dioxide
OR	Odds ratio
PAR	Population attributable risk
PBDE	Polybrominated diphenyl ethers
PCB	Polychlorinated biphenyl
PFAS	Perfluoroalkyl and polyfluoroalkyl substances

PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulphonate
PM	Particulate matter
POP	Persistent organic pollutants
PUFA	Polyunsaturated fatty acid
RCT	Randomized clinical trial
ROS	Reactive oxygen species
RR	Relative risk
SD	Standard deviation
SFA	Saturated fatty acid
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TWI	Tolerable weekly intake

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