PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open where it was re-reviewed and accepted.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The future of population registers: linking routine health datasets to assess a population's current glycaemic status for quality improvement
AUTHORS	Chan, Wing Cheuk; Jackson, Gary; Wright, Craig; Orr-Walker, Brandon; Drury, Paul; Boswell, D; Lee, Mildred; Papa, Dean; Jackson, Rod

VERSION 1 - REVIEW

REVIEWER	Professor Sir Denis Pereira Gray OBE MA HonDSc FRCP FRCGP FMedSci Emeritus Professor University of Exeter, Honorary Professor University of Exeter Medical School, UK
REVIEW RETURNED	18-Apr-2012

GENERAL COMMENTS	Summary The nine authors report important work analysing data in pathology laboratories, specifically blood sugar and HbA1c. By linking data sets in Auckland, New Zealand they report the numbers and the proportions of the resident population who have been screened and who have diabetes. Consequently they can identify those people who are unscreened or appearing to have less than optimal follow up. The coverage they report is high, as high as is known anywhere. They confirm the very high prevalence of diabetes in some ethnic groups. STRENGTHS This manuscript has many strengths. • The use of laboratory based data, whilst not new, is developed here in new ways • The reconciliation of population data is good • The population defined is much bigger than in some previous reports • New confirming data are presented of the very high prevalence of diabetes in several Asian ethnic groups confirming Ramachandran (2010). • The extent of population coverage for screening is impressive and may the highest recorded, even though the time period is 5.5 years (see below). • This calls for recognition of this achievement by the general practitioners in the area as screening is a general practice not a hospital function • An overall population prevalence for diabetes of 5.3% (page 10) is reported. • An impressive potential for medical audit is demonstrated.

	• Their conclusions about the proportion of undiagnosed diabetes are new interesting and of international significance On the basis of these the presumption should be to accept for publication. However, there are a number of academic weaknesses. Some as shown are inherent and need to be more clearly acknowledged. Some are capable to being corrected, as shown, when the article will be very powerful. WEAKNESSES Title The title is not appropriate. The authors are not describing a diabetic register as is usually understood in either primary or secondary care. The group of people whom they have identified are those people who have had a blood sugar or HbA1c estimation and they are clear (page 6) that they are studying those people with diabetes and also those in risk groups for diabetes. There are good clinical reasons for identifying such people, but it is not academically acceptable to say they have modified a widely used international definition of the disease diabetes itself. Nor is their register a pure register of diabetes as their title implies. They have stronger titles available such as starting the title with Linking..... or The Use of Laboratory Data for Medical Audit and Quality Improvement in people with hyperglycaemia. Publically-funded and private medical services The authors correctly make it clear they are reporting for publically funded medical services in their part of New Zealand. But they are submitting to the BMJ which is an international medical journal and read in many different countries. Indeed I am assessing their work from the other side of the world. They therefore need to give some estimate of the size of the private medical sector in New Zealand so readers can judge how many people and data they may be missing. Cut-off point at 5.5 years The authors cut off for analysis at 5.5 years ie they report people who had had a test within this period of time. This is understandable and pragmatic as this is the period they can study. But this is not a unit of time that makes much sense for clinicians in general practice as a person at risk for diabetes is not adequately screened if their last test was as long ago as 5.5 years. In this context quoting the New Zealand expectation for general practices re the frequency of screening would add value. It would be helpful if they acknowledged this more clearly or they re-analyse their data using a shorter cut off at a shorter period of say three years. Types of diabetes The article does not distinguish between Type one and Type 2 diabetes. This is understandable as the great majority of the authors are not primarily clinicians. But it is recognised that these two types of diabetes have different characteristics and the high prevalence in the Asian people is likely to be from Type 2. The authors may not have access to clinical information to split these two entities and this should not debar publication, but they need to be more explicit that they are combining the two types. Guidelines in New Zealand The main point of the their tables 1 and 2 is to relate performance in screening to the population at risk. The guide line indication for screening appears to stop at age 74. This is obviously, as their table shows, being ignored by their local

clinicians particularly the GPs, since the percentages in the 70-74 and 75-79 age groups are so similar.
Moreover their interesting figures 1 and 2 confirm that even in the ethnic group with the lowest prevalence of diabetes, the rate is as high as about one in eight. It does not make clinical sense to stop opportunistic screening at age 74 and this merits comment.
Use of laboratory data in diabetes
There have been earlier articles reporting the use of laboratory data in diabetes for defined areas. These are not referenced and should be eg Wilson et al (2009)
Potential for medical audit
The authors could do more to emphasise the potential of their system for medical audit, especially of general practice/primary care where most of the action for Type 2 diabetes now lies.
Final section of discussion (page 14)
The final section of the discussion on page 14 is weak and disappointing and needs cutting.
1. Writing about coding disease registers manually in primary care is out of date when in the UK, for example, 99% of general practices are computerised and the GP contract (QOF) specifically includes diabetes care.
2. Population churn is indeed an issue in all countries, but it is inappropriate to write about Britain in terms of impeding diabetes registers as the national returns for the NHS GP contract show this is not so. Their references do not support their sentence on Britain.
3. They write: “It would be challenging to retrospectively diagnose all enrolled patients based on the latest international recommendations in a consistent manner.” But this has been done and published four years ago (Langley et al., 2008).
4. They seriously overstate the risk of primary care not receiving abnormal blood sugar or HbA1c test at least in the UK where discharge letters from hospital are sent to GPs.
5. They weaken their article with these comments and much of this discussion is not needed and could be cut with advantage.
6. Although there are nine authors, none comes for general practice/ primary care and they are weak on this perspective at a time when some authors (Langley et al, 2008) report 96% of all diagnoses of Type 2 diabetes being made in general practice. In the UK over 90% of screening takes place in general practice/primary care and where over two thirds of all medical care for people with Type 2 diabetes now takes place (Khunti et al., 2000; Piarce et al., 2000).
RECOMMENDATION
This is an interesting and important article which should be able to make a useful contribution to the literature.
It is, in its present form, marred by some weaknesses as set out. If the authors deal with these, then I recommend acceptance.
Denis Pereira Gray
Professor Sir Denis Pereira Gray OBE
MA HonDSc FRCP FRCGP FMedSci
Emeritus Professor University of Exeter, UK; Honorary Professor, Peninsula College of Medicine and Dentistry , UK

References
Langley P Evans P and Pereira Gray D (2008) Diagnosing Type 2 Diabetes before patients complain of diabetic symptoms: clinical opportunistic screening in a single general practice Fam Pract, 25, 378-89.
Khunti K and S Gargoli (2000) Who looks after people with diabetes: primary or secondary care? Journal of the Royal Society of Medicine 93, 183-86.

	Pierce M Agarwal G Ridout D et al (2000) A survey of diabetes care in general practice Br J Gen Pract, 59, 1310. Ramachandran A Wan Ma RC Snehalatha C (2010) Diabetes in Asia Lancet, 375, 408-18. Wilson SE Lipscombe LG Rosella LC and Manuel DG (2009) Trends in laboratory testing for diabetes in Ontario Canada 1995-2005: a population based study BMC Health Services Research 9, 41.

- This manuscript received two reviews at The BMJ but the other referee had declined to make his review public.

VERSION 1 – AUTHOR RESPONSE

Summary

The nine authors report important work analysing data in pathology laboratories, specifically blood sugar and HbA1c. By linking data sets in Auckland, New Zealand they report the numbers and the proportions of the resident population who have been screened and who have diabetes. Consequently they can identify those people who are unscreened or appearing to have less than optimal follow up. The coverage they report is high, as high as is known anywhere. They confirm the very high prevalence of diabetes in some ethnic groups.

STRENGTHS

This manuscript has many strengths.

• The use of laboratory based data, whilst not new, is developed here in new ways

• The reconciliation of population data is good

• The population defined is much bigger than in some previous reports

• New confirming data are presented of the very high prevalence of diabetes in several Asian ethnic groups confirming Ramachandran (2010).

• The extent of population coverage for screening is impressive and may the highest recorded, even though the time period is 5.5 years (see below).

• This calls for recognition of this achievement by the general practitioners in the area as screening is a general practice not a hospital function

• An overall population prevalence for diabetes of 5.3% (page 10) is reported.

• An impressive potential for medical audit is demonstrated.

• Their conclusions about the proportion of undiagnosed diabetes are new interesting and of international significance

Thank you for the comments above. Reference added as suggested.

On the basis of these the presumption should be to accept for publication. However, there are a number of academic weaknesses. Some as shown are inherent and need to be more clearly acknowledged. Some are capable to being corrected, as shown, when the article will be very powerful.

WEAKNESSES

Title

The title is not appropriate. The authors are not describing a diabetic register as is usually understood in either primary or secondary care. The group of people whom they have identified are those people who have had a blood sugar or HbA1c estimation and they are clear (page 6) that they are studying those people with diabetes and also those in risk groups for diabetes. There are good clinical reasons for identifying such people, but it is not academically acceptable to say they have modified a widely used international definition of the disease diabetes itself. Nor is their register a pure register of diabetes as their title implies. They have stronger titles available such as starting the title with Linking..... or The Use of Laboratory Data for Medical Audit and Quality Improvement in people with hyperglycaemia.

The title has been amended to: “The future of population registers: linking routine health datasets to assess a population’s current glycaemic status for quality improvement.” The entire manuscript has been amended as a study of dysglycemic status rather than labelling it as a novel diabetes register accordingly.

Publically-funded and private medical services

The authors correctly make it clear they are reporting for publically funded medical services in their part of New Zealand. But they are submitting to the BMJ which is an international medical journal and read in many different countries. Indeed I am assessing their work from the other side of the world. They therefore need to give some estimate of the size of the private medical sector in New Zealand so readers can judge how many people and data they may be missing.

This is further clarified in the method section: “Individual patient laboratory tests can be requested by general practitioners, privately or publicly funded specialists, resident medical staff or other allied health workers.” The private funded sector (specialist) orders the publicly funded laboratory tests.

Also the discussion section: “The HSU population (n=1,475,347) was very similar to the estimated population of the three Auckland metropolitan District Health Boards from Statistics New Zealand in June 2010 (n=1,477,600). In practical terms, virtually everyone with significant disease who resides in the Auckland metropolitan area is likely to be currently enrolled in a primary care practice and/or have had a contact with publicly funded health services in the year.”

Cut-off point at 5.5 years

The authors cut off for analysis at 5.5 years ie they report people who had had a test within this period of time. This is understandable and pragmatic as this is the period they can study. But this is not a unit of time that makes much sense for clinicians in general practice as a person at risk for diabetes is not adequately screened if their last test was as long ago as 5.5 years. In this context quoting the New Zealand expectation for general practices re the frequency of screening would add value. It would be helpful if they acknowledged this more clearly or they re-analyse their data using a shorter cut off at a shorter period of say three years.

The objective of the study was to determine screening levels and the glycaemic status of all individuals within a defined geographic location in a consistent way to facilitate systematic disease prevention and management. The study aims to determine the population groups who are yet to be

screened or groups with dysglycaemia. The rationale of the cut off point at 5.5 years (the longest followup period) is to give the best sensitivity in identifying people who would benefit from followup and active management. Having a shorter cut off point would lead to significant under count of dysglycemia.

Types of diabetes

The article does not distinguish between Type one and Type 2 diabetes. This is understandable as the great majority of the authors are not primarily clinicians. But it is recognised that these two types of diabetes have different characteristics and the high prevalence in the Asian people is likely to be from Type 2.

Acknowledged that we cannot distinguish between Type 1 and Type 2 diabetes as a limitation

The authors may not have access to clinical information to split these two entities and this should not debar publication, but they need to be more explicit that they are combining the two types.

We acknowledged that the lack of clinical information as a limitation.

Guidelines in New Zealand

The main point of the their tables 1 and 2 is to relate performance in screening to the population at risk. The guide line indication for screening appears to stop at age 74.

This is obviously, as their table shows, being ignored by their local clinicians particularly the GPs, since the percentages in the 70-74 and 75-79 age groups are so similar.

Moreover their interesting figures 1 and 2 confirm that even in the ethnic group with the lowest prevalence of diabetes, the rate is as high as about one in eight. It does not make clinical sense to stop opportunistic screening at age 74 and this merits comment.

Significant number of tests might be occurring in the hospital setting in the older age groups (noted in discussion). A detailed discussion on screening criteria is beyond the scope of the paper and is covered elsewhere in the literature (e.g. the references listed below for reviewer 2). There are many other considerations such as the degree of benefit from interventions in the older age groups, and the resource implications for the publicly funded sector, the proportions of known versus unknown diabetes etc.

Use of laboratory data in diabetes

There have been earlier articles reporting the use of laboratory data in diabetes for defined areas. These are not referenced and should be eg Wilson et al (2009)

Reference included.

Potential for medical audit

The authors could do more to emphasise the potential of their system for medical audit, especially of general practice/primary care where most of the action for Type 2 diabetes now lies.

There is a refined discussion regarding the potential for quality improvement. “The way the HSU population was defined means that if identifiable data were used as part of a population register, it can identify any potential performance gaps that a health care provider can address at the individual level. Eligible patients could be readily recalled based on latest contact details from primary care enrolment or from the last health service contact. This is particularly important in a context where the actual care that patients received might be suboptimal.[17] For example, a systematic recall system can

theoretically be set up for those people who are yet to be screened using the identical record linkage carried out by this study. As pharmaceutical dispensing data can be linked by NHI in New Zealand, a similar systematic system could also be implemented to monitor the care provision for people who are at high risk of complications. For example, it would be possible to recall those with diabetes and microalbuminuria that were not dispensed an angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist, or people with poorly-controlled diabetes who may need further clinical review or self-management support."

Final section of discussion (page 14)

The final section of the discussion on page 14 is weak and disappointing and needs cutting.

1. Writing about coding disease registers manually in primary care is out of date when in the UK, for example, 99% of general practices are computerised and the GP contract (QOF) specifically includes diabetes care.
2. Population churn is indeed an issue in all countries, but it is inappropriate to write about Britain in terms of impeding diabetes registers as the national returns for the NHS GP contract show this is not so. Their references do not support their sentence on Britain.
3. They write: "It would be challenging to retrospectively diagnose all enrolled patients based on the latest international recommendations in a consistent manner." But this has been done and published four years ago (Langley et al., 2008).

The section has been shorten substantially, and updated with the latest references that noted the current challenges with existing records on diagnosis: "While the UK NHS Quality and Outcomes Framework (QOF) recommends a systematic approach to diagnose diabetes, primary care providers are not required to provide supporting description on how the diabetes diagnoses are made, other than a record of a diabetes diagnosis for the purpose of the QOF indicator.[28] Indeed, QOF openly acknowledges that there are a substantial number of people who are undiagnosed or misdiagnosed.[28] The ability to keep an up to date record of people with 'diagnosed' diabetes would also be more challenging in places where there is a highly mobile population such as in New Zealand, certain parts of Great Britain and the United States.[29-31] Furthermore, a significant number of blood test results may not be requested by the general practices that are currently responsible for the patients' care. For example, as demonstrated in this study, significant numbers of laboratory tests were carried out in hospitals."

Langley's study quoted by reviewer 1 is different from this study: Langley's study searched Read codes in primary care to define the cohort with diabetes and then examine the HbA1c results, rather than not analysing all available the laboratory data of the entire practice population. It did not determine the number of people who might be diagnosed with diabetes, had the regional community and hospital laboratories results were examined.

4. They seriously overstate the risk of primary care not receiving abnormal blood sugar or HbA1c test at least in the UK where discharge letters from hospital are sent to GPs.

As noted by the NHS QOF, the information related to the quality of the primary care records is not comprehensively captured, (noted in the discussion above). The discussion covers the possible reasons that may explain why a primary health care provider (as opposed to primary health care sector as a whole) may not have an accurate record of diagnosis compared to might be known if one examined the data available to entire health system.

5. They weaken their article with these comments and much of this discussion is not needed and could be cut with advantage.

Discussion had been refined, and shortened as recommended.

6. Although there are nine authors, none comes for general practice/ primary care and they are weak on this perspective at a time when some authors (Langley et al, 2008) report 96% of all diagnoses of Type 2 diabetes being made in general practice. In the UK over 90% of screening takes place in general practice/primary care and where over two thirds of all medical care for people with Type 2 diabetes now takes place (Khunti et al., 2000; Piarce et al., 2000).

As noted by this large population study, a substantial number of laboratory tests were undertaken by hospitals. "There were 1,458,350 tests performed in laboratories based in hospitals (34% of the total) and 2,823,249 tests performed by community laboratories (66%)."

RECOMMENDATION

This is an interesting and important article which should be able to make a useful contribution to the literature.

It is, in its present form, marred by some weaknesses as set out. If the authors deal with these, then I recommend acceptance.

Denis Pereira Gray

Professor Sir Denis Pereira Gray OBE

MA HonDSc FRCP FRCGP FMedSci

Emeritus Professor University of Exeter, UK; Honorary Professor, Peninsula College of Medicine and Dentistry , UK

References

Langley P Evans P and Pereira Gray D (2008) Diagnosing Type 2 Diabetes before patients complain of diabetic symptoms: clinical opportunistic screening in a single general practice Fam Pract, 25, 378-89.

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Wilson SE Lipscombe LG Rosella LC and Manuel DG (2009) Trends in laboratory testing for diabetes in Ontario Canada 1995-2005: a population based study BMC Health Services Research 9, 41.

VERSION 2 – REVIEW

REVIEWER	Professor Sir Denis Pereira Gray OBE MA HonDSc FRCP FRCGP FMedSci Emeritus Professor University of Exeter, Honorary Professor University of Exeter Medical School, UK
REVIEW RETURNED	11-Oct-2013

GENERAL COMMENTS	STRENGTHS This manuscript has strengths: • The principle of developing laboratory data bases to support clinical care is correct, important, and underutilised • They survey a good sized population of 1.4 million people and this incudes ethnically diverse populations • It has long been known that the prevalence of diabetes is much higher n several Asian communities and they virtually confirm and extend this extend this knowledge (however see below re diagnosing diabetes and dysglycaemia). • They make an interesting case for the use of databases of this type for medical audit. • I had the privilege of assessing an earlier version of this manuscript and the authors have made a number of changes in the light of that assessment. However the manuscript also has weaknesses: • Their stated objective is to "determine …..the glycaemic status of all individuals within a defines population". This is ambiguous as they only have a measure of the glycaemic status for about half their population. • The world has moved on re the use of units. It is no longer usual to record glycaemic status in mg/% of HBA1c but new internationally accepted units of mmols are now in use, with 48 mmols as the cut-off level (which they mention). • They report (page 6) using a modified definition of the well known WHO and American Diabetic Association criteria for the for the diagnosis of diabetes. They introduce the term "dysglycaemia". • They define this as a person having: At least least one HbA1c of >6.5% (equivalent to 48 mmols). At least one 2 hour post glucose load >11.1 mmol and or At least one fasting glucose of =>7.0 mmols/l on a different day • However there are significant problems with this approach as the last two criteria indicate diabetes under the new criteria and the first indicates probable diabetes, but needing a second test. • They justify their approach as identifying a "cohort of people with abnormalities of metabolism who are at high risk of cardiovascular complications rather than only the people who had a confirmed diagnosis of diabetes". p7, My italics • These are the words usually used to refer to people with so called "pre-diabetes" also known as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) ie people with HbA1c levels between 42 and 47 mmols. • The authors therefore mix these people with true diabetes. • Diabetes as internationally defined is therefore lost. • But diabetes is an internationally defined and very important disease, it is not helpful for local groups to create their own definitions for their own purposes. • It is important that researchers world wide compare and contrast their findings and this requires that everyone uses internationally agreed definitions. • Tables 1 and 2 illustrate the percentage uptake of tests by males and females and show in yellow the recommended ages for screening in the New Zealand cardiovascular guidelines. • These tables show that New Zealand clinicians are continuing to test at ages older than this and have good reason to do so as the incidence of true diabetes rises with age. • Their analyses cannot distinguish between type 1 and type 2

	diabetes. OTHER FACTOR I am not competent advise on the ethical guide lines currently applied in New Zealand. But the authors' suggestion that individual care (with personally identifiable data) can/should be audited and perhaps a reminder system developed, raises confidentiality issues which need clarification. This is a hot topic in the UK. CONCLUSION The authors deserve credit for exploring the considerable potential of laboratory data bases of the kind they describe. However, their use of a non- standard and idiosyncratic diagnostic category of "dyslipidaemia" is not well justified. It mixes true diabetes with prediabetes and is not helpful. It undervalues prediabetes and prevents comparisons between studies. I can't myself advise publication but suggest another opinion.

REVIEWER	Harvey, John North Wales Clinical School
REVIEW RETURNED	31-Oct-2013

GENERAL COMMENTS	The authors combine datasets to generate a register of individuals whose dysglycaemia status is known. This generates epidemiological data by gender and ethnic category. The authors identify this as a way forward to support care in common chronic diseases such as diabetes. I have a number of comments: The authors have not actually demonstrated that database linkage supports clinical care in the way they suggest because they have not actually done that. They have generated results at the population level showing differences in prevalence rates with age and ethnic category but not intervention at the individual level. They should therefore be more circumspect with their conclusions in the abstract, discussion and final conclusion. The databases are linked using an encrypted identifier (NHI) "to protect privacy and confidentiality". But for a clinician to identify which individual needs intervention and who to contact he needs all their details: name, age, address, lab results etc without encryption or confidentiality. If the authors were to get on to clinical intervention as they discuss, how would they get round this issue? What is the point of the encryption/privacy/confidentiality procedure if it has to be removed to achieve this main aim of the process? Some explanation needs to be added to the text. The authors have studied major demographic factors (gender, date of birth, ethnicity) which one could expect to be accurately listed in the databases. However, when investigators go beyond these basic factors one will come up against omissions and anomalies such that data cleansing is required. This is virtually impossible with anonymised data and I feel is a fundamental problem with the methodology being promoted here. Abstract seems to be inaccurate in certain respects. The Objectives surely were: 1. To show that datasets could be linked to provide good population coverage. 2. To determine the prevalence of dysglycaemia by age, gender and ethnic group. 3. To assess the possibility of obtaining individual information for quality improvement. What are "screening levels"?

	In the conclusion I would question whether the authors have demonstrated that individual level clinical information has been achieved because it is anonymised and has not been used for clinical purposes. The information on prevalence of dysglycaemia by age, gender and race does not seem particularly “relevant to quality improvement”. Methods At several points the analysis is claimed to be longitudinal. But for many patients the diagnosis is based on a single measure at a single time point. Surely the analysis is cross-sectional, not longitudinal? Is it really necessary to refer to the white Caucasian ethnic group as “others”? I appreciate this may be taken directly from New Zealand national statistics but it seems to cloud things rather. This group is used in the analysis as the Caucasian group so why not label it as such with whatever caveats are necessary? Results It is interesting that the prevalence of dysglycaemia seems to decline markedly in Pacific islanders, Maoris and Indians as they get older much more than in the other racial groups. Does this indicate greater premature mortality from diabetes in these ethnic groups? Discussion The finding that the HSU population (Discussion paragraph 5) is really almost equal to the estimated population of the three Auckland Health Boards seems quite important to me indicating that one can consider the analysis to be population-based without bias. I feel this should be in Results rather than a comment buried in the Discussion. Paragraph 3: The sentence “The age specific prevalence of Pacific and Indian people…” is difficult to follow and should be redrafted. The authors are unduly hard on capture-recapture analysis (table 4). This is the only method to correct for under-ascertainment. Simply combining various datasets means that completeness is limited by the completeness of the datasets. If one particular group tends not to appear in government datasets generally then there is a potential for bias in the results. This does not appear to be a problem in this study because of the completeness of ascertainment but it is a potential problem with the method. The statement in Table 4 under capture-recapture “Assumes…probability of being captured by each dataset is the same” is incorrect. Datasets can be of any size and larger ones are more likely to capture an individual. I think what is meant here is that within each source the potential to capture each member of the population should be the same. Recommendation This study provides good data on the prevalence of dysglycaemia (which by definition here seems very close to diabetes) in different populations. The numbers studied are large and ascertainment close to complete which would effectively seem to eliminate bias. Most important is the demonstration of a method which, as the authors emphasise, has the potential to achieve more and be of direct clinical value. I would recommend acceptance if the above points can be addressed.

VERSION 2 – AUTHOR RESPONSE

Reviewer Name Professor Sir Denis Pereira Gray OBE MA HonDSc FRCP FRCGP FMedSci
Institution and Country Emeritus Professor University of Exeter, Honorary Professor University of Exeter Medical School, UK
Please state any competing interests or state 'None declared': None declared

STRENGTHS
This manuscript has strengths:

- The principle of developing laboratory data bases to support clinical care is correct, important, and underutilised
- They survey a good sized population of 1.4 million people and this incudes ethnically diverse populations
- It has long been known that the prevalence of diabetes is much higher n several Asian communities and they virtually confirm and extend this extend this knowledge (however see below re diagnosing diabetes and dysglycaemia).
- They make an interesting case for the use of databases of this type for medical audit.
- I had the privilege of assessing an earlier version of this manuscript and the authors have made a number of changes in the light of that assessment.

No specific comments to address.

However the manuscript also has weaknesses:

- Their stated objective is to "determine …..the glycaemic status of all individuals within a defines population". This is ambiguous as they only have a measure of the glycaemic status for about half their population.

The objective has been clarified to 'known' glycaemic status of all individuals within health service utilisation population.'

All individuals in health service utilisation population were reviewed by the study. However, understandably not all individuals had glycaemia-related blood testing in a real world study. It is worth noting that not all individuals have definite indications for glycaemia-related blood testing, e.g. not all young children necessarily require a routine glycaemia-related blood test.

- The world has moved on re the use of units. It is no longer usual to record glycaemic status in mg/% of HBA1c but new internationally accepted units of mmols are now in use, with 48 mmols as the cut-off level (which they mention).

Manuscript has been updated to new units.

- They report (page 6) using a modified definition of the well known WHO and American Diabetic Association criteria for the for the diagnosis of diabetes. They introduce the term "dysglycaemia".
- They define this as a person having:

At least least one HbA1c of >6.5% (equivalent to 48 mmols).
At least one 2 hour post glucose load >11.1 mmol and or
At least one fasting glucose of =>7.0 mmols/l on a different day

- However there are significant problems with this approach as the last two criteria indicate diabetes under the new criteria and the first indicates probable diabetes, but needing a second test.

- They justify their approach as identifying a “cohort of people with abnormalities of metabolism who are at high risk of cardiovascular complications rather than only the people who had a confirmed diagnosis of diabetes”. p7, My italics

- These are the words usually used to refer to people with so called “pre-diabetes” also known as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) ie people with HbA1c levels between 42 and 47 mmols.
- The authors therefore mix these people with true diabetes.
- Diabetes as internationally defined is therefore lost.

- But diabetes is an internationally defined and very important disease, it is not helpful for local groups to create their own definitions for their own purposes.

The main reasons that justify the definition as defined by the study were noted in the manuscript. Some additional background information are presented here.

The key of this study is to demonstrate the potential value of the methods and the use of the regional laboratory repository. It is worth noting that the internationally defined definitions for diabetes have changed over time. ACC and WHO guidelines regarding HbA1c as a diagnostic test were published in 2010 and 2011 respectively,[1,2] and many of the HbA1c tests that were examined by this study would be prior to the publication of the recommendations (of the need to have two abnormal HbA1C tests to diagnose diabetes) being formally published. Furthermore, it is worth noting that the biological variability of HbA1c (<1%) is much less compared to fasting glucose, and analytical variability of HbA1c was estimated to be about 2%.[3] If two abnormal HbA1c tests were used, it would lead to substantial decrease in sensitivity of the study because of data coverage artefact (leading to falsely low prevalence estimated) with a small marginal gain in specificity.

The potential of the methods of this study is to enable a systematic way to review historical glucose and HbA1c results for an individual that may limit unnecessary duplication of testing and prioritise population subgroups who may need further assessment and/or ongoing followup.

The study was designed pragmatically, as there may be subgroups with one off test with HbA1c level that is consistent in the diabetes range, who may not have repeated test immediately but yet they would benefit from ongoing followup as noted in the manuscript.

“People with borderline elevated HbA1c (>48mmol/mol) may be offered dietary advice and the HbA1C test may not necessarily be repeated immediately in the “real-world” as it does not change immediate management. Strictly speaking, these people would not yet have met the diagnostic criteria of diabetes. However, they should have follow up tests to confirm or exclude the diagnosis of diabetes.”

As noted in the manuscript, one of the limitations of this study is that it did not have information related to patients’ symptoms or the ability to differentiate type 1 and type 2 diabetes. Indeed, the manuscript clearly stated not everyone with dysglycaemia had met the definition of diabetes but a register of dysglycemia has the potential to inform providers the population subgroup that require follow up or further assessment. This study is not challenging the current definition of diabetes or introducing new terminology to be used clinically. It is describing a method to assist with case finding of people with diabetes.

Moreover, the proposed method of this study can be refined further in the future if different diagnostic thresholds of HbA1C were recommended according to ethnicity or to local recommendations. Using

two abnormal Hba1c measures to define diabetes would be more appropriate once the use of HbA1c screening is much more widely established for a number of years. (note: the discussion regarding sensitivity and specificity above).

"People with abnormalities of glucose metabolism, who are at high risk of cardiovascular complications" is one of the main rationale to define diabetes, and the phrase does not necessarily refer to "pre-diabetes" group such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).

- It is important that researchers world wide compare and contrast their findings and this requires that everyone uses internationally agreed definitions.

International comparison can be difficult to interpret because of other systemic biases (e.g. consistency in clinical coding) as noted in the discussion. Having a method that enables consistency in assessing the glycaemic status of a defined population of over 1.4 million people may be a step towards consistency towards international comparison.

"While some registers have sourced data from primary care, the quality of input data and consistency of coding could be highly variable.[4-6] While the UK NHS Quality and Outcomes Framework (QOF) recommends a systematic approach to diagnose diabetes, primary care providers are not required to provide supporting description on how the diabetes diagnoses are made, other than a record of a diabetes diagnosis for the purpose of the QOF indicator.[7] Indeed, QOF openly acknowledges that there are a substantial number of people who are undiagnosed or misdiagnosed.[7] The ability to keep an up to date record of people with 'diagnosed' diabetes would also be more challenging in places where there is a highly mobile population such as in New Zealand, certain parts of Great Britain and the United States.[8-10]"

Finally, there is existing literature that uses one off HbA1c testing to estimate prevalence of abnormal HbA1c may enable one to compare and contrast findings in different populations.[11]

- Tables 1 and 2 illustrate the percentage uptake of tests by males and females and show in yellow the recommended ages for screening in the New Zealand cardiovascular guidelines.
- These tables show that New Zealand clinicians are continuing to test at ages older than this and have good reason to do so as the incidence of true diabetes rises with age.

The comprehensive discussion regarding the optimal age range for diabetes screening is beyond the scope of the current paper. There are many other considerations other than incidence of disease to determine to optimal age range for diabetes screening, such as the absolute benefit from interventions in the older age groups in terms of reduction in morbidity and mortality, the prevalence of co-morbidities, and the resource implications for the health sector, the prevalence of known versus undiagnosed diabetes etc. However, it is also worth noting that a significant number of tests might be occurring in the hospital setting in the older age groups (as noted in discussion) considering the risk of hospitalisation increases progressive with age.

- Their analyses cannot distinguish between type 1 and type 2 diabetes.

This was stated as a limitation in the original manuscript.

OTHER FACTOR

I am not competent advise on the ethical guide lines currently applied in New Zealand. But the authors' suggestion that individual care (with personally identifiable data) can/should be audited and perhaps a reminder system developed, raises confidentiality issues which need clarification. This is a hot topic in the UK.

An additional section has been added to cover this important point raised.

"Data security and appropriate access and use of health data across the whole of health system are vital components to enable a population register to succeed. The balance between patient confidentiality and the adaptable use of identifiable health data to enable proactive health services should be vigorously debated. While the rationale to develop such a population register is to improve population health and equity through systematic medical audit, appropriate safeguards should be in place to limit any unintended misuse of possible confidential health data.

Clinicians ideally should have timely access to all the available health information for the group of patients that they are clinically responsible for. However, the capacity and capability required to analyse health data from the whole of health system into clinically meaningful and actionable health information at the point of care are not universally available from all health care providers. Therefore, a central system that can apply the methods of this study has a tremendous potential to review some of the possible quality gaps exist in the current system."

CONCLUSION
The authors deserve credit for exploring the considerable potential of laboratory data bases of the kind they describe.
However, their use of a non- standard and idiosyncratic diagnostic category of "dyslipidaemia" is not well justified. It mixes true diabetes with prediabetes and is not helpful. It undervalues prediabetes and prevents comparisons between studies.
I can't myself advise publication but suggest another opinion.

The main reasons that justify the definition as defined by the study were noted above.

This study is not challenging the current definition of diabetes or introducing new terminology to be used clinically. The term dysglycemia is to describe the group of people that were identified by the study's method which has the potential to be helpful to assist case finding and follow up of people with diabetes.

Considering the biological and analytical variability of HbA1c is around 2-3%,[3] the proportion of people who will have a subsequent abnormal HbA1c test is likely to be high if they are already had a prior abnormal HbA1c test.

It is worth noting the definition of dysglycaemia (described by this study) is not consistent with the definition pre-diabetes.

- at least one HbA1c test ≥ 6.5% (equivalent to 48 mmol/mol) or
- at least one 2 hour post glucose load ≥ 11.1 mmol/l on a Glucose tolerance test (GTT)
- two or more tests of random glucose ≥ 11.1 mmol/L and/or fasting glucose ≥ 7.0 mmol/L on a different day.

Comparisons between studies can be challenging between studies because of other systematic biases, e.g QOF openly acknowledges that there are a substantial number of people who are undiagnosed or misdiagnosed.[7] Having a method that enables consistency in assessing the glycaemic status of a defined population of over 1.4 million people may be a potentially helpful step towards better comparability between studies.

Authors' response to reviewer 2

Reviewer Name Harvey, John
Institution and Country North Wales Clinical School
Please state any competing interests or state 'None declared': None

The authors combine datasets to generate a register of individuals whose dysglycaemia status is known. This generates epidemiological data by gender and ethnic category. The authors identify this as a way forward to support care in common chronic diseases such as diabetes. I have a number of comments:

The authors have not actually demonstrated that database linkage supports clinical care in the way they suggest because they have not actually done that. They have generated results at the population level showing differences in prevalence rates with age and ethnic category but not intervention at the individual level. They should therefore be more circumspect with their conclusions in the abstract, discussion and final conclusion.

Thank you for the above comment, the abstract, discussion and conclusion has been re-phrased as recommended.

The databases are linked using an encrypted identifier (NHI) “to protect privacy and confidentiality”. But for a clinician to identify which individual needs intervention and who to contact he needs all their details: name, age, address, lab results etc without encryption or confidentiality. If the authors were to get on to clinical intervention as they discuss, how would they get round this issue? What is the point of the encryption/privacy/confidentiality procedure if it has to be removed to achieve this main aim of the process? Some explanation needs to be added to the text.

The authors have studied major demographic factors (gender, date of birth, ethnicity) which one could expect to be accurately listed in the databases. However, when investigators go beyond these basic factors one will come up against omissions and anomalies such that data cleansing is required. This is virtually impossible with anonymised data and I feel is a fundamental problem with the methodology being promoted here.

An additional reference that provides further contextual information for the reader has been added in the manuscript.[12] In brief, the NHI index is widely used by both primary care and secondary care services in New Zealand. The specific data elements that are routinely collected were listed in the data dictionary.[13] The NHI database has identifiable information such as name, address, data of birth, self-reported ethnicity. The NHI number has been used in other settings of proactive care such as immunisation.[14] The duplicated NHI are regularly cleaned and mapped back to the Master NHI. Regular audits are performed and Primary Health Organisations are required to provide their patient registries to the New Zealand Ministry of Health (MOH) every quarter. The NHI enables linkage to other datasets such as other MOH routinely collected administration datasets or regional laboratory repository such as Testsafe. The encrypted NHI is often used to protect privacy and confidentiality in a research setting. The encrypted NHI is a one to one match to the NHI. The encryption method is only known to the MOH. It would be worth noting that much of the ‘data cleansing’ are carried out routinely by the New Zealand health information system. Indeed, this study highlights one of the advantages of having a national unique identifier that is regularly used in a wide range of clinical settings as well as administrative purposes.

An extra section has been added in regard to privacy and data security.

“Data security and appropriate access and use of health data across the whole of health system are vital components to enable a population register to succeed. The balance between patient confidentiality and the adaptable use of identifiable health data to enable proactive health services should be vigorously debated. While the rationale to develop such a population register is to improve

population health and equity through systematic medical audit, appropriate safeguards should be in place to limit any unintended misuse of possible confidential health data.

Clinicians ideally should have timely access to all the available health information for the group of patients that they are clinically responsible for. However, the capacity and capability required to analyse health data from the whole of health system into clinically meaningful and actionable health information at the point of care are not universally available from all health care providers. Therefore, a central system that can apply the methods of this study has a tremendous potential to review some of the possible quality gaps exist in the current system."

Abstract seems to be inaccurate in certain respects. The Objectives surely were: 1. To show that datasets could be linked to provide good population coverage. 2. To determine the prevalence of dysglycaemia by age, gender and ethnic group. 3. To assess the possibility of obtaining individual information for quality improvement. What are "screening levels"?

The excellent population coverage from New Zealand routine datasets have already been established as referenced in the manuscript.[15] The objective in the abstract has been rephrased: "To determine diabetes screening levels and the known glycaemic status of all individuals by age, gender and ethnicity within a defined geographic location in a timely and consistent way to potentially facilitate systematic disease prevention and management."

In the conclusion I would question whether the authors have demonstrated that individual level clinical information has been achieved because it is anonymised and has not been used for clinical purposes.

The laboratory results from data repository were used clinically on an ongoing basis. However, the exact method of this study has not been piloted in a clinical setting. Accordingly, the abstract and discussion have been re-phrased highlighting the potential of great clinical value. However, as noted above, similar NHI linked system that enables proactive preventive care such as screening and immunisation has been implemented in New Zealand.[16]

The information on prevalence of dysglycaemia by age, gender and race does not seem particularly "relevant to quality improvement".

The purpose of the study to develop a method that enables a health care provider to identify people who are eligible to undertake diabetes screening (as part of cardiovascular risk assessment) but yet to do so. The eligibility of cardiovascular risk assessment is defined by age, gender, and ethnicity.

Secondly, the value of dysglycaemia is a very useful reference that enables the health care provider to undertake medical audit in regard to followup. As noted in the discussion, the abnormal results may exist somewhere in the health system, but not necessarily be readily available at the general practices that are currently responsible for the patients' care for many reasons including patients' movement/ churn.

The potential for a patient proactive recall system includes improvement in coverage and quality of clinical follow up.

Methods: At several points the analysis is claimed to be longitudinal. But for many patients the diagnosis is based on a single measure at a single time point. Surely the analysis is cross-sectional, not longitudinal?

The study population is a cross sectional. However, their corresponding laboratory results were examined up to 6 years. A person can have more than one test over a different time period. The fasting and random glucose tests require 2 abnormal results on different days to be considered as

dysglycaemia. The term “longitudinal” was replaced by a description of the time frame of the laboratory result coverage to limit possible confusion.

Is it really necessary to refer to the white Caucasian ethnic group as “others”? I appreciate this may be taken directly from New Zealand national statistics but it seems to cloud things rather. This group is used in the analysis as the Caucasian group so why not label it as such with whatever caveats are necessary?

The ethnicity is self-identified in New Zealand. There is a standard form to record ethnicity information. ‘Caucasian’ is not a term that was used in the self reported form. However, while ‘others’ ethnic group include, European, New Zealand European, Middle Eastern, Latin American, and African, majority would be from the European and New Zealand European category.

Results It is interesting that the prevalence of dysglycaemia seems to decline markedly in Pacific islanders, Maoris and Indians as they get older much more than in the other racial groups. Does this indicate greater premature mortality from diabetes in these ethnic groups?

Maori, Pacific Islanders and Indians are known to have higher incidence of cardiovascular disease than the other ethnic group,[17] and Maori and Pacific populations are known to have higher age standardised all-cause mortality (aged 1-74).[18]

Discussion The finding that the HSU population (Discussion paragraph 5) is really almost equal to the estimated population of the three Auckland Health Boards seems quite important to me indicating that one can consider the analysis to be population-based without bias. I feel this should be in Results rather than a comment buried in the Discussion.

The estimated population of the three District Health Boards in Auckland metro by Statistic New Zealand has been added to the result section.

Paragraph 3: The sentence “The age specific prevalence of Pacific and Indian people…” is difficult to follow and should be redrafted.

The sentence has been amended. “This study demonstrated Pacific and Indian people have the highest age standardised prevalence of dysglycemia. Almost one in two Pacific women aged 70-74 had evidence of dysglycemia.” This study demonstrated Pacific and Indian people have the highest age standardised prevalence of dysglycemia. Almost one in two Pacific women aged 70-74 had evidence of dysglycemia (Figure 2).“

The authors are unduly hard on capture-recapture analysis (table 4). This is the only method to correct for under-ascertainment. Simply combining various datasets means that completeness is limited by the completeness of the datasets. If one particular group tends not to appear in government datasets generally then there is a potential for bias in the results. This does not appear to be a problem in this study because of the completeness of ascertainment but it is a potential problem with the method. The statement in Table 4 under capture-recapture “Assumes…probability of being captured by each dataset is the same” is incorrect. Datasets can be of any size and larger ones are more likely to capture an individual. I think what is meant here is that within each source the potential to capture each member of the population should be the same.

The table 4 has been amended regarding capture-recapture analysis. “Assumes list independence, and all individuals have the same probability of being captured by each dataset.”

The method of this study could be a possible alterative way to estimate the degree of under ascertainment of some of the other methods.

Recommendation

This study provides good data on the prevalence of dysglycaemia (which by definition here seems very close to diabetes) in different populations. The numbers studied are large and ascertainment close to complete which would effectively seem to eliminate bias.
Most important is the demonstration of a method which, as the authors emphasise, has the potential to achieve more and be of direct clinical value. I would recommend acceptance if the above points can be addressed.

Thank you both reviewers’ for thier helpful comments.

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VERSION 3 - REVIEW

REVIEWER	Denis Pereira Gray St Leonard's Research Practice
REVIEW RETURNED	10-Mar-2014

GENERAL COMMENTS	Thank you for asking me to assess the submitted article by Chan et al. on diabetic tests undertaken in regional pathology laboratories. I am pleased to do so. I previously assessed an earlier version of this work. I was then critical , especially on the point about definitions of diabetes. Declaration I have never met any of the ten authors and have no connection or link with them and I work on the other side of the world. STRENGTHS This article has many strengths: • It deals with a substantial multi-ethnic population. • It cover all the relevant tests over several consecutive years • It crosses the primary secondary care boundary. • Reporting in this way from regional laboratories is relatively unusual and needs t be encouraged. • The authors have made a substantial attempt to respond to the previous adverse assessment • The findings confirm the well- known association between diabetes and ethnic groups of Asian and Pacific origin. • The analysis shows relatively high coverage. • The authors are correct that there is an international trend towards making better use of “real world” health service data. . • • WEAKNESSES Criteria and use of term dysglycaemia Whilst the authors have made useful changes to the crucial issue of definitions, they have not entirely resolved the problem. They write line 58 that they have modified the ADA and WHO definitions. This is important and unfortunate as the whole point of internationally accepted definitions is that they enable colleagues all round the world to compare patients. The process of modification breaks this key link and reduced the value of the work . In fact, with these new criteria the authors have moved their categorisation, which they ‘dysglycaemia’ much closer to internationally accepted criteria for the diagnosis of diabetes ie ,most of the patients they describe had diabetes. Prediabetes One of the criteria of 58 mmols HbA1c , if repeated, leads to a diagnosis of diabetes. But if not ,no comment is made. All such are categorised as dysglycaemia There is a rich international literature on prediabetes, which can take

	one of two forms: Impaired Fasting Glucose, or Impaired Glucose Tolerance. These terms are not mentioned nor referenced . “Elimination of the numerator/denominator bias” (p12 line 49) The authors are too confident. All the internationally known biases about differential access, differential uptake, and communications in the clinical setting are extremely likely to be present in New Zealand as in the rest of the world. Similarly the line of discussion at the top of page 13 is over played. Ambiguity in writing In line 41 it is said that that hospitals tests were probably taken for symptoms of diabetes “rather than opportunistic screening” whereas tin the same paragraph it is written that there is much routine testing of older people. CONCLUSION This version is a considerable improvement on the earlier version which I was shown. Its main advantage is that it illustrates the potential and also use of regional pathological services . Whether or not this justifies publication in BMJ Open must be an Editorial decision. If the decision is to go ahead attention to the weaknesses listed would improve this draft still further.