労災疾病臨床研究事業費補助金
分担研究報告書

4-1．一般健康診断の事後措置の有効な報告のあり方に関する質的調査

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研究要旨

本研究は、健康診断の事後措置のあり方について検討することを前提として、健康診断結果の企業および従業員への報告の目的、方法について明らかにすることを目的に、統括産業医 11 名によるフォーカス・グループ・ディスカッションを実施した。その結果、主に以下の意見を得た。

就業制限が必要かも知れない人についてについて、

・就業制限の要否の判断は、労働安全衛生法第 68 条（病者の就業禁止）に紐づけて明確に認識する必要がある。就業規則やその他の社内規程に定めて運用されるべき事柄である。

・就業制限の要否の判断基準は、業務内容により異なる。

・就業制限に関わる健康状態の有所見について企業に報告すべきである。企業に報告することにより、顕著に改善が進むことがある。

・企業で基準を定め、有所見率を算出している。ただし、全社統一基準とはせず、事業所毎に基準を定めて運用している場合がある。

・会社に報告する際には、個人情報保護に配慮しつつ、理解が得られるよう伝え方の工夫が必要である。特に管理監督者が部下の健康管理を確実に行う役割があることが認識されておらず、教育を行うことが必要である。

・労働者本人にも、自己健康管理の必要性について、就業制限のことも踏まえつつ教育を行うこと効果的であり、また、重要なことである。

ポピュレーションアプローチについて、

・経営層に健診結果を報告する場合は、生活習慣を組織別・部門別に可視化すると関心が得られやすい。同業他社との比較も関心が高いが、比較可能なデータがない場合が多い。

・企業・部門全体で健診結果を活用して目標を定め、競い合いながら健康度を高める取り組みを行っている。

データを示す場合の注意点について、

・データ活用の目的と使い方を明確にしたうえで、その目的に合ったデータを出す必要がある。全体の健康度の指標であれば、性別・年齢ごとに集計する、または、調整を行う必要があり、誤った改善施策に繋がることが無いよう、注意する必要がある。

これらの結果をふまえ、就業制限が必要か否かの判断が必要となる人については、労働安全衛生法で事業者に義務づけている定期健康診断結果の監督署への報告様式のなかで「所見のあつた者の人数（有所見者数）」および「医師の指示人数」の定義を明確にし、事後措置の実施状況を確認することで健診事後措置の確実な実施を促すことが有用である。また、健診結果に基づき医療機関への受診が必要な者（要受診者）や睡眠や運動等の問診データにつ

いて、事業者の多くは同業他社との比較に関心が高く、業種別・性年齢別の比較データを社会で整備することが有用である。

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A．はじめに

健康診断の事後措置は、労働安全衛生法第66条の4〜7に規定された活動である。具体的な内容は「健康診断結果に基づき事業者が講ずべき措置に関する指針」に記述されているものの、その実態は事業所規模・業種等により様々である。本研究課題の平成29年度の調査において、専門家産業医に対するフォーカス・グループ・ディスカッション（FGD）を実施し、次のような結果を得た[1)]。

（1）健診事後措置を行うべき優先順位は、1．業務により健康影響が出ているもの、2．就業制限等、何らかの措置が必要であるもの、3．要受診レベルのもの、4．要保健指導レベルのもの、である。

（2）就業上の措置の判断は、ある程度、自動判定で振るい分けを行ったうえで、最終的に専門家による判定をするのが効率的である。

（3）産業医（特に嘱託産業医）の業務時間が限られており、保健師や衛生管理者との分業が求められる。

（4）小規模事業所では、健診結果が紙しかない（電子データ化されていない）ため、結果を集計すること自体が困難であることが多い。

（5）ベンチマークとして、有所見率と、その後の行動（要医療の人がその後、受療したかどうか等）を追っていくことが重要である。

これらの結果を受け、健康診断結果の企業および従業員への報告の目的、方法について明らかにすることを目的に、専門家によるFGDを実施した。

B．研究の方法

企業内に複数の産業医がおり、全社の健康施策に関わっている産業医（以下、統括産業医という）11名でのフォーカス・グループ・ディスカッション（FGD）を実施した。本グループは過去4回程、産業保健に関する様々な内容を議論しているメンバーであり、お互いの考え方もおおよそ理解し、自由に議論することが可能な関係性もできていることから、11名全員によるFGDを実施した。

テーマは以下の通りである。

1．産業保健活動（実務）のなかで、健康診断結果(データ)を、どのような目的で、どのように利用すると有効か？（対労働者と対組織）

（例)対労働者:健康への関心を高める目的で、個別指導の際に全社員の分布（ヒストグラム）を示したうえで本人の結果を示す

（例）対組織（経営者）：健康施策の成果を示す目的で、有所見率の経年比較を示す

（例）対組織（施策立案）：健康の中期経営計画立案の際に、目標値を設定する

1-1．指標化する場合は、条件・基準は、どのように設定するか？

1-2．　どのようなベンチマークが存在すると有用か？

C．結果

就業制限が必要かも知れない人について

・就業制限の要否の判断は、労働安全衛生法第68 条に紐づけて明確に認識する必要がある。就業規則やその他の社内規程に定めて運用されるべき事柄である。

（参考）

第六十八条（病者の就業禁止）

事業者は、伝染性の疾病その他の疾病で、厚生労働省令で定めるものにかかつた労働者については、厚生労働省令で定めるところにより、その就業を禁止しなければならない。

「労働安全衛生法の第 68 条に関わる話なんで、安全配慮義務といっても、もう少しレベルが高いんですよ。68 条の就業禁止っていうのは、あれはみんなあんまり関心がないんだけど、伝染性の疾患に関してはもちろんそういうことがあると思うけども、一般的な健康の問題での、腎機能なんかのことは、元々例として挙げられてるんですね。心不全とか腎不全とかっていうことを、最近は血糖値もか。そこをね、ちょっと再認識して、その条件みたいなことで提案すると、法律とのひもがついて、できるんじゃないかと。（中略）全体的な健康上の問題は、そこにひもづけた方がいいと思いますね。」

「68 条ですかね。あれは、会社の中のマネジメント・システムの中で健康安全管理規程を作って、その中にこういう数字と一緒に、そこを根拠にして「こういう人は働かせちゃいけない」という、数字化してるんです。」

「就業規則の中にあるべきものですよね。」

・就業制限の要否の判断基準は、業務内容により異なる。

「オフィスワーカーには、確かにこれ² は検討が必要なレベルかもしれないんですけど、エアコンが効いてないとこで働いてる現場の人にとっては、検討の余地なく制限かけている。」

「現場に出てる人で 1.8 以上ある人は、確実に悪くなっていきますよね。そういう人は、早めにオフィスワークに変えてやったりとか、そういう必要があるんで。これはもう、検討が必要というよりも、絶対的な就業制限。例えば、HbA1c が 10 あれば、休業にさせたりする。」

就業制限の要否の検討が必要となるレベル

収縮期血圧　180 mmHg，拡張期血圧　110 mmHg

空腹時血糖 200 mg/dL，随時血糖 300 mg/dL

HbA1c 10%

Hb 8 g/dL

ALT 200 mg/dL

クレアチニン 2.0 mg/dL

・就業制限に関わる健康状態の有所見につい

て企業に報告すべきである。企業に報告することにより、顕著に改善が進むことがある。

「基本的な考えとして、組織に言う場合にね、非常にハイリスクな人の問題があります就業制限に関わるような人が何パーセントぐらいいるのかなと。それが、まさに経年変化としてどうなっていくかということが見たいわけで。（中略）自分の企業をする中で、そういう人が何人いるかということが経年的に分かるようなデータっていうのは、あった方がいいですよね。」

「工場とかそういったところだと、医師の聴取も含めて、グループ独自で決めた管理部門っていうのがあって、それを伝えて、個人個人の分も伝えてるんですけども、（中略）11 年から、いわゆる先ほど言われた勤務制限にかかるレベルの人たちの人数と、14 年以降の人数とって見たときに、糖尿病の A1c だけだったんですけども、例えばA1c 9 を超えるぐらいのレベルの人が 3%弱ぐらいいたんですけども、2%を完全に切ってきて、そのあとが。だから、やっぱり、もちろんそれを伝える時には、ちゃんと「あなたたちの管理部門は伝えますよ」っていうのを全員アナウンスして、伝えるようにしたんですけど、それだけでも現場の重症化の方たちが少し減ったなっていうのは、実感としてありましたですね。」

・企業で基準を定め、有所見率を算出している。ただし、全社統一基準とはせず、事業所毎に基準を定めて運用している場合がある。

「グループ会社も含めて規模がいろいろございまして、事業所やグループ会社で更に詳細なものを決めてもいいという前提を持っていながら、いわゆる高血圧の、具体的に言うと上が 180、下が 110 まで。それから、A1c が 10.0 のところ。それから、実は私とは意見が違うんだけれども、ヘモグロビンが 8 を下回っているというようなもので、もうちょっといろんなもの入れた方がいいっていう意見もあったんだけども、そういったものを、安全配慮義務の担保という観点でやっています。」

「ただ、それが全部の事業所に適用できないんで、それが統括産業医の仕事の一つかもしれないんですけど、各事業所を回って、そこの作業員と話し合ってですね、この事業所の標準というのを決めて。だから、本社から「幾らにしろ」っていうのは、出してないです。各事業所でばらばらに決めてるんですけど、決めた中ではちゃんと運用されてるんで、（略）」

・会社に報告する際には、個人情報保護に配慮しつつ、理解が得られるよう伝え方の工夫が必要である。特に管理監督者が部下の健康管理を確実に行う役割があることが認識されておらず、教育を行うことが必要である。

「A1c が 8 以上の人が何人いました、とかっていう話をしても、ピンとくる人とピンとこない人は結構多いので。で、ややもすると、経営層の意識が低ければ、「それは誰と誰が、何で名簿が出るのか」みたいな話になったりするんで、（略）」

「健診の事後措置の仕組みがゼロで、何にも就業上の配慮はやってなかったんです。そのときのやり方として、（中略）これ [2] を基にして健保の先生たちと話し合って、●●（会社名）用語なんですけど、A 判定、B 判定、C 判定、D 判定、E 判定という呼び方を完全に●●の中だけの用語で決めて、E 判定っていうのが、（＊）のところなんですけど、それを基に健診事後措置の仕組みを入れたっていうことと、あとは、A 判定、B 判定、C 判定、D 判定、E 判定という言い方をして、「E 判定はまずいよ」という教育をすることによって、みんな細かい意味は分からなくても、「E 判定はだめらしい」っていうことを管理監督者が認識をするようにな

って、管理監督者が「おまえ、E判定だったらしいな」みたいなことを言うような感じになって。それまでは、「管理監督者に責任がありますよ」みたいなことを教育をして分かってもらうといっても、分かったような、分かんないような感じだったのが、そういう使い方をしてフィードバックをすることによって、管理監督者の意識を高められる。共通言語を作ることができたっていう感じはします。」

「安全配慮義務のね、実行責任が管理監督者にあるという、管理監督者は部下の健康状態を把握しなきゃいけないという、このことに関して、ほとんど手が打ててないんですよ。」

「管理監督者の方は、（略）安全衛生規程の中の衛生管理規程の中に、ちゃんとうたってるんで。「管理監督者に責任がある」と。」「「安全配慮義務の実行責任は、あなたにあるよ」と言ったときに、たいてい出てくる質問は、「われわれは医者でもない。健康状態分かんないでしょ」って、そういうことなんですよ。僕はそのときに、いつも「毎日あなたは会ってるんだから、いつもと違うかどうかを見てね。それでいいんだ」って言うんだけど、（中略）「こういうふうにすればいいんだ」ということは、ちゃんと会社側が教育の場で言わなきゃいけない。管理監督者研修で必ず言わなきゃいけないんですよね。」

・労働者本人にも、自己健康管理の必要性について、就業制限のことも踏まえつつ教育を行うこと効果的であり、また、重要なことである。

「病気を理由に休まさせられて喜ぶ人は、ほとんどいないんですね。ものすごくみんな一生懸命努力して戻ってこようとするんで、激変するんですよ、今まで悪かった人が。だから、最初、こう、厳しくやるのもいいかなと思います。特にHbA1cとか、血圧とか、みんな軽く考えてる人が多いので、教育効果は抜群ですね。」

受診が必要な人（要受診者）

・要受診者率の報告も重要であるが、あまり実施されていない。

「医療を要する人たちの抽出は必要なことで、それは、健康診断で何パーセントぐらいだったかっていうことですよね。これは、あんまりされてないような気がしますね。」

ポピュレーションアプローチ

・経営層に健診結果を報告する場合は、生活習慣を組織別・部門別に可視化すると関心が得られやすい。同業他社との比較も関心が高いが、比較可能なデータがない場合が多い。

「どちらかというと、標準的な問診とかの、法定項目に特化した話なんでちょっとあれなんですけど、うちでしている体力テストとか健康度調査とかの結果を、組織部門とかに分けてやると、かなり食いつきがいいです。」

「問診表の方の活用で、いい健康習慣を八つ挙げといて、それのその組織の点数化して、「あなたのところは、まだ全社平均に届いてないよ」とか、「ここのところはいいね」とか、40歳以上と40歳未満に分けてどこに問題があるかという、組織として健康習慣が持ててるかどうかという動きを、今、動かしてるというところなんですね。」

「社長とか、そういう人たちと健康管理的な話をする時に必ず言われるのは、「うちの会社は、よそと比べてどうなんだ」と言われる場合がある。そのときに、比較する手法がないんですよね。（中略）よその会社と比べてどうなんだというときに、回答がなかなか難しかったりする。」

「「他の会社はどうなのか」っていうのは聞かれるんだけど、ないんですよね。」

・企業・部門全体で健診結果を活用して目標を定め、競い合いながら健康度を高める取り組み

を行っている。

「健康経営を進める中で、グループ会社を含めて、競争させながらやるっていう仕組みを持っていて、各会社ごとに健康スコアっていうのを、健康診断のデータとか、それ以外の傷病手当金だとか、いろいろな要素が入ってるんですけど、そういうのでスコア化して競わせるっていうことをしてて。ただ、単純に競わせるっていうよりは、健康スコアの通知表みたいなものなので、それをフィードバックを個別にそれぞれの子会社のトップとやる中で、次年度の、そこから課題を見いだして、むしろ計画立案に直接役立ててるという感じですかね。目標値そのものは、グループ全体で決めたものがあるので、目標値を設定するというよりは、年間の課題抽出と実行計画を立てるというのに使ってます。」

「トータルの順位を経営者レベルでは一番気にしてます。ただ、各会社にフィードバックというか、スコアが出たものを持っていって説明したりだとか、ディスカッションして計画に落とし込むっていうのは、本当の子会社のトップっていうよりは、もうちょっと下のレベルの人と実務的にやっているので、そこでは個別にもっとしっかりと見れてるかなと思います。」

データを示す場合の注意点

・データ活用の目的と使い方を明確にしたうえで、その目的に合ったデータを出す必要がある。全体の健康度の指標であれば、性別・年齢ごとに集計する、または、調整を行う必要があり、誤った改善施策に繋がることが無いよう、注意する必要がある。

「（他社との比較を行う場合）経営者も 2 種類あって、よそよりコストをかけたくないっていう人もいますんで、そこは、単純に比較は難しいんですけどね。だけども、基準は欲しいですよね。欲しいけれども、使い方は、いつも善とは限らない。」

「●●（会社名）は、全社データを集めて、年齢階層別に標準化をして、標準データを作って、各事業所に対しては、例えば BMI の年齢定性有所見率は幾らだと。そのデータを年齢階層別に全部開示していて、事業所は事業所で、自分たちが集めたデータと全社データを比較して。つまり、皆さんのように社長が見るんじゃなくて、うちは健康管理所がそれを見て、「うちが悪いのか」と思ってるというパターンになっているということですね。ですから、生活習慣病の有所見率に関しては、年齢階層ごとに全部出してるので、それを見れば、「うちは 20 代が悪いのか」とか、そういうことが分かる仕組みにはしてあります。それを見ながら、自分たちで来年度の労働衛生の課題を考えてもらって、具体体に何をするかは、そこで考えろという仕組みになってます。それを社長とかそういう人たちが見てるかというと、工場では工場長とかはですね、必ずマネジメント・レビューがあるので、健康管理室のマネジメント・レビューを聞いてるので、他の事業所に比べて悪いとか、それを気にするし、そういうことも分かってると。」

「健診データになると、かなり年齢階層が効いてくるので、なかなか使いづらいなという気はしますよね。よく思うのは、ああいう医学的なデータを正しく表現しないと、誤解が起こる方が嫌で、100 人の関係会社に「おたくは肥満が多い」って言うのが、本当に妥当なのかと。それって、ただの年齢のかせぎじゃないのって思うから、小さな集団に対してああいうデータを開示していくことが正しい理解につながるかというと、そうじゃないような気はしてるんです。」

「どの目的でどのように利用するか、何を定量化すればいいかだけだと思っていて、素晴らしいなと思ったのは、●●も●●も、ちゃんと年齢調整をしたり、スコアリングをするんであれ

ば、きちんと正しいデータにしてお伝えするならいいけれども、「おまえのところは不健康者が多かった」とか、そういう使い方をすることしかうちはできないので、そのデータを使っていないってことがあるんで。定量化するのであれば、正しく表現し直した形で定量化して使わないと、ものすごい誤解が生じると思っていて。」

「ハイリスクな人たちの比率って、そんなめんどくさいこと考えなくていいんですよ。正直、何パーセントいるか。つまり、非常にリスクが高い人たちの比率に関するデータなんて、年齢調整も何もなくていい。いるという事実と、それが何人かというレベルで、多いか、少ないかを考えればいい。実は減らせばいい。ところが、集団の健康を表すような指標っていうのは、年齢によって大きく左右されるわけだから、そういう見せ方をするんだったら、年齢階層の調整とか、男女比の調整とかをしてかないと、間違いを起こす。だから、何のために何を見せるかという議論なしにデータの切り口を考えても、なかなか結論はうまくまとまっていかないと思います。」

D．考察

本研究では、11 名の統括産業医に対するFGD を実施し、一般健康診断結果の有効な活用方法について検討した。

就業制限が必要か否かの判断が必要となる人については、一般健康診断の事後措置として、最も対応の優先順位の高い集団であることで見解が一致していた。就業制限は労働安全衛生法第 68 条と関連し、社内規則で整備する等、適切に対応が行われるよう事後措置を行う必要があるとの指摘がなされた。就業制限の要否の判断基準は業務内容と異なり一律に定めることは困難ではあるものの、産業衛生専門家のコンセンサス調査の結果 [2]は目安として参考になる。現在、労働安全衛生法で事業者に定期健康診断結果の監督署への報告義務を課している一方で、報告様式にある「所見のあつた者の人数（有所見者数）」および「医師の指示人数」の定義が明確でなく、専門家産業医の認識も様々であるのが実態である [3]。報告様式の各所見の定義を明確にし、特に「医師の指示人数」では「医師の指示」の定義を明確にしたうえで事後措置の実施状況を把握するようにすることで、就業制限が必要か否かの判断が必要となる人への対応が、中小企業も含め実施徹底されるのではと考えられる。

次に、健診結果に基づき医療機関への受診が必要な者（要受診者）について、社内に報告を行うことは重要であるとの意見が見られた。また、検査値のデータよりも、睡眠や運動等、問診データの方が理解しやすく、経営者に結果提示した際にも「響く」との意見が見られた。既に国レベルでは国民健康・栄養調査のデータ 4）や特定健康診査・特定保健指導に関するデータ 5）が公開されており、比較して結果を提示することができる。ただし、データの提示方法には注意を要する。例えば、組織別、部門別の比較を行う場合には、性・年齢の影響を考慮して、性･年齢別にデータを共有する、または、性・年齢を調整した値を示す等、正しくデータを示すことが必要である。また、経営者は同業他社との比較に関心が高いため、業種別の比較データが存在すると有用である。今後、ベンチマーク指標が社会で広く活用できるための情報基盤の整備が必要である。

1）平成 29 年度 厚生労働省 労災疾病臨床研究事業費補助金「健康診断結果の経年変化に視点をおいた望ましい健診結果の活用と事後措置のあり方に関する研究（170301）研究代表者：立道昌幸」研究報告書

2) Tateishi S, et al. The opinions of occupational physicians about maintaining healthy workers by means of medical examinations in Japan using the Delphi method. J Occup Health. 2016; 58(1): 72-80.
3) 平成 30 年度 厚生労働省 労災疾病臨床研究事業費補助金「健康診断の有所見のあり方に関する研究　研究代表者：森晃爾」研究報告書
4) 国民健康・栄養調査（https://www.mhlw.go.jp/bunya/kenkou/kenkou_eiyou_chousa.html　2019 年 4 月 15 日アクセス）
5) 特定健康診査・特定保健指導に関するデータ（https://www.mhlw.go.jp/bunya/shakaihosho/iryouseido01/info02a-2.html　2019 年 4 月 15 日アクセス）

Ｅ．倫理的配慮

本調査に関して、産業医大学倫理委員会の承認を得て実施した。FGD の前に参加者に対して説明を行い、同意書に署名を得て実施した。

Ｆ．健康危険情報

該当せず。

Ｇ．研究発表

１．論文発表

なし。

２．学会発表

該当せず。

労災疾病臨床研究事業費補助金
分担研究報告書

4-2．一般健康診断の事後措置の有効性に関する調査

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研究要旨

労働安全衛生法に基づく健康診断は、企業に実施義務が課されており、単に健診を行うのみでなく、健康診断の事後措置を適切に行うことが法令で規定されている。平成 29 年度の本研究では、就業制限が必要か否かの判断が必要な人への対応に次いで、要受診レベルの人への対応が挙げられている。今回、要受診レベルの人への対応方法について検討した。医療サービスが必要な人が適切に医療機関に受診しているか否かを Crude coverage（CC）という指標で明らかにした。その結果、某製造業では専属の産業保健スタッフがいる事業所で CC が高血圧は有意に高く（aOR 1.28: 95%CI 1.07-1.54）、糖尿病と脂質異常症は有意な差を認めなかった。（糖尿病　aOR 1.17: 95%CI 0.85-1.62、脂質異常症　aOR 1.00: 95%CI 0.89-1.13）。次に、本人のヘルスリテラシーと血糖有所見者の受療行動では、ヘルスリテラシーが高いほど、有意に受療していた（CC が高かった）。以上から、特に生活習慣に関連する疾患に対して、産業保健スタッフが本人の疾患に対する理解を高めながら介入を行うことが有効であり、また、その効果を crude coverage（CC）等のベンチマークを活用しながら評価することが重要である。

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A．はじめに

労働安全衛生法に基づく健康診断は、企業に実施義務が課されており、単に健診を行うのみでなく、健康診断の事後措置を適切に行うことが法令で規定されている（労働安全衛生法第 66 条の 4〜7）。具体的な内容は「健康診断結果に基づき事業者が講ずべき措置に関する指針」に記述されている。具体的には、就業上の配慮の要否の判断や受診勧奨、栄養・運動指導等であり、この順に優先順位が高いことが専門家によるフォーカス・グループ・ディスカッションで明らかになっている。

本研究では、受診勧奨に注目し、以下の 2 つのテーマについて検討する。

研究 1：産業保健専門職（産業医、保健師等）が健診事後措置に関与することにより、受診勧奨が促され、また、治療による疾患のコントロールが良好となるか否か

研究 2：健康情報を入手し、理解し、評価し、活用するための知識、意欲、能力（以下、ヘル

スリテラシー）[1]が高い人は、医療が必要な際に適切に医療機関へ受診しているか

以上のことを明らかにすることにより、受診勧奨に対する産業保健専門職の関わり方について検討する。

B．研究の方法

【研究１】

本研究は、某企業での断面調査である。一般健康診断、人事データ、診療報酬明細書（レセプト）を用い、2011 年 4 月から 2012 年 3 月まで所属する男性社員 91351 人を対象とした。対象者を 40〜59 歳に絞り、心筋梗塞、脳卒中、悪性腫瘍、腎不全または透析の者、また、データ欠損がある者を除外し、最終的に残った 53720 人を本研究の対象とした。

産業保健専門職の有無

2011 年度において、対象者は 1914 事業所で勤務していた。研究対象企業では、1914 事業所のうち、265 事業場(8,559 名)が産業医および保健師が不在、 146 事業場(3,872 名)が嘱託の産業医および保健師が執務、393 事業場(14,690 名）が嘱託の産業医と専属の保健師が執務、そして、555 事業場(26,599 名)が専属の産業医および保健師が執務していた。

研究対象企業においては、健康診断実施後に各個人に健診結果が返却される。健診結果には、「要受診（医療機関での治療が必要)」「要保健指導（治療は必要ないが生活習慣を改善する必要がある)」「異常なし」の判定が行われ、個人に通知される。専属の産業保健スタッフがいる事業所では、産業保健スタッフが、「要受診」の判定を受けた人が適切に受診したかどうかの確認を行い、また、「要保健指導」の判定を受けた人に対して保健指導を実施することが通常行われるが、専属の産業保健スタッフがいない事業所では、そのようなきめ細かいフォローアップが実施できていない。そこで、専属の産業保健スタッフ（産業医または産業看護職）がいる事業所（948 事業場、41,289 名）を OH 群、専属の産業保健スタッフがいない事業所(411 事業場、12,431 名)を non-OH 群と定義した。

健康情報

2011 年度に実施された定期健康診断のデータのうち、属性（性・年齢、職種)、自記式の質問票（喫煙歴、現在の内服状況（血糖、血圧、脂質の内服)、および既往歴（心筋梗塞、脳卒中、悪性腫瘍および腎不全・透析))と客観的な検査結果（body mass index (BMI)、空腹時血糖、脂質 (low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides)、収縮期血圧/拡張期血圧を用いた。

社会経済的情報

2011 年度の標準報酬月額を用いた。研究参加企業における母集団の標準報酬月額がおよそ 3 分位となるように分類し、low (≥41 万円); middle (41-56 万円)、high (>56 万円)とした。

医療機関への受診記録

各個人が医療機関に受診したかどうかを把握する目的で診療報酬明細書（レセプト）を用いた。レセプトには、受診日、傷病名、医療費等の情報が記載されている。2011 年 4 月 1 日から 2012 年 3 月 31 日までのレセプトを用いて、高血圧、糖尿病、脂質異常症の病名で受診したか否かを把握した。ここで把握した受診は、各疾患の治療薬が内服されているか否かに関わらず、受診したか否かのみで判断した。各疾患での受療ありのものを、Use（高血圧)、Use（糖尿病)、Use（脂質異常症）と定義した。

Crude coverage (CC)

医療サービスを必要とする人を、本研究では高血圧、糖尿病、脂質異常症毎に、以下の通り

に定義した。

Need（高血圧）: 収縮期血圧 160mmHg 以上、または、拡張期血圧 100mmHg 以上、または、降圧薬の内服あり

Need（糖尿病）: FBS160mg/dL 以上、または、血糖降下薬・インスリンの使用あり

Need（脂質異常症）: LDL コレステロール 160mg/dL 以上、または、HDL コレステロール 35mg/dL 未満、または、中性脂肪(TG)300mg/dL 以上、または、コレステロールを改善する薬の内服あり

この基準は、健診で「要受診」の判定となり、かつ、研究参加企業において専属の産業保健スタッフが個別の介入を行う基準である。

Crude coverage（CC）は、特定の医療サービスを必要とする人のうち、医療サービスの利用している者の割合であり、
Crude coverage（CC）= Use / Need

統計

Non-OH 群と OH 群の年齢、BMI、喫煙歴、職種、標準報酬月額の各カテゴリーの割合を計算した。また、non-OH 群と OH 群の Crude coverage(CC)を計算した。

次に、医療サービスを必要とする人（Need）を対象とし、実際に医療機関に受療したか否かをアウトカムとし、nonOH 群と比較して OH 群のオッズ比および 95%信頼区間を、高血圧、糖尿病、脂質異常症の疾患毎に、ロジスティック回帰で分析した。年齢、標準報酬月額、職種を調整した。本解析は、個人を一次レベル、事業所を二次レベルとしたマルチレベル分析を行った。

【研究２】

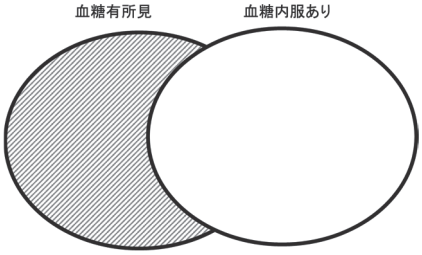
本研究は、コラボヘルス研究会に加入している 12 社を対象に実施した。2015 年または 2016 年に、一般健康診断、診療報酬明細書（レセプト）および質問紙調査の情報がある 22,512 人を研究対象とした。

血糖にテーマを絞り、対象者の選定に 2 つの情報を用いた。
血糖有所見：一般健康診断のデータを用いて、「HbA1c(NGSP)6.5 % or 空腹時血糖 126mg/dL or 随時血糖 200mg/dL 以上の者」を血糖有所見者と定義した。
血糖内服あり：一般健康診断の問診を用いて、「インスリン注射又は血糖を下げる薬の使用の有無」で、はいと回答した者を血糖内服ありと定義した。

ヘルスリテラシーは、職場で使用することを想定し、石川らが日本のオフィスワーカーで使用した 5 問からなる質問紙[2)]を使用した。具体的には、
A.新聞、本、テレビ、インターネットなど、いろいろな情報源から情報を集められる
B.たくさんある情報の中から、自分が求める情報を選び出せる
C.情報を理解し、人に伝えることができる
D.情報がどの程度信頼できるかを判断できる
E.情報をもとに健康改善のための計画や行動を決めることができる
の 5 つの質問について、全くそうおもわない、から強くそう思うまで、5 択で聴取した。5〜25 点で点数化（点数が高い方がヘルスリテラシーが高い）し、3 分位で Low（5-17 点）、Middle（18-20 点）、High(21-25 点)のカテゴリーに分類した。

医療機関への適切な受診を明らかにするうえで、さらに 2 つの対象に分けて解析を行った。

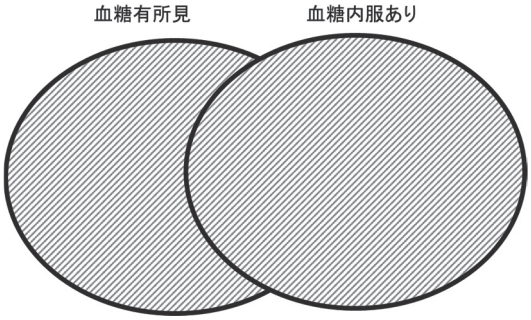
【研究 2-1】



血糖有所見であり、かつ、健診時に血糖内服なしの者を対象とし、本対象者が健診後の 3 ヵ月間に医療機関に受診したかどうかを観察した。
目的変数：健診受診月、翌月、翌々月の 3 ヵ月間で一度でも糖尿病の病名で医療機関への受診があるものは「受診あり」、一度も医療機関へ受診していないものは「受診なし」とした。

ヘルスリテラシーの各カテゴリーの者が、医療機関に受診するオッズ比をロジスティック回帰分析で算出した。性別、年齢、企業を調整したうえで、調整後オッズ比、95%信頼区間を計算した。

【研究 2-2】



血糖有所見であり、または、健診時に血糖内服ありの者を対象とし、健診時に血糖内服ありか否かを観察した。

目的変数：血糖内服あり

ヘルスリテラシーの各カテゴリーの者が、血糖内服ありであるオッズ比をロジスティック回帰分析で算出した。性別、年齢、企業を調整したうえで、調整後オッズ比、95%信頼区間を計算した。

C．結果

【研究 1 】

対象者の詳細を Table 1.に示す。53,720 名のうち、 12,431 名が non-OH 群、41,289 名が OH 群であった。

CC(crude coverage)を Figure 1.に示す。OH-群の方が、高血圧、糖尿病、脂質異常症のいずれの所見においても CC が高かった。

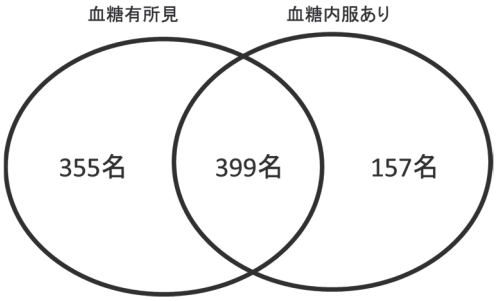
高血圧、糖尿病、脂質異常症ごとに、治療が必要な人が、実際に医療機関に受診しているオッズ比を Table 2.に示す。nonOH 群と比較して、OH 群の受診は、高血圧のみ有意に受診しているが（aOR 1.28: 95%CI 1.07-1.54)、糖尿病と脂質異常症は有意な差を認めなかった。（糖尿病　aOR 1.17: 95%CI 0.85-1.62、脂質異常症　aOR 1.00: 95%CI 0.89-1.13）

【研究 2 】

血糖有所見であり、または、健診時に血糖内服ありの者は 925 名（男性 862 名、女性 63 名）であった。年齢は 50 歳以上が全体の約 70%であった。

	人数	%
29歳以下	4	0
30−39歳	45	5
40−49歳	244	26
50−59歳	518	56
60歳以上	114	12

血糖有所見、および、血糖内服ありの内訳は以下の通りである。



【研究 2-1】

	aOR	95% CI		p value
ヘルスリテラシー				
Low	reference			
Middle	1.10	0.66	1.81	0.722
High	1.09	0.56	2.15	0.797

Adjusted for 性別，年齢，企業

【研究 2-2】

	aOR	95% CI		p value
ヘルスリテラシー				
Low	reference			
Middle	1.46	1.07	2.00	0.016
High	1.65	1.11	2.46	0.014

Adjusted for 性別，年齢，企業

D．考察

本研究では、健康診断の事後措置における受診勧奨に注目し、以下の 2 つのテーマについて検討した。

研究 1 ：産業保健専門職（産業医、保健師等）が健診事後措置に関与することにより、受診勧奨が促され、また、治療による疾患のコントロールが良好となるか否か

研究 2 ：健康情報を入手し、理解し、評価し、活用するための知識、意欲、能力（以下、ヘルスリテラシー）が高い人は、医療が必要な際に適切に医療機関へ受診しているか

研究 1 において、所属する事業場に産業医や産業看護職といった産業保健スタッフが常勤し、日常的に産業保健サービスを提供していることが、高血圧の crude coverage (CC)に有意な影響を及ぼしていた。これは、健康診断後に行われた常勤の産業保健スタッフによる徹底した受診指導の効果が考えられる。実際、中小企業において保健師による保健指導がある場合には精密検査の受診が有意に増加していたとの報告[3)]や、保健所の成人健診後の医療機関受診の指示の際に紹介状の発行によって医療機関受診が向上したことなどが報告されている[4)]。しかし、糖尿病に関しては CC に差が認められなかった。このことは、non-OH 群においても 87%と高率であったことから、多くの受診者が結果表の受診指導の指示のみで、医療機関を受診しており、両群間で差が出にくかったことが考えられる。脂質については、non-OH 群の CC が 33%と低率にもかかわらず、OH 群においても 35%であり、産業保健サービスの効果が観察されなかった。このことに関して、Tateishi et al. は、プロフェッショナルレベルの産業医は血圧や血糖の異常高値については単独でも就業制限を検討するが、脂質項目の異常高値では就業制限を検討する割合が低いことを報告しており、産業保健スタッフの指導が積極的でない可能性が想定される[5)]。また脂質異常については、直接的な指導があっても、治療開始をさせることが容易ではないことが示唆されている。Tatemichi et al.は、産業保健体制が整っている大規模事業場において、健康診断の結果で高コレステロール血症に対する治療が必要と判断された労働者のうち、3 か月間の食事療法によって改善しなかった対象に対して保健専門職が服薬治療を指導したが、そのうち治療に応じた対象者は約半数であり、応じなかった対象者のうち 3 分の 1 は食事療法にも応じなかったことを報告している[6)]。その背景として、脂質のコントロール不良であっても他の疾病に比べて自覚症状が乏しく、プレゼンティーイズムが生じにくいこと[7)]が影響している可能性がある。

研究２において、血糖有所見であり、かつ、健診時に血糖内服なしの者が、健診後の３ヵ月間に医療機関に受診することに関して、本人のヘルスリテラシーの違いによる差はみとめなかった【研究 2-1】。一方で、断面調査である【研究 2-2】においては CC が有意に高かった。日本では健康診断が毎年行われており、【研究 2-1】の研究対象者（血糖有所見あり、かつ、内服なし）のなかには前年度も有所見があったが受療していない人（有所見でも受療しない人）が含まれている可能性があり、このことが結果に影響した可能性がある。年１回の健診が義務化されている日本においては、受療行動は crude coverage（CC）というベンチマークを利用することが、より実態を把握しているかも知れない。この点は、今後、検証する必要がある。

以上から、特に生活習慣に関連する疾患に対して、産業保健スタッフが本人の疾患に対する理解を高めながら介入を行うことが有効であり、また、その効果を crude coverage（CC）等のベンチマークを活用しながら評価することが重要である。

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Ｅ．倫理的配慮

本調査に関して、研究１、研究２ともに、産業医大学倫理委員会の承認を得て実施した。

Ｆ．健康危険情報

該当せず。

Ｇ．研究発表

１．論文発表

なし。

２．学会発表

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Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
該当なし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hu H, S, Mizoue T, et al.	Development and validation of risk models to predict the 7-year risk of type 2 diabetes: The Japan Epidemiology Collaboration on Occupational Health Study	J Diabetes Investig	9(5)	1052-1059	2018
Hu H, Mizoue T, et al.	Prediabetes and cardiovascular disease risk: A nested case-control study	Atherosclerosis	278	1-6	2018
Hu H, Mizoue T, et al.	Cumulative Risk of Type 2 Diabetes in a Working Population: The Japan Epidemiology Collaboration on Occupational Health Study	J Epidemiol	28(11)	465-469	2018

Ⅳ．研究成果の刊行物・別刷

JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Development and validation of risk models to predict the 7-year risk of type 2 diabetes: The Japan Epidemiology Collaboration on Occupational Health Study

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Keywords
Japanese, Risk model, Type 2 diabetes

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ABSTRACT

Aims/Introduction: We previously developed a 3-year diabetes risk score in the working population. The objective of the present study was to develop and validate flexible risk models that can predict the risk of diabetes for any arbitrary time-point during 7 years.

Materials and Methods: The participants were 46,198 Japanese employees aged 30–59 years, without diabetes at baseline and with a maximum follow-up period of 8 years. Incident diabetes was defined according to the American Diabetes Association criteria. With routine health checkup data (age, sex, abdominal obesity, body mass index, smoking status, hypertension status, dyslipidemia, glycated hemoglobin and fasting plasma glucose), we developed non-invasive and invasive risk models based on the Cox proportional hazards regression model among a random two-thirds of the participants, and used another one-third for validation.

Results: The range of the area under the receiver operating characteristic curve increased from 0.73 (95% confidence interval 0.72–0.74) for the non-invasive prediction model to 0.89 (95% confidence interval 0.89–0.90) for the invasive prediction model containing dyslipidemia, glycated hemoglobin and fasting plasma glucose. The invasive models showed improved integrated discrimination and reclassification performance, as compared with the non-invasive model. Calibration appeared good between the predicted and observed risks. These models performed well in the validation cohort.

Conclusions: The present non-invasive and invasive models for the prediction of diabetes risk up to 7 years showed fair and excellent performance, respectively. The invasive models can be used to identify high-risk individuals, who would benefit greatly from lifestyle modification for the prevention or delay of diabetes.

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INTRODUCTION

Type 2 diabetes affects various populations around the world[1]. Globally, the number of adults with diabetes was estimated to 415 million in 2015, and is projected to increase by 55%, to a total of 642 million in 2040[1]. Japan is one of the top 10 countries with the highest number of adults with type 2 diabetes[1]. Its prevalence has been projected to rise from 7.9% in 2010 to 9.8% by 2030 in the Japanese adult population[2]. To combat the increasing burden of diabetes and its complications, identifying high-risk individuals is important in the prevention of diabetes or delaying its progression.

More than 100 risk assessment tools were developed worldwide to identify people at the risk of developing diabetes[3,4]. However, these risk models might not be applied to external populations, particularly if ethnicities and countries differ from the derivation populations[3,4]. In Japan, a few risk models have been developed[5–10] using data from health checkups at hospital[5,6,8] or local community[7,9] settings. Among these, some were developed utilizing a small sample (n < 2,000)[6,7], and excluded individuals aged >40 years[7–9]. Furthermore, some models included variables that were not routinely collected at regular health checkups (e.g., family health history and exercise)[5–8], limiting the wider use of these prediction tools.

Using checkup data of the Japan Epidemiology Collaboration on Occupational Health (J-ECOH) Study, we previously developed a 3-year diabetes risk score[10]. The risk score, however, can only predict risk in a short- and fixed-time period. To overcome this limitation, the present study aimed to develop and validate non-invasive and invasive risk prediction models that can more flexibly predict the risk of diabetes at any time-point within 7 years, based on the J-ECOH Study data with an extended follow-up period. We also created risk calculators and charts to make these models easier to use in practice.

METHODS

The J-ECOH Study is an ongoing cohort study among workers from 12 companies in Japan, and has been described in our previous studies[10–12]. Briefly, participants in the J-ECOH Study underwent a health examination each year under the Industrial Safety and Health Act. They underwent anthropometric measurements, physical examination and laboratory examination (blood sugar, blood lipids, etc.) at annual health examinations. Additionally, a questionnaire that covered medical history, health-related lifestyle and work environment was completed. So far, the annual health examination data between 2008 and 2016 have been collected from 11 companies.

The J-ECOH Study was announced in each company using posters. Verbal or written informed consent was not obtained, but the participants were given the opportunity to refuse to participate, according to the Japanese Ethical Guidelines for Epidemiological Research[13]. The study obtained ethics approval from the ethics committee of the National Center for Global Health and Medicine, Japan.

In the present study, the baseline data mainly comprised data from the 2008 health checkup. If the 2008 dataset had large amounts of missing data, then the data collected for the 2009 or 2010 (two companies) health checkups were treated as the baseline data. The outcome was ascertained using the annual health examination data after the baseline examination through March 2016.

Participants

Of the 75,857 participants aged 30–59 years, we excluded people who self-reported receiving treatment for diabetes (n = 2,496), lacked data on diabetes treatment status (n = 1,171), blood glucose (n = 6,064), glycated hemoglobin (HbA1c; n = 566) or had blood drawn while they were non-fasted (n = 7,218) at baseline. Furthermore, we excluded people with fasting plasma glucose (FPG) ≥126 mg/dL (n = 1,570) or HbA1c ≥6.5% (n = 599) at baseline. Participants with self-reported cancer (n = 484) or cardiovascular disease (n = 599) at baseline were also excluded. Of the remaining 55,090 participants, we excluded those with the following missing variables used in developing the risk prediction model for diabetes: smoking status, waist circumference, body mass index (BMI), hypertension status and dyslipidemia status (n = 7,000). After further excluding participants without subsequent health checkups (n = 1,794) or who attended but received neither glucose measurement nor HbA1c measurement (n = 98), 46,198 participants, comprising 39,276 men and 6,922 women, remained.

Two-thirds of the eligible participants stratified by worksite and sex were randomly allocated to the derivation cohort (25,927 men and 4,573 women), saving the remaining one-third for the validation cohort (13,349 men and 2,349 women). The derivation cohort was used to derive risk models for estimating diabetes risk and validated using the validation cohort.

Predictor variables

We selected and categorized the following predictor variables as we did for predicting the 3-year diabetes risk[10]: sex, age (30–39, 40–49 or 50–59 years), BMI (<21, 21–<23, 23–<25, 25–<27, 27–<29 or ≥29 kg/m^2), abdominal obesity (waist circumference ≥90 cm for men and ≥80 cm for women), smoking status (never, former or current), hypertension status, dyslipidemia status, FPG level (<100, 100–<110 or 110–<126 mg/dL) and HbA1c level (<5.6, 5.6–<6.0 or 6.0–<6.5%). In a sensitivity analysis, BMI and age were treated as continuous variables. Data collection methods, which have been described in detail in previous papers[10–12], are provided in the Appendix S1.

Outcome

Incident diabetes was ascertained using the data obtained from annual health checkups after the baseline health checkup. Diabetes was defined as a FPG level of at least 126 mg/dL or a random plasma glucose level of at least 200 mg/dL, an HbA1c level of at least 6.5%, or receiving antidiabetic treatment[14]. Participants were considered to have type 2 diabetes if they met the above definition of diabetes.

Statistical analysis

Characteristics of participants were expressed as percentages and means for categorical and continuous variables, respectively. The χ-test for categorical variables and *t*-test for continuous variables were used to examine the differences in baseline characteristics between participants in the derivation and validation cohorts.

The 7-year risk prediction models of diabetes were developed using the Cox proportional hazards regression analysis, with a backward selection procedure to determine predictors ($P < 0.05$). The coefficients of each predictor and baseline survivor function were used to develop risk models, as in other studies[15,16]. We initially developed a non-invasive prediction model (containing sex, age, abdominal obesity, BMI, smoking status and hypertension status), and subsequently the invasive prediction models (containing dyslipidemia, either HbA1c or FPG, or both).

Predictive performance of prediction models was assessed by examining measures of discrimination and calibration. Discrimination is the ability of the risk model to differentiate between people who develop diabetes during the study and those who do not. This measure is quantified by calculating the time-dependent area under receiver operating characteristic (ROC) curve (AUROC). In addition, integrated discrimination improvement and net reclassification improvement were computed to show the improved performance of the invasive models as compared with the non-invasive model for predicting diabetes[17]. Calibration refers to the agreement between the predicted and observed 7-year risk of diabetes. This was assessed for each decile of predicted risk by plotting the observed risk vs the predicted risk[18,19]. More spread between the deciles was associated with a better discriminating model. Finally, discrimination and calibration of the prediction models were assessed in the validation cohort to check internal validity. Furthermore, risk calculators and charts (see Figures S1–S5) were created using these models.

All statistical analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC, USA). A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

In the derivation cohort, 2,216 participants (2,055 men and 161 women) developed diabetes during follow up. In the validation cohort, 1,169 participants (1,085 men and 84 women) developed diabetes. The incidence rates of diabetes were 12.5 and 12.8 per 1,000 person-years, respectively. Table 1 shows that the mean age, waist circumference, FPG and HbA1c, as well as the prevalence of smoking, hypertension and dyslipidemia showed no significant difference between the validation and derivation cohorts.

Table 2 shows the coefficients associated with each predictor of diabetes. The non-invasive prediction model revealed that increased risk of diabetes is associated with sex (male), higher BMI, older age, abdominal obesity, smoking and hypertension.

Table 1 | Baseline characteristics of study participants in the derivation and validation cohorts, Japan Epidemiology Collaboration on Occupational Health Study, 2008–2015

Characteristics	Derivation cohort	Validation cohort	*P*-value
No. participants	30,500	15,698	
Age (years)	45.4 ± 7.7	45.5 ± 7.6	0.09
Women (%)	15.0	15.0	0.93
BMI (kg/m^2)	23.3 ± 3.2	23.2 ± 3.2	0.03
Waist circumference (cm)	82.3 ± 8.8	82.2 ± 8.9	0.24
Smoking status (%)			
Current smoker	36.7	37.3	0.41
Past smoker	20.6	20.2	
Never smoker	42.7	42.5	
Hypertension (%)	18.2	18.2	0.99
Dyslipidemia (%)	44.4	43.8	0.17
FPG (mg/dL)	96.5 ± 9.0	96.4 ± 9.0	0.37
HbA1c (%)	5.5 ± 0.4	5.5 ± 0.4	0.74

Data are mean ± standard deviation unless otherwise indicated. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin.

By contrast, the invasive prediction model containing dyslipidemia, HbA1c and FPG showed that the coefficients associated with older age, higher BMI and hypertension attenuated, sex and abdominal obesity were no longer related with the risk of diabetes. Thus, sex and abdominal obesity were excluded from this model.

The time-dependent ROC curve of risk models for predicting the development of diabetes within 7 years are shown in Figure 1. The AUROC in the derivation cohort increased from 0.73 (95% confidence interval [CI] 0.72–0.74) for the non-invasive prediction model to 0.89 (95% CI 0.89–0.90) for the prediction model containing both HbA1c and FPG. When age and BMI were treated as continuous variables, the predictive performance was similar, with an AUROC of 0.74 (95% CI 0.73–0.75) for the non-invasive prediction model, and 0.89 (95% CI 0.89–0.90) for the prediction model containing both HbA1c and FPG.

The invasive models showed improved integrated discrimination and reclassification performance, as compared with the non-invasive prediction model (Table 3). The net reclassification improvement was 0.50 (95% CI 0.47–0.53) for the prediction model containing HbA1c, 0.56 (95% CI 0.53–0.59) for the prediction model containing FPG, and 0.74 (95% CI 0.71–0.77) for the model containing both HbA1c and FPG, as referenced to the non-invasive prediction model. With regard to integrated discrimination improvement, the values were 0.17 (95% CI 0.16–0.18) for the prediction model containing HbA1c, 0.18 (95% CI 0.17–0.19) for the prediction model containing FPG and 0.26 (95% CI 0.25–0.27) for the model containing both HbA1c and FPG. Calibration appeared good between predicted risk and observed risk (Figure 2).

Table 2 | Multivariate regression coefficients (standard errors) of diabetes risk prediction models in the derivation cohort, Japan Epidemiology Collaboration on Occupational Health Study, 2008–2015

	No. participants	No. cases	Non-invasive model		Invasive model including FPG		Invasive model including HbA1c		Invasive model including FPG and HbA1c	
			β (SE)	*P*	β (SE)	*P*	β (SE)	*P*	β (SE)	*P*
Sex										
Women	4,412	161	Reference							
Men	23,872	2,055	0.365 (0.089)	<0.01	–	–	–	–	–	–
Age (years)										
30–<40	8,569	390	Reference		Reference		Reference		Reference	
40–<50	11,380	842	0.380 (0.061)	<0.01	0.157 (0.062)	<0.01	0.131 (0.062)	<0.01	0.063 (0.063)	<0.81
50–<60	8,335	984	0.961 (0.062)	<0.01	0.447 (0.063)	<0.01	0.446 (0.063)	<0.01	0.248 (0.063)	<0.01
BMI (kg/m^2)										
<21	6,819	201	Reference		Reference		Reference		Reference	
21–<23	7,565	395	0.396 (0.087)	<0.01	0.167 (0.086)	<0.01	0.304 (0.088)	<0.01	0.121 (0.087)	0.12
23–<25	6,927	525	0.677 (0.085)	<0.01	0.297 (0.083)	<0.01	0.434 (0.086)	<0.01	0.181 (0.084)	0.03
25–<27	3,987	484	1.016 (0.092)	<0.01	0.525 (0.087)	<0.01	0.611 (0.089)	<0.01	0.320 (0.089)	<0.01
27–<29	1,819	274	1.152 (0.111)	<0.01	0.694 (0.098)	<0.01	0.694 (0.099)	<0.01	0.464 (0.099)	<0.01
≥29	1,167	337	1.715 (0.114)	<0.01	1.131 (0.099)	<0.01	1.019 (0.099)	<0.01	0.758 (0.101)	<0.01
WC[†] (cm)										
<90	22,500	1,310	Reference							
≥90	5,784	906	0.182 (0.065)	<0.01	–	–	–	–	–	–
Smoking status										
Never smoker	12,301	718	Reference		Reference		Reference		Reference	
Past smoker	5,767	523	0.162 (0.060)	<0.01	0.044 (0.059)	0.34	0.199 (0.059)	<0.01	0.074 (0.059)	0.16
Current smoker	10,216	975	0.325 (0.051)	<0.01	0.356 (0.051)	<0.01	0.202 (0.051)	<0.01	0.221 (0.052)	<0.01
Hypertension										
No	23,475	1,467	Reference		Reference		Reference		Reference	
Yes	4,809	749	0.471 (0.049)	<0.01	0.251 (0.050)	<0.01	0.550 (0.050)	<0.01	0.375 (0.051)	<0.01
Dyslipidemia										
No	16,164	782			Reference		Reference		Reference	
Yes	12,120	1,434			0.325 (0.047)	<0.01	0.208 (0.048)	<0.01	0.158 (0.049)	<0.01
FPG (mg/dL)										
<100	19,783	437			Reference				Reference	
100–<110	6,947	682			1.257 (0.063)	<0.01			0.937 (0.065)	<0.01
110–<126	1,554	1,097			2.950 (0.062)	<0.01			2.221 (0.068)	<0.01
HbA1c (%)										
<5.6	16,589	300					Reference		Reference	
5.6–<6.0	10,138	842					1.348 (0.068)	<0.01	1.019 (0.069)	<0.01
6.0–<6.5	1,557	1,074					3.083 (0.069)	<0.01	2.295 (0.076)	<0.01

In invasive models, sex and waist circumference (WC) were not statistically significant, and thus were excluded. [†]WC was 80 cm for women. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; SE, standard error.

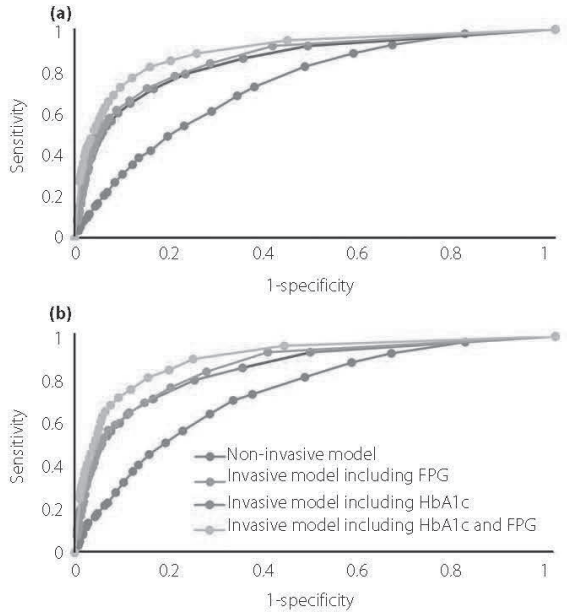

Figure 1 | Receiver operating characteristic curves for each risk model in predicting 7-year diabetes risk, Japan Epidemiology Collaboration on Occupational Health Study, 2008–2015. (a) In the derivation cohort, the area under the receiver operating characteristic curve were 0.73 (95% confidence interval [CI] 0.72–0.74) for the non-invasive model, 0.86 (95% CI 0.85–0.87) for the model including fasting plasma glucose (FPG), 0.85 (95% CI 0.84–0.86) for the model including glycated hemoglobin (HbA1c) and 0.89 (95% CI 0.89–0.90) for the model including both FPG and HbA1c. (b) In the validation cohort, the corresponding values were 0.73 (95% CI 0.68–0.77) for the non-invasive model, 0.86 (95% CI 0.82–0.89) for the model including FPG, 0.85 (95% CI 0.82–0.88) for the model including HbA1c and 0.90 (95% CI 0.87–0.92) for the model including both FPG and HbA1c.

These prediction models performed well in the validation cohort, with an AUROC of 0.73 (95% CI 0.68–0.77) for the non-invasive prediction model and 0.89 (95% CI 0.87–0.92) for the prediction model containing both HbA1c and FPG (Figure 1). The calibration plots also showed a good agreement between the predicted and observed risks (Figure 3).

DISCUSSION

Based on a large-scale working population-based cohort study in Japan, two types of models were developed to predict the risk of diabetes within 7 years: the non-invasive prediction model (containing sex, age, abdominal obesity, BMI, smoking status and hypertension status) and the invasive prediction models (containing dyslipidemia, either HbA1c or FPG, or both). The non-invasive prediction model showed a fair performance for predicting diabetes, whereas the invasive prediction models showed excellent performance. These prediction models also performed well in the validation cohort.

We previously reported that a 3-year diabetes risk score was developed based on the logistic regression models[10]. In the same study population with extended follow up, the risk models were developed to predict the 7-year diabetes risk using the Cox proportional hazards regression model to account for loss to follow up. The prediction models in the present study can also be used to predict the 3-year diabetes risk by replacing the value of the baseline survival function at 7 years with the value at 3 years. The performance of our models in predicting the 3-year diabetes risk (data not shown in the table; an AUROC of 0.74 for the non-invasive prediction model and 0.91 for the invasive prediction model containing both HbA1c and FPG) was slightly improved, as compared with the previous 3-year diabetes risk score (an AUROC of 0.72 for the non-invasive prediction model and 0.89 for the invasive prediction model containing both HbA1c and FPG)[10]. We also created risk calculators and charts, useful in estimating the future risk of diabetes. Taken together, the present risk models have more utilities than our previous ones[10].

The non-invasive prediction model showed fair predictive ability, with an AUROC of 0.73, which was within the reported range based on previous studies carried out in Japan (AUROC ranged between 0.68 and 0.77)[5–8] and other countries (AUROC ranged between 0.62 and 0.87)[4]. As expected, our invasive model including both HbA1c and FPG showed a convincing performance for predicting diabetes. The AUROC value (0.89) was equal to or greater than that in the previously published models including both HbA1c and FPG, which ranged from 0.80 to 0.89[5,8,20]. Furthermore, our calibration plot for the invasive model showed improved agreement between the observed outcomes and predictions. In case both FPG and HbA1c were not measured during the health checkup, we also created another two invasive models including either FPG or HbA1c, with slightly decreased AUROC values (0.85 for the prediction model containing FPG and 0.86 for the prediction model containing HbA1c). Given the high performance of these invasive models, they are suitable for identifying at-risk individuals for diabetes at settings where the data on FPG or HbA1c are available (i.e., annual health checkup in Japan). Unlike the existing risk models in Japan[5–8], our models were derived from routinely collected health checkup data from a working population. Therefore, these models can be easily incorporated into strategies for diabetes prevention at worksites. Furthermore, our sample size is large, which ensures the precision in the estimate of diabetes risk. These advantages make our models highly applicable in the working population for diabetes prevention.

The large population-based cohort, long-term follow up and sufficient number of diabetes events were strengths of the present study. In addition, a comprehensive assessment of the multiple measures was used for the diagnosis of incident diabetes. However, several limitations warrant mention. First, our participants were mainly from large companies. Thus, caution should be exercised when applying the risk models to people working in small companies or other

Table 3 | Discriminative ability of invasive risk models in comparison with the non-invasive model in the derivation and validation cohorts, Japan Epidemiology Collaboration on Occupational Health Study, 2008–2015

	NRI (95% CI)	IDI (95% CI)
Derivation cohort		
Non-invasive model	Reference	Reference
Invasive model including HbA1c	0.50 (0.47–0.53)	0.17 (0.16–0.18)
Invasive model including FPG	0.56 (0.53–0.59)	0.18 (0.18–0.19)
Invasive model including HbA1c and FPG	0.74 (0.71–0.77)	0.26 (0.25–0.27)
Validation cohort		
Non-invasive model	Reference	Reference
Invasive model including HbA1c	0.46 (0.42–0.51)	0.16 (0.15–0.17)
Invasive model including FPG	0.53 (0.49–0.59)	0.17 (0.16–0.19)
Invasive model including HbA1c and FPG	0.71 (0.66–0.76)	0.24 (0.23–0.26)

FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

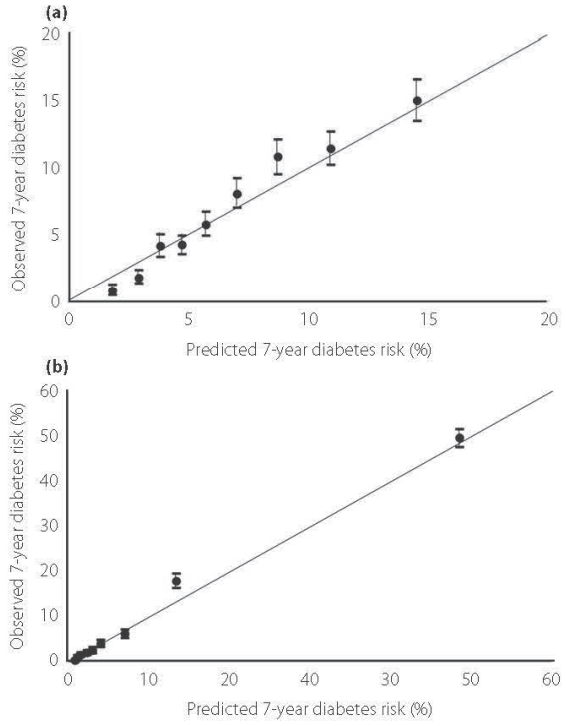

Figure 2 | Calibration plot for type 2 diabetes risk models in the derivation cohort, by deciles of predicted risk, Japan Epidemiology Collaboration on Occupational Health Study, 2008–2015. (a) Non-invasive risk model. (b) Invasive risk model including both glycated hemoglobin and fasting plasma glucose.

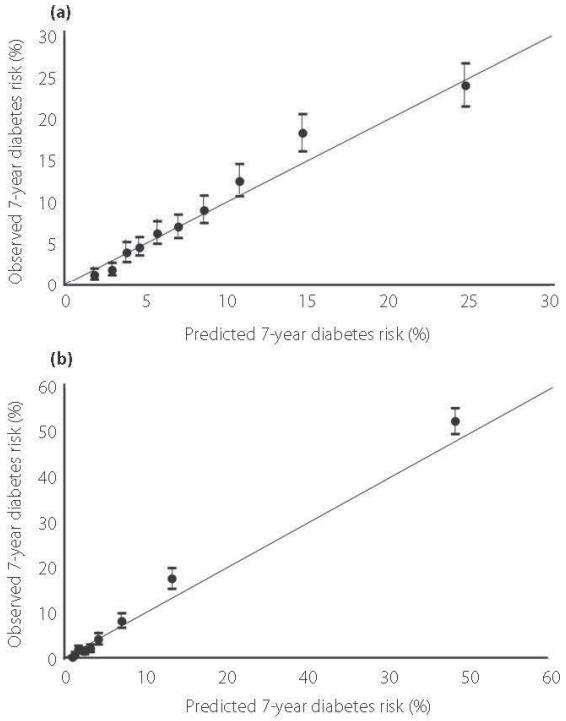

Figure 3 | Calibration plot for type 2 diabetes risk models in the validation cohort, by deciles of predicted risk, Japan Epidemiology Collaboration on Occupational Health Study, 2008–2015. (a) Non-invasive risk model. (b) Invasive risk model including both glycated hemoglobin and fasting plasma glucose.

populations. Future study should validate the present risk models in these populations. Second, because data about socioeconomic status, lifestyle (except for smoking) and family health history, such as diabetes and CVD, were not collected, these potential predictors were not added in our prediction models. However, the performance of our models is comparable with the previous published models for predicting diabetes. Third, we cannot distinguish between type 1 and type 2 diabetes. However, as new cases of type 1 diabetes are rare after 30 years-of-age, we expect that virtually

all incident cases in this cohort correlate with type 2 diabetes. We also did not have data on other types of diabetes, such as gestational diabetes. Given that just 38 cases of diabetes occurred among young women aged 30–39 years in the present study, and that just 2% of pregnant women are known to develop gestational diabetes[21], we believe that the impact of gestational diabetes, if any, was negligible in the present study.

In conclusion, the present non-invasive and invasive models for the prediction of diabetes risk up to 7 years showed fair and excellent performance, respectively. The invasive models can be used to identify high-risk individuals, who would benefit greatly from lifestyle modification for the prevention or delay of diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Predicted risk of diabetes within 7 years based on non-invasive model (risk calculator).
Figure S2 | Predicted risk of diabetes within 7 years based on invasive model (risk calculator).
Figure S3 | Predicted risk of diabetes within 7 years based on non-invasive model (risk chart).
Figure S4 | Predicted risk of diabetes within 7 years based on invasive model (risk chart, including dyslipidemia and glycated hemoglobin).
Figure S5 | Predicted risk of diabetes within 7 years based on invasive model (risk chart, including dyslipidemia and fasting plasma glucose).
Appendix S1 | Data collection method.

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Prediabetes and cardiovascular disease risk: A nested case-control study

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HIGHLIGHTS

- Prediabetes assessed at single time points was associated with an elevated risk of CVD.
- Much higher risk of CVD was observed among people with persistent prediabetes compared with persistent normoglycemia.
- Prediabetes is associated with a higher risk of CVD.

ARTICLE INFO

Keywords:
Prediabetes
Diabetes
Cardiovascular disease
Nested case-control study

ABSTRACT

Background and aims: We aimed to examine the risk of cardiovascular disease (CVD) with persistent prediabetes during the last four years prior to a CVD event in a large occupational cohort in Japan.
Methods: We performed a nested case-control study using data from the Japan Epidemiology Collaboration on Occupational Health Study. A total of 197 registered cases of CVD were identified and matched individually with 985 controls according to age, sex, and worksite. Prediabetes was defined as fasting plasma glucose 100-125 mg/dL and/or HbA1c 5.7–6.4%. Persistent prediabetes was defined as having prediabetes at years one and four prior to the onset/index date; persistent normoglycemia was similarly defined. Associations between prediabetes and CVD risk were assessed using conditional logistic regression models.
Results: Compared with people with persistent normoglycemia over the four years prior to the onset/index date, the unadjusted odds ratio (95% confidence interval) for CVD was 2.88 (1.56, 5.32) for people with persistent prediabetes. After adjusting for BMI, smoking, hypertension, and dyslipidemia assessed four years before the onset/index date, the association was slightly attenuated to an OR (95% confidence interval) of 2.62 (1.31, 5.25). Prediabetes assessed at single time points was also associated with an elevated risk of CVD, with

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multivariable-adjusted odds ratio (95% confidence interval) of 1.72 (1.12, 2.64) and 2.13 (1.32, 3.43) for prediabetes at one and four years prior to the onset/index date, respectively.
Conclusions: Prediabetes is associated with an increased risk of CVD. Identification and management of prediabetes are important for the prevention of CVD.

1. Introduction

Prediabetes represents a high-risk state for type 2 diabetes and affects various populations around the world [1]. Globally, 352 million adults are living with prediabetes (impaired glucose tolerance), and this number is projected to increase to 587 million in 2040 [2]. Japan is one of the top ten countries with the highest number of adults with prediabetes [2]. Meta-analyses of cohort studies, in which only baseline glycemia levels were measured, show that prediabetes is associated with an increased risk of cardiovascular disease (CVD) [3,4]. However, given that 5%–10% of individuals with prediabetes develop diabetes annually [1], it remains unclear whether this elevated risk of CVD is due to prediabetes or the transition from prediabetes to diabetes during follow-up.

To the best of our knowledge, only two prospective studies have examined the prediabetes-CVD association while excluding people who developed diabetes during follow-up [5,6]. A U.K. study reported an increased risk of CVD associated with prediabetes in Europeans but not South Asians [5], and a Finnish study showed increased morbidity and mortality of CVD associated with prediabetes [6]. One important limitation of these studies is that people who had prediabetes at baseline but returned to normoglycemia during follow-up were not identified and therefore were not excluded from the analyses, leading to exposure misclassification. To better assess the association between prediabetes and CVD, studies using repeated measurements of blood glucose are needed.

Using data from the Japan Epidemiology Collaboration of Occupational Health (J-ECOH) Study, in which annual health checkup

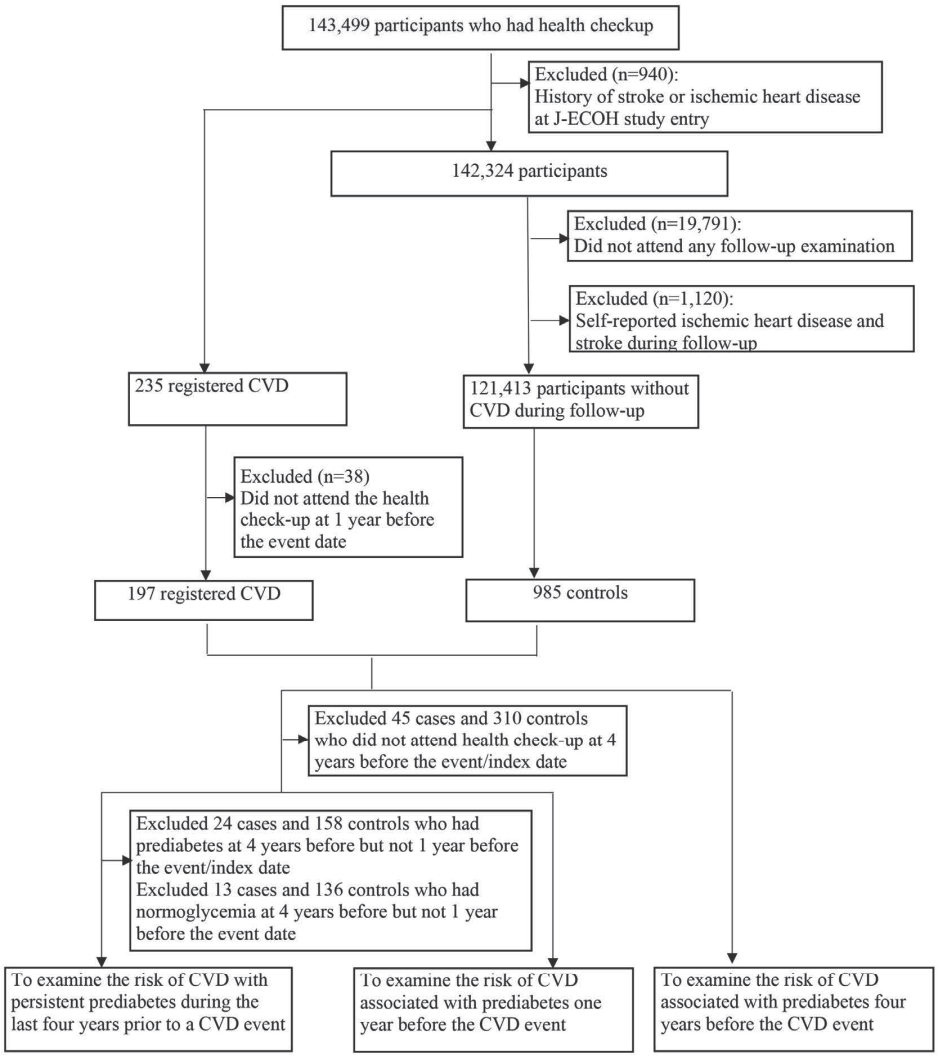

Fig. 1. Flow diagram of study population, J-ECOH Study, Japan, 2008–2016.

data were available throughout the follow-up period [7,8], we performed a nested case-control study to examine the risk of CVD posed by persistent prediabetes during the four years immediately prior to a CVD event in comparison to cases of persistent normoglycemia. We also investigated the risks of CVD associated with prediabetes one year or four years before the CVD event, respectively.

2. Materials and methods

2.1. Study design

The J-ECOH Study is an ongoing multicenter, health checkup-based cohort study among workers from several companies in Japan, and has been described elsewhere [7,8]. In Japan, workers are obliged to undergo a health checkup at least once a year under the Industrial Safety and Health Act; nearly all workers attend their health checkup each year. Briefly, participants in the J-ECOH Study underwent routine physical and laboratory examinations (blood glucose, blood lipids, etc.) each year. Additionally, a questionnaire that covered medical history, health-related lifestyle, and work environment was completed. Annual health checkup data between January 2008 and December 2016 or between April 2008 and March 2017 were collected from over 100,000 employees in 11 participating companies. The study protocol, including the consent procedure, was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan. Using the J-ECOH Study data, we performed a nested case-control study to investigate the association between prediabetes and incident CVD.

2.2. Health checkup

Body height and weight were measured using a scale with participants wore light clothes and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured using an automatic blood pressure monitor. Hypertension was defined as either systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or use of treatment for hypertension [9]. Blood glucose was measured using either the enzymatic or glucose oxidase peroxidative electrode method based on each company's protocol. HbA1c was measured using either a latex agglutination immunoassay, high-performance liquid chromatography, or the enzymatic method. Triglyceride, low-density lipoprotein-cholesterol, and high-density lipoprotein-cholesterol levels were measured using the enzymatic method. Dyslipidemia was defined as either a low-density lipoprotein-cholesterol level of at least 140 mg/dL, high-density lipoprotein-cholesterol level of less than 40 mg/dL, triglyceride level of at least 150 mg/dL, or use of medications for dyslipidemia [10]. All of the laboratories involved in the health checkups of the participating companies received satisfactory scores (rank A or a score > 95 out of 100) from external quality-control agencies.

2.3. Ascertainment of CVD cases and control selection

CVD cases were identified through a disease registry, which was set up in April 2012 within the J-ECOH study to collect data on CVD events from the occupational health physicians of the participating companies [8]. For most nonfatal cases, occupational physicians confirmed the diagnosis of each CVD event based on medical certificates, which were written by a treating physician and submitted to the company through the worker. Because the submission of a medical certificate is required when taking long-term sick leave, this registry primarily covers relatively severe cases. For fatal cases, occupational physicians judged the cause of death based on available information, including death certificates and information obtained from the bereaved family or colleagues. In the CVD registry, approximately 80% cases were confirmed through medical certificates, 10% were self-reported or from family members or colleagues, and 10% were from other sources. Each case was coded according to the 10th revision of the International Classification of Diseases.

In the present study, cases were patients with a first event of myocardial infarction or stroke between April 2012 and March 2017. A total of 235 incident CVD cases were identified. After removing patients (n = 38) who did not attend health checkup one year before the onset date, 197 CVD cases (137 strokes and 60 myocardial infarctions; 36 fatal cases) remained in the present study (Fig. 1).

Controls were selected from study participants who did not self-report stroke or heart disease at J-ECOH Study entry and did not develop CVD during the follow-up period. Those who self-reported a history of CVD at annual health checkups during the study period were also excluded. For each case, we created a pool of controls who were matched by worksite, sex, and date of birth (± 2 years). Controls were assigned an index date that corresponded to the onset date of their matched case. We excluded people who did not attend health checkup at one year prior to the index date. Finally, for a given case, we randomly selected up to five controls from the pool of eligible controls. Once a control was sampled, he/she was not again chosen as a control for other cases. A total of 985 matched controls were included in the present study.

Using data from the 197 cases and 985 matched controls, we examined the risk of CVD associated with prediabetes at one year prior to the CVD event. After removing people who did not attend a health checkup four years before the onset/index date, we investigated the risk of CVD associated with having prediabetes four years before the CVD event in 152 cases and 675 controls. We further excluded people who had prediabetes at four years before but not one year before the onset/index date and those who had normoglycemia at four years before but not one year before the onset/index date, leaving 115 cases and 381 controls for examining the risk of CVD with persistent prediabetes over the last four years before the CVD event.

2.4. Exposures

We retrieved data on diabetes treatment status, fasting plasma glucose (FPG), and HbA1c collected at one and four years before the onset/index date. Diabetes was defined as either FPG ≥126 mg/dL, HbA1c ≥ 6.5%, or receiving medical treatment for diabetes according to the American Diabetes Association criteria [11]. Prediabetes was defined as FPG 100-125 mg/dL and/or HbA1c 5.7–6.4% [11]. Normoglycemia was defined as FPG < 100 mg/dL and HbA1c < 5.7%. Persistent prediabetes was defined for those who had prediabetes at both one and four years prior to the onset/index date. Persistent normoglycemia was defined for those who had normoglycemia at both one and four years prior to the onset/index date. We also defined prediabetes using either FPG (100-125 mg/dL) or HbA1c (5.7–6.4%) to examine whether the risk of CVD associated with prediabetes differs between the two definitions.

2.5. Statistical analysis

Characteristics of participants were expressed as percentages and means for categorical and continuous variables, respectively. Chi-square tests for categorical variables and t-tests for continuous variables were used to examine differences in characteristics between cases and controls.

Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the development of CVD associated with persistent prediabetes. In model 1, the analysis was conditioned on the matching variables (sex and age). In model 2, we adjusted for a priori-specified potential confounders, including BMI, smoking (current smoker, non-current smoker), hypertension, and dyslipidemia assessed at four years before the onset/index date. We also examined the associations between CVD risk and prediabetes assessed at different time points: one and four years before the onset/index date, respectively.

The present study had 73% power to detect a relative risk of 2.0 with statistical significance (two-sided alpha level of 0.05), based on the given condition of the proportion of people with persistent prediabetes among controls (50%), and the number of cases (47 persistent prediabetes and 23 persistent normoglycemia) and number of matched controls (350). All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A two-sided $p < 0.05$ was considered statistically significant.

3. Results

Table 1 shows the characteristics of cases and controls at one year prior to the onset/index date. Cases had higher means for BMI, triglyceride, low-density lipoprotein cholesterol, blood pressure, FPG, and HbA1c than controls. The prevalence rates of smoking, hypertension, dyslipidemia, and diabetes were higher among cases compared with controls. There was no material difference in the proportion of patients who were receiving medication for hypertension or dyslipidemia between cases and controls.

Table 2 shows the association between prediabetes and CVD. Compared with people with persistent normoglycemia over the past four years before the onset/index date, the unadjusted OR (95% CI) for CVD was 2.88 (1.56, 5.32) for people with persistent prediabetes. After adjusting for BMI, smoking, hypertension, and dyslipidemia, the association was slightly attenuated to an OR (95% CI) of 2.62 (1.31, 5.25). For people with prediabetes one year before, the OR (95% CI) was 1.72 (1.12, 2.64) compared with those with normoglycemia, after adjusting for BMI, smoking, hypertension, and dyslipidemia assessed one year before the onset/index date. For people with prediabetes four years before, the OR (95% CI) was 2.13 (1.32, 3.43), with adjustment for BMI, smoking, hypertension, and dyslipidemia assessed four years before the onset/index date.

Table 3 shows the risk of CVD associated with prediabetes as defined using either FPG or HbA1c. When prediabetes was defined as FPG 100-125 mg/dL, people with prediabetes tended to have a higher risk of CVD compared with those without prediabetes. Multivariable-adjusted ORs (95% CI) were 1.76 (0.91, 3.38), 1.33 (0.88, 2.01), and 1.77 (1.10, 2.86) for people with persistent prediabetes, prediabetes one year before, and prediabetes four years before, respectively. When prediabetes was defined as HbA1c 5.7–6.4%, the corresponding ORs (95% CI) were 2.07 (1.09, 3.97) 1.28 (0.82, 2.02), and 1.93 (1.21, 3.08), respectively.

4. Discussion

In this nested case-control study, we found that prediabetes (defined as FPG 100-125 mg/dL and/or HbA1c 5.7–6.4%) one or four years prior to the onset/index date was associated with significantly increased risk of CVD. More importantly, a much higher risk for CVD was observed among people with persistent prediabetes. To our knowledge, this is one of the few studies to examine whether prediabetes is associated with the development of CVD.

The present findings are in line with those of the existing yet limited studies [5,6]. We found that prediabetes one and four years prior to the onset/index date was associated with a 1.7- and 2.1-fold increased risk of CVD, respectively. However, when the analyses were limited to those who had prediabetes, both one and four years before the onset/index date, people with persistent prediabetes were 2.6 times more likely to develop CVD. This difference in the strength of associations implies that the association between prediabetes and CVD risk may not be accurately captured if prediabetes was assessed at a single time point due to changes in glycemia levels over time. In our study, out of 291 controls with prediabetes four years before the index date, 22 developed diabetes within three years, and 68 returned to normoglycemia. Of 303 controls with normoglycemia four years prior, 92 developed prediabetes three years later. Using multiple measures of glycemia to minimize the misclassification of exposure, our data confirm that prediabetes is a risk factor for CVD. Proactive identification and management of prediabetes are warranted to reduce future risk of CVD.

We observed a more pronounced association with HbA1c-based prediabetes than FPG-based prediabetes, consistent with findings from the Whitehall II Study [12]. A meta-analysis showed no significant difference in the risk of CVD between baseline prediabetes defined using FPG (100-125 mg/dL) and that defined using HbA1c (5.7–6.4%) [3]. Of 16 studies included in that meta-analysis, only three made a head-to-head comparison between the two definitions; two reported a significant association with HbA1c-based prediabetes but not with FPG-based prediabetes, and another did not detect any association with these definitions [3]. Taken together, prediabetes defined by HbA1c appears to be more strongly associated with CVD than prediabetes defined by FPG.

Non-glucose-mediated and glucose-mediated mechanisms have been proposed as explanations for the association between prediabetes and CVD. One of the non-glucose-mediated mechanisms involves insulin resistance, which is an underlying condition of prediabetes [13]. It promotes atherogenesis and atherosclerotic plaque formation via down-regulation of insulin signaling at the level of the intimal cells that participate in atherosclerosis, including macrophages, vascular smooth muscle cells, and endothelial cells [14,15]. The other non-glucose-mediated mechanisms involve obesity and inflammation (adipocytokines and oxidative stress), dyslipidemia (atherogenic lipoproteins and increased circulating free fatty acids), and prothrombosis state (increased levels of PAI-1 and platelet activation), which are commonly present in people with prediabetes [14,15]. As for glucose-mediated mechanisms, hyperglycemia could promote atherosclerosis through increased oxidative stress, activation of thrombosis, and epigenetic changes (increased expression of inflammatory genes via NF-κB), which can be induced even by transient or episodic hyperglycemia [14,15].

4.1. Strengths and limitations

A major advantage of the present study was the periodic assessment of diabetic status using HbA1c and FPG until one year before the onset of CVD, which enabled us to maximally reduce the degree of misclassification of prediabetes. In addition, potential confounders such as smoking, dyslipidemia, and hypertension were also assessed annually.

Table 1
Characteristics of cases and controls at one year before the onset/index date.

	Cases	Controls
N	197	985
Age (years)	52.9 ± 7.3	52.8 ± 7.3
Men, %	91.9	91.9
BMI (kg/m^2)	25.0 ± 4.0	23.9 ± 3.6[a]
Current smoker, %	54.8	31.8[a]
TG (mg/dL)	149.9 ± 96.9	125.0 ± 84.5[a]
HDL-C (mg/dL)	53.4 ± 15.1	58.8 ± 15.8[a]
LDL-C (mg/dL)	129.2 ± 37.9	123.6 ± 29.4
Dyslipidemia, %	69.0	51.5[a]
Lipid-lowering treatment, %[b]	19.9	20.9
SBP (mmHg)	134.7 ± 17.3	124.4 ± 15.8[a]
DBP (mmHg)	85.2 ± 10.6	78.9 ± 11.2[a]
Hypertension, %	65.5	34.9[a]
Anti-hypertensive treatment, %[c]	52.7	57.6
FPG (mg/dL)	120.3 ± 50.5	102.9 ± 18.2[a]
HbA1c (%)	6.2 ± 1.3	5.7 ± 0.7[a]
Diabetes, %	33.5	13.7[a]

BMI: body mass index; CVD, cardiovascular disease; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride.

[a] $p < 0.05$.

[b] The denominator is the total number of people with dyslipidemia.

[c] The denominator is the total number of people with hypertension.

Table 2
Associations between prediabetes and risk of cardiovascular disease.

	Case	Control	Odds ratio (95% CI)	
			Model 1	Model 2
Over the four years prior to the onset/index date				
Persistent normoglycemia	23	161	1	1
Persistent prediabetes	47	155	2.88 (1.56, 5.32)	2.62 (1.31, 5.25)
Diabetes	45	65	6.50 (3.31, 12.8)	4.11 (1.81, 9.30)
One year before the onset/index date				
Normoglycemia	47	418	1	1
Prediabetes	84	432	1.98 (1.33, 2.96)	1.72 (1.12, 2.64)
Diabetes	66	135	5.19 (3.28, 8.22)	3.41 (2.05, 5.69)
Four years before the onset/index date				
Normoglycemia	36	303	1	1
Prediabetes	71	291	2.40 (1.53, 3.77)	2.13 (1.32, 3.43)
Diabetes	45	81	5.66 (3.29, 9.74)	3.43 (1.87, 6.32)

Model 1, unadjusted.
Model 2, adjusted for BMI, current smoker (yes or no), hypertension, and dyslipidemia.

Table 3
Associations between prediabetes (defined as FPG 100-125 mg/dL or HbA1c 5.7–6.4%, respectively) and risk of cardiovascular disease.

	Case	Control	Odds ratio (95% CI)	
			Model 1	Model 2
FPG (mg/dL)				
Over the four years prior to the onset/index date				
Persistent FPG < 100	42	274	1	1
Persistent FPG 100-125	31	133	2.12 (1.16, 3.89)	1.76 (0.91, 3.38)
Diabetes	45	80	4.34 (2.40, 7.83)	2.36 (1.17, 4.75)
One year before the onset/index date				
< 100	68	518	1	1
100-125	63	332	1.64 (1.11, 2.42)	1.33 (0.88, 2.01)
Diabetes	66	135	4.29 (2.82, 6.54)	2.73 (1.71, 4.36)
Four years before the onset/index date				
< 100	57	381	1	1
100-125	49	204	2.02 (1.28, 3.18)	1.77 (1.10, 2.86)
Diabetes	45	80	4.55 (2.74, 7.57)	2.77 (1.56, 4.91)
HbA1c (%)				
Over the four years prior to the onset/index date				
Persistent HbA1c < 5.7	46	376	1	1
Persistent HbA1c 5.7–6.4	26	111	2.38 (1.34, 4.22)	2.07 (1.09, 3.97)
Diabetes	45	83	4.95 (2.86, 8.59)	3.27 (1.71, 6.26)
One year before the onset/index date				
< 5.7	86	613	1	1
5.7–6.4	45	237	1.48 (0.98, 2.23)	1.28 (0.82, 2.02)
Diabetes	66	135	3.82 (2.58, 5.65)	2.57 (1.65, 4.01)
Four years before the onset/index date				
< 5.7	57	421	1	1
5.7–6.4	53	196	2.19 (1.43, 3.37)	1.93 (1.21, 3.08)
Diabetes	45	83	4.45 (2.75, 7.20)	2.77 (1.60, 4.78)

Model 1, unadjusted.
Model 2, adjusted for BMI, current smoker (yes or no), hypertension, and dyslipidemia.

Nevertheless, this study has some limitations. First, the present study had a power less than 80% to detect an association with a relative risk of 2.0. Using repeated assessment of diabetic status, however, we found a stronger association (relative risk of 2.5 or more) between prediabetes and CVD risk, increasing the power of our study to 90%. Second, we only have recent data on diabetes status (within the past four years prior to the onset of CVD). The lack of data for earlier periods precludes us from analyzing the effect of long-term exposure to prediabetes on CVD development. Third, only workers who took long-term sick leave were required to submit a medical certificate to the company; thus, milder forms of CVD were not well-covered by this registration system. Fourth, we defined prediabetes using FPG and IIbA1c but not 2-h oral glucose tolerance test, which has not been used in regular health checkups. As such, people with impaired glucose tolerance may be misclassified as normoglycemia, resulting in an underestimation of the association between prediabetes and CVD. Lastly, due to lack of data on socioeconomic status, family history of CVD, and lifestyle characteristics other than smoking (e.g., diet, physical activity), we were unable to control for the potential effects of these factors.

In conclusion, the present nested case-control study based on repeated measurements of fasting glucose and HbA1c indicates that prediabetes is associated with an increased risk of CVD. Identification and management of prediabetes are important for the prevention of CVD. More research is required to confirm or refute whether pre-diabetic patients who are free of conventional risk factors such as hypertension and hypercholesterolemia are at increased risk of CVD.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

S.D. and T.Mizoue were involved in the design of the study as the principal investigators; N.S., T.O., K.T., S.N., A.H., A.Nishihara, T.I., M.Y., M.E., T.K., T.Miyamoto, T.H., T.N., S.Y., H.O., A.U., M.S., T.Murakami, I.Kabe., and S.D. collected health check-up data; M.K. and A.Nanri cleaned CVD data; T.Mizoue, M.K., and K.K. created database; H.H. and T.Mizoue drafted the plan for the data analysis; H.H. conducted data analysis; H.H. drafted manuscript; HH and T Mizoue had primary responsibility for final content; and all authors were involved in interpretation of the results and revision of the manuscript and approved the final version of the manuscripts, had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. HH and T Mizoue are guarantors.

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Cumulative Risk of Type 2 Diabetes in a Working Population: The Japan Epidemiology Collaboration on Occupational Health Study

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ABSTRACT

Background: We estimated the cumulative risk of type 2 diabetes from age 30 to 65 years in a large working population in Japan.

Methods: We used data from the Japan Epidemiology Collaboration on Occupational Health Study. Participants (46,065 men and 7,763 women) were aged 30–59 years, free of diabetes at baseline, and followed up for a maximum of 7 years. Incident type 2 diabetes was defined based on fasting and casual glucose, glycated hemoglobin, and current medical treatment for type 2 diabetes. We calculated the sex-specific cumulative risk of type 2 diabetes using the Practical Incidence Estimator macro, which was created to produce several estimates of disease incidence for prospective cohort studies based on a modified Kaplan-Meier method.

Results: During 274,349 person-years of follow-up, 3,587 individuals (3,339 men and 248 women) developed type 2 diabetes. The cumulative risk was 34.7% (95% confidence interval, 33.1–36.3%) for men and 18.6% (95% confidence interval, 15.5–21.7%) for women. In BMI-stratified analysis, obese (BMI $\geq$30 kg/m^2) and overweight (BMI 25–29.9 kg/m^2) men and women had a much higher cumulative risk of type 2 diabetes (obese: 77.3% for men and 64.8% for women; overweight: 49.1% and 35.7%, respectively) than those with BMI <25 kg/m^2 (26.2% and 13.4% for men and women, respectively).

Conclusions: The present data highlight the public health burden of type 2 diabetes in the working population. There is a need for effective programs for weight management and type 2 diabetes screening, especially for young obese employees, to prevent or delay the development of type 2 diabetes.

Key words: type 2 diabetes; cumulative risk; epidemiology; Japanese

INTRODUCTION

Diabetes, mainly type 2 diabetes, is a major global public health issue, and Asian countries contribute to more than 60% of the world's diabetic population.[1,2] In Japan, there are 10.8 million patients with diabetes.[1] Lifetime risk of type 2 diabetes has been estimated to determine the risk of developing type 2 diabetes for a general population[3]; however, such data are scarce for the working population. Identifying the cumulative risk of type 2 diabetes during the working lifetime of individuals would provide a better understanding of the development of type 2 diabetes and could urge workers, employers, occupational

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health professionals, and policy makers to take actions for its prevention.

In Japan, employees are required by law to undergo annual health examinations, which include glycemic measurements. We used this data to estimate the cumulative risk of type 2 diabetes from age 30 to 65 years.

METHODS

Study design

The Japan Epidemiology Collaboration on Occupational Health (J-ECOH) Study is an ongoing multicenter health checkup-based cohort study among workers from several companies in Japan.[4,5] As of May 2015, 11 participating companies provided health checkup data of their employees, obtained between January 2008 and December 2014 or between April 2008 and March 2015. The study protocol, including the consent procedure, was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan.

In the present study, the data from the earliest health checkup (mostly carried out in 2008) were regarded as the baseline data; however, if the 2008 dataset contained a large number of missing data, then the data from the 2009 or 2010 (one company each) health checkups were used as the baseline. The outcome was determined using health checkup data from baseline through March 2015.

Participants

Of 75,857 participants aged 30–59 years who received health checkup during the baseline period, we excluded participants who had a history of diabetes or undiagnosed diabetes at baseline ($n = 4,924$); who had missing information on glucose ($n = 6,246$), glycated hemoglobin (HbA1c; $n = 1,085$), or medical treatment for diabetes ($n = 407$); and who had blood drawn in the non-fasting state ($n = 7,022$). Of the remaining 56,173 participants, we excluded participants who did not attend any subsequent health checkups ($n = 2,217$) and those who attended but did not receive glucose measurements ($n = 128$). A total of 53,828 participants, comprising 46,065 men and 7,763 women, were included for analysis.

Health checkup

Participants received annual health checkups that included measurements of weight, height, blood pressure, blood glucose, and lipids. The details of health checkups have been described elsewhere.[4,5] Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. We classified BMI into three groups according to the international overweight and obesity criteria: $<25\,kg/m^2$, 25 to $29.9\,kg/m^2$ (overweight), and $\geq 30\,kg/m^2$ (obesity).[6]

Outcome

Incident diabetes was identified using data from the health checkups after the baseline examination. Diabetes was defined according to the American Diabetes Association criteria for the diagnosis of diabetes as glycated hemoglobin (HbA1c) ≥6.5%, fasting plasma glucose ≥126 mg/dL, random plasma glucose ≥200 mg/dL, or currently under medical treatment for diabetes.[7] Individuals without diabetes at baseline who met any of the above conditions in the subsequent checkups were considered to have an incident case of type 2 diabetes.

Statistical analysis

Characteristics of the study participants were described as means for continuous variables and percentages for categorical variables. Trend association was assessed by assigning ordinal numbers to each BMI group and was tested using a linear regression analysis and the Cochran-Armitage trend test for continuous and categorical variables, respectively.

We calculated sex-specific cumulative risk of type 2 diabetes from age 30 years to age 65 years using the Practical Incidence Estimator macro.[8] Details of the macro have been extensively described in previous papers.[8–10] Briefly, this macro uses age as a time scale of analysis and can produce several estimates of disease incidence (eg, age-specific incidence, cumulative incidence, and reaming lifetime risk) for prospective cohort studies, based on a modified Kaplan-Meier method.[8] It combines information on participants who entered the cohort study at different ages and takes into account varying duration of follow-up of participants.[8] All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

The characteristics of participants by sex and BMI groups are shown in Table 1. Among cohort participants, 24.7% of men and 11.5% of women had a BMI of 25 to $29.9\,kg/m^2$, and 3.2% of men and 2.7% of women had a BMI $\geq 30\,kg/m^2$. For both sexes, the waist circumference, systolic and diastolic blood pressure, fasting plasma glucose, HbA1c, and triglyceride and low-density lipoprotein-cholesterol levels increased with BMI (P for trend <0.001). The prevalence rates of hypertension and dyslipidemia were higher in people with higher levels of BMI (P for trend <0.001). During 274,349 person-years of follow-up, 3,587 individuals (3,339 men and 248 women) developed type 2 diabetes. The crude incidence rate of type 2 diabetes (per 1,000 person-years) was 14.2 for men and 6.4 for women. Sex- and age-specific incidence rates of type 2 diabetes are provided in eTable 1.

Figure 1 shows the cumulative incidence functions in individuals aged 30 years. The cumulative risk of developing type 2 diabetes from age 30 years to age 65 years was 34.7% (95% confidence interval, 33.1–36.3%) for men and 18.6% (95% confidence interval, 15.5–21.7%) for women. Stratification by BMI showed that people with a BMI $\geq 30\,kg/m^2$ had much higher cumulative risk of type 2 diabetes (77.3% for men and 64.8% for women) than people with a BMI of 25 to $29.9\,kg/m^2$ (49.1% for men and 35.7% for women) or people with a BMI $<25\,kg/m^2$ (26.2% for men and 13.4% for women). We estimated that more than 1 in 3 obese men aged 30 years would develop type 2 diabetes by age 45 years.

DISCUSSION

Based on a large-scale cohort study among Japanese employees, we estimated that one-third of men and one-fifth of women at age 30 years will develop type 2 diabetes by age 65 years. Furthermore, the cumulative risk of type 2 diabetes substantially increased among people with a BMI $\geq 25\,kg/m^2$. To our knowledge, this is the first study to estimate the cumulative risk of type 2 diabetes from age 30 years to age 65 years in the working population.

Similar to the present study, high lifetime risk of diabetes has been reported in the USA (40% at age 20 years),[11] Australia (31%

Table 1. Baseline characteristics by sex and baseline BMI

	Men			*P* for trend	Women			*P* for trend
	BMI <25 kg/m^2	BMI ≥25 to <30 kg/m^2	BMI ≥30 kg/m^2		BMI <25 kg/m^2	BMI ≥25 to <30 kg/m^2	BMI ≥30 kg/m^2	
N	33,212	11,387	1,466		6,662	891	210	
BMI, kg/m^2[a]	22.1 (1.9)	26.8 (1.3)	32.4 (2.6)		20.6 (2.1)	26.9 (1.4)	32.7 (2.7)	
Age, years[a]	45.4 (7.9)	45.6 (7.6)	42.9 (7.0)	<0.001	43.9 (7.5)	45.9 (7.6)	44.7 (7.2)	<0.001
WC, cm[a]	80.0 (6.0)	91.0 (5.0)	103.5 (7.0)	<0.001	73.5 (7.0)	88.0 (5.8)	98.8 (7.1)	<0.001
SBP, mm Hg[a]	119.6 (14.5)	126.6 (14.2)	132.8 (14.8)	<0.001	113.7 (15.5)	124.6 (14.5)	132.2 (15.2)	<0.001
DBP, mm Hg[a]	75.8 (10.2)	80.8 (10.0)	84.6 (10.2)	<0.001	70.7 (10.3)	77.7 (9.8)	82.0 (10.6)	<0.001
Hypertension, %[b]	15.7	29.5	46.9	<0.001	8.2	20.8	39.1	<0.001
Anti-hypertension treatment, %[c]	43.4	48.6	49.8	<0.001	39.3	48.1	34.2	<0.001
FPG, mg/dL[a]	96.2 (8.7)	99.1 (9.0)	100.0 (9.7)	<0.001	90.5 (7.8)	94.5 (8.6)	97.6 (10.1)	<0.001
HbA1c, %[a]	5.4 (0.4)	5.6 (0.4)	5.7 (0.4)	<0.001	5.4 (0.3)	5.6 (0.4)	5.7 (0.4)	<0.001
TG, mg/dL[a]	116.8 (84.0)	160.2 (109.2)	174.8 (125.4)	<0.001	71.8 (40.9)	103.6 (58.6)	117.0 (67.5)	<0.001
LDL-C, mg/dL[a]	118.2 (29.0)	129.1 (29.4)	133.7 (31.5)	<0.001	111.7 (28.8)	130.7 (30.6)	131.9 (30.3)	<0.001
HDL-C, mg/dL[a]	59.0 (14.7)	51.1 (11.6)	47.7 (9.8)	<0.001	71.3 (15.4)	59.9 (12.9)	56.3 (13.7)	<0.001
Dyslipidemia, %[d]	40.0	65.1	75.4	<0.001	20.2	48.2	53.8	<0.001
Lipid-lowering treatment, %[e]	8.5	11.1	15.8	<0.001	12.8	13.8	12.4	<0.001
Smoking, %	41.5	41.8	46.1	0.006	11.1	10.9	13.9	0.437

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference.

[a]Mean (standard deviation).

[b]Hypertension was defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or as receiving medical treatment for hypertension, based on the criteria of The Japanese Society of Hypertension Guidelines for the Management of Hypertension.

[c]The denominator is the total number of people with hypertension.

[d]Dyslipidemia was defined as TG ≥150 mg/dL, LDL-C ≥140 mg/dL, HDL-C <40 mg/dL, or as receiving medical treatment for dyslipidemia, based on the criteria of the Japan Atherosclerosis Society.

[e]The denominator is the total number of people with dyslipidemia.

at age 45 years),[12] and the Netherlands (31% at age 45 years).[3] However, our study differed from previous studies in design, target population, and target period (cumulative risk from age 30 to 65 years in the present study compared to overall lifetime risk in previous studies). Furthermore, we defined incident type 2 diabetes based on fasting and casual glucose, HbA1c, and current medical treatment for diabetes, while researchers of previous studies did not use HbA1c[3,12] or only used self-reported diabetes.[11] Therefore, caution should be exercised when comparing the current estimate with those reported previously.

Previous studies have reported sex differences in type 2 diabetes prevalence in the Japanese population.[13,14] One meta-regression analysis of 160,000 Japanese adults showed that the age-standardized diabetes prevalence was 9.3% and 6.6% among men and women, respectively, in 2010.[13] We also found that the cumulative risk of type 2 diabetes among women (18.6%) was lower compared with men (34.7%). This may be partly ascribed to the lower prevalence rates of risk factors for type 2 diabetes (eg, obesity, smoking, hypertension, and dyslipidemia) in women than in men. Further efforts focusing on these risk factors may not only reduce diabetes risk in the working population but also narrow the gender gap in diabetes risk.

Obese workers (BMI ≥30 kg/m^2) were at markedly increased risk of developing type 2 diabetes; more than 1 in 3 obese men at age 30 years were predicted to develop type 2 diabetes by age 45 years (Figure 1). Lifetime risk of type 2 diabetes increases with increasing BMI.[3,15] Obesity reduces the time lived with normal glucose metabolism.[3] These findings underscore the importance of weight management in the prevention of type 2 diabetes.

The strengths of our study include its large sample size and sufficient number of type 2 diabetes events. In addition, we used a comprehensive assessment of multiple measures for the diagnosis of incident type 2 diabetes. Several limitations also warrant attention. First, the present findings from a working population may not be generalizable to a wider population. Given the lower sex- and age-specific prevalence of overweight/obesity (BMI ≥25 kg/m^2) in the present study than that in the National Health and Nutrition Survey,[16] higher cumulative incidence would be expected in the general population. Second, the cumulative risk of developing type 2 diabetes would be somewhat overestimated due to the lack of adjustment for competing risks, such as death. Third, the estimates of cumulative risk are subject to birth-cohort effects; thus, caution should be exercised when age-specific incidence rates are rapidly changing over time. Finally, we could not discriminate between type 1 and type 2 diabetes. However, since type 1 diabetes is rare in people aged 30 years and older, we expect that virtually all incident cases in this cohort correlate with type 2 diabetes.

The present data highlight the public health burden of type 2 diabetes among the working population. There is a need for effective weight management and type 2 diabetes screening programs, especially for young obese employees, to prevent or delay the development of type 2 diabetes.

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Conflicts of interest: None declared.

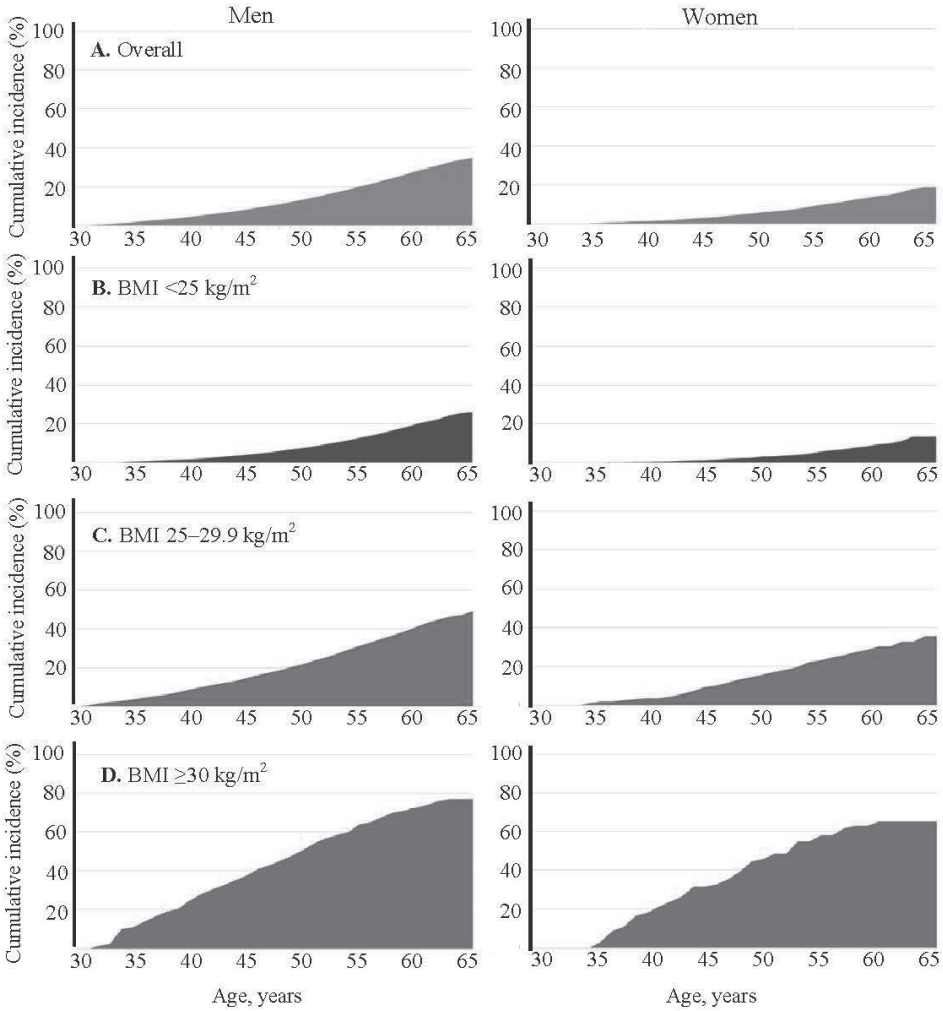

Figure 1. Cumulative risk of diabetes in individuals aged 30 years. A. Overall; B. BMI <25 kg/m^2; C. BMI 25–29.9 kg/m^2; D. BMI ≥30 kg/m^2.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.2188/jea.JE20170093.

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