

Online Supplement

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Appendix A: Electronic Searches

Search Strategies

The search phrase was as follows:

(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM) AND (metformin OR biguanides OR biguanide) AND (B₁₂ OR B₁₂ deficiency OR Vitamin B₁₂ OR Vitamin B₁₂ deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency).

Searches

Unless otherwise stated, search terms were free text terms. Language restrictions were that of English and human studies only were considered. Details of the date of the last search and database searched is also documented in the text below in addition to the period searched and an outline of the initial search results.

Database – The Cochrane Library - this search covered all Cochrane databases for all years and for all document statuses via <http://www.thecochranelibrary.com/view/0/index.html>.

Database host – Cochrane Library, Issue 5, 2013

Date of search – June 30th 2013

Years covered – All years

Search terms:

- 1 *diabet** (29876)
 - 2 *"type 1"* (6945)
 - 3 *"type 2"* (11018)
 - 4 *IDDM* (604)
 - 5 *NIDDM* (1066)
 - 6 *insulin dependent diabet** (3896)
 - 7 *non-insulin dependent diabet** (2086)
 - 8 *non insulin dependent diabet** (3075)
 - 9 *metformin* (2108)
 - 10 *metformin hydrochloride* (46)
 - 11 *biguanide** (325)
 - 12 *b12 deficiency* (200)
 - 13 *vitamin b12* (735)
 - 14 *vitamin b12 deficiency* (192)
 - 15 *cobalamin* (102)
 - 16 *cobalamin deficiency* (54)
 - 17 *cyanocobalamin* (211)
 - 18 *cyanocobalamin deficiency* (76)
 - 19 *hydroxocobalamin* (47)
 - 20 *hydroxocobalamin deficiency* (9)
 - 21 *hydroxycobalamin* (9)
 - 22 *hydroxycobalamin deficiency* (3)
 - 23 *b12* (781)
 - 24 *(1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11) and (12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23)* (166)
-

There were 166 results from the combined search of which 77 were Cochrane Reviews, 6 were other reviews, 80 were trials, 2 were Economic Evaluations and 1 was Cochrane Groups.

From the 166 reports identified from the combined search then 161 were excluded at title and abstract screening, leaving 5 to go forward for duplicate analysis and full text review.

The Cochrane Library includes the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cochrane Methodology Register, NHS Economic Evaluation Register, Cochrane Groups and the Health Technology Assessment Database (HTA).

Database – Centre for Reviews and Dissemination (CRD) – the University of York CRD is an initiative to establish an international register of systematic reviews in order to identify the

cost effectiveness and effectiveness of healthcare interventions. This was an advanced search covering all document statuses via www.crd.york.ac.uk/.

Database host – CRD Interface

Date of search – June 29th 2013

Years covered – From inception to the date of the search.

Search terms:

- 1 *diabet** (3527)
 - 2 *"type 1"* (594)
 - 3 *"type 2"* (1211)
 - 4 *IDDM* (17)
 - 5 *NIDDM* (32)
 - 6 *insulin dependent diabet** (110)
 - 7 *non-insulin dependent diabet** (49)
 - 8 *non insulin dependent diabet** (49)
 - 9 *metformin* (276)
 - 10 *metformin hydrochloride* (1)
 - 11 *biguanide** (9)
 - 12 *b12 deficiency* (9)
 - 13 *vitamin b12* (34)
 - 14 *vitamin b12 deficiency* (7)
 - 15 *cobalamin* (2)
 - 16 *cobalamin deficiency* (0)
 - 17 *cyanocobalamin* (6)
 - 18 *cyanocobalamin deficiency* (0)
 - 19 *hydroxocobalamin* (1)
 - 20 *hydroxocobalamin deficiency* (0)
 - 21 *hydroxycobalamin* (1)
 - 22 *hydroxycobalamin deficiency* (0)
 - 23 *b12* (42)
 - 24 *1 or 2 or 3 or 4 or 5 or 6 or 7 or 8* (3715)
 - 25 *9 or 10 or 11* (282)
 - 26 *12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23* (44)
 - 27 *24 and 25 and 26* (1)
 - 28 *24 and 25* (226)
 - 29 *26 ad 28* (1)
-

There was a total of 1 combined result identified which was excluded at title and abstract.

CRD databases include DARE (Database of Abstracts of Reviews of Effects), NHS EED (NHS Economic Evaluation Database) and HTA (Health Technology Assessment). It also includes links to NHS Evidence, TRIP Database, The Cochrane Library, Virtual Health Library, Health Systems Evidence, SUMSearch and the Knowledge Network of NHS Scotland.

CRD links into Endnote referencing software only.

CRD search screen results are shown with the report title. Of the one report identified from the combined search, this was included at subsequent abstract screening. In addition the 226

diabetes and metformin related records (search 28) and the B12 related records (search 25) were screened at title. From these, one report at abstract reading from each was identified. This report was the same as the included report identified in the combined search above. For search titles which suggested a relevant report then the abstract was also reviewed.

Database – CINALH (Cumulative Index to Nursing and Allied Health Literature) with Full Text - this was an advanced search using Boolean logic covering all document statuses via <http://www.ebscohost.com/academic/cinahl-plus-with-full-text> (<http://web.ebscohost.com/ehost/search/advanced?sid=e669d755-0bb2-476c-b9de-531d58fe73a7%40sessionmgr110&vid=1&hid=112>).

Database host – EBSCO

Date of search – June 29th 2013

Years covered – 1981-2013

Search terms:

Free text terms:

(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM)
AND

(metformin OR metformin hydrochloride OR biguanides OR biguanide)

AND

(B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)

There were 31 results of which 27 were from academic journals and 4 from magazines. CINALH also searches CEU's (Continuing Education Units within CINALH that relate to Journal articles that qualify for continuing education).

From the 31 reports identified from the combined search then 8 were excluded at title and abstract screening, leaving 23 to go forward for duplicate analysis and full text review.

Database – EMBASE - this was an advanced search looking at human studies in English covering all document statuses via <http://www.elsevier.com/online-tools/embase#> (<http://web.ebscohost.com/ehost/search/advanced?sid=1387d809-3f38-4ac4-807a-1d5e1e500de9%40sessionmgr113&vid=1&hid=112>).

Database host – Elsevier

Date of search – June 29th 2013

Years covered – 1974 -2013

Search terms:

1. *diabet* AND [english]/lim AND [humans]/lim (434,850)*
2. *'type 1' AND [english]/lim AND [humans]/lim (100,053)*
3. *'type 2' AND [english]/lim AND [humans]/lim (97,378)*
4. *'iddm'/exp OR iddm AND [english]/lim AND [humans]/lim (53,450)*
5. *'niddm'/exp OR niddm AND [english]/lim AND [humans]/lim (96,548)*
6. *'insulin'/exp OR insulin AND dependent AND diabet* AND [english]/lim AND [humans]/lim (143,041)*
7. *'non insulin' AND dependent AND diabet* AND [english]/lim AND [humans]/lim (97,504)*
8. *non AND ('insulin'/exp OR insulin) AND dependent AND diabet* AND [english]/lim AND [humans]/lim (102,635)*
9. *'metformin'/exp OR metformin AND [english]/lim AND [humans]/lim (22,568)*
10. *'metformin'/exp OR metformin AND ('hydrochloride'/exp OR hydrochloride) AND [english]/lim AND [humans]/lim (187)*
11. *biguanide* AND [english]/lim AND [humans]/lim (26,133)*
12. *'b12'/exp OR b12 AND deficiency AND [english]/lim AND [humans]/lim (6,420)*
13. *'vitamin'/exp OR vitamin AND ('b12'/exp OR b12) AND [english]/lim AND [humans]/lim (16,860)*
14. *'vitamin'/exp OR vitamin AND ('b12'/exp OR b12) AND deficiency AND [english]/lim AND [humans]/lim (6,371)*
15. *'cobalamin'/exp OR cobalamin AND [english]/lim AND [humans]/lim (18,022)*
16. *'cobalamin'/exp OR cobalamin AND deficiency AND [english]/lim AND [humans]/lim (6,552)*
17. *'cyanocobalamin'/exp OR cyanocobalamin AND [english]/lim AND [humans]/lim (17,710)*
18. *'cyanocobalamin'/exp OR cyanocobalamin AND deficiency AND [english]/lim AND [humans]/lim (7,513)*
19. *'hydroxocobalamin'/exp OR hydroxocobalamin AND [english]/lim AND [humans]/lim (930)*
20. *'hydroxocobalamin'/exp OR hydroxocobalamin AND deficiency AND [english]/lim AND [humans]/lim (309)*
21. *'hydroxycobalamin'/exp OR hydroxycobalamin AND [english]/lim AND [humans]/lim (903)*
22. *'hydroxycobalamin'/exp OR hydroxycobalamin AND deficiency AND [english]/lim AND [humans]/lim (302)*
23. *'b12'/exp OR b12 AND [english]/lim AND [humans]/lim (17,711)*
24. *diabet* AND [english]/lim AND [humans]/lim OR ('type 1' AND [english]/lim AND [humans]/lim) OR ('type 2' AND [english]/lim AND [humans]/lim) OR ('iddm'/exp OR iddm AND [english]/lim AND [humans]/lim) OR ('niddm'/exp OR niddm AND [english]/lim AND [humans]/lim) OR ('insulin'/exp OR insulin AND dependent AND diabet* AND [english]/lim AND [humans]/lim) OR ('non insulin' AND dependent AND diabet* AND [english]/lim AND [humans]/lim)*

[humans]/lim) OR (non AND ('insulin'/exp OR insulin) AND dependent AND diabet AND [english]/lim AND [humans]/lim) OR ('metformin'/exp OR metformin AND [english]/lim AND [humans]/lim) OR ('metformin'/exp OR metformin AND ('hydrochloride'/exp OR hydrochloride) AND [english]/lim AND [humans]/lim) OR (biguanide* AND [english]/lim AND [humans]/lim) AND ('b12'/exp OR b12 AND deficiency AND [english]/lim AND [humans]/lim) OR ('vitamin'/exp OR vitamin AND ('b12'/exp OR b12) AND [english]/lim AND [humans]/lim) OR ('vitamin'/exp OR vitamin AND ('b12'/exp OR b12) AND deficiency AND [english]/lim AND [humans]/lim) OR ('cobalamin'/exp OR cobalamin AND [english]/lim AND [humans]/lim) OR ('cobalamin'/exp OR cobalamin AND deficiency AND [english]/lim AND [humans]/lim) OR ('cyanocobalamin'/exp OR cyanocobalamin AND [english]/lim AND [humans]/lim) OR ('cyanocobalamin'/exp OR cyanocobalamin AND deficiency AND [english]/lim AND [humans]/lim) OR ('hydroxocobalamin'/exp OR hydroxocobalamin AND [english]/lim AND [humans]/lim) OR ('hydroxocobalamin'/exp OR hydroxocobalamin AND deficiency AND [english]/lim AND [humans]/lim) OR ('hydroxycobalamin'/exp OR hydroxycobalamin AND [english]/lim AND [humans]/lim) OR ('hydroxycobalamin'/exp OR hydroxycobalamin AND deficiency AND [english]/lim AND [humans]/lim) OR ('b12'/exp OR b12 AND [english]/lim AND [humans]/lim)) AND [english]/lim AND [humans]/lim (2,056)*

There were 2,056 results from the combined search.

From the 2,056 reports identified from the combined search then 1,962 were excluded at title and abstract screening, leaving 94 to go forward for duplicate analysis and full text review.

Database – Google Scholar - this was an advanced search covering all document statuses via <http://scholar.google.co.uk/>.

Database host – Google

Date of search – June 17th 2013

Years covered – 1957-2013

Search terms:

Free text terms;

B12 deficiency or vitamin b12 deficiency in diabetics on metformin or biguanides

There were a total of 694 results identified.

From the 694 reports identified from the combined search then 668 were excluded at title and abstract screening, leaving 26 to go forward for duplicate analysis and full text review.

Database – Index to Thesis - this was an advanced search on the Proquest platform looking for dissertations and thesis in the UK and Ireland for Health and Medicine databases covering all document statuses via <http://www.theses.com/> (<http://search.proquest.com/pqdtuk/advancedhttp://search.proquest.com/pqdtuk?accountid=17256>).

Database host – Proquest

Date of search – June 30th 2013

Years covered – All years.

Search terms:

1. *(metformin OR metformin hydrochloride OR biguanides OR biguanide) (94)*
2. *(B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency) (255)*
3. *(metformin OR metformin hydrochloride OR biguanides OR biguanide) AND (B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency) (0)*
4. *(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM) AND (metformin OR metformin hydrochloride OR biguanides OR biguanide) (42)*
5. *(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM) AND (B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency) (30)*
6. *(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM on metformin OR metformin hydrochloride OR biguanides OR biguanide) AND (B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency) (0)*

There were no results identified in the combined searches. On the individual searches there were 94, 255, 42 and 30 records respectively and these were also screened at title and abstract to check eligibility and none relevant were identified.

Database – IngentaConnect - this was an advanced search covering all document statuses via <http://www.ingentaconnect.com/>. Boolean operation is available for title, keyword and abstract only and not full text. A full text advanced search was carried out for specific terms as specified below in order to search for reports not identified in the title, abstract and keyword search but that were critical to any relevant results being identified.

Database host – Publishing Technology

Date of search – June 30th 2013

Years covered – All years

Search terms:

Free text terms:

In full text:

metformin metformin hydrochloride biguanides biguanide (20)

In abstract, title or keywords:

metformin and b12 (10)

metformin and vitamin b12 (9)

metformin and b12 deficiency (5)

metformin and vitamin b12 deficiency (5)

metformin and cobalamin (2)

metformin and cobalamin deficiency (0)

metformin and cyanocobalamin (3)

metformin and cyanocobalamin deficiency (0)

metformin and hydroxocobalamin (0)

metformin and hydroxocobalamin deficiency (0)

metformin hydrochloride (with all the above options) (0)

biguanide or biguanides and b12 (2)

biguanide or biguanides and vitamin b12 (2)

biguanide or biguanides and b12 deficiency (2)

biguanide or biguanides and vitamin b12 deficiency (2)

biguanide or biguanides and cobalamin (3)

biguanide or biguanides and cobalamin deficiency (0)

biguanide or biguanides and cyanocobalamin (0)

biguanide or biguanides and cyanocobalamin deficiency (0)

biguanide or biguanides and hydroxocobalamin (0)

biguanide or biguanides and hydroxocobalamin deficiency (0)

There was 65 results identified of which 12 were relevant. There were 11 duplicates amongst these and 1 went forward for full text review.

Database – Journal Citation Reports (JCR) - this was an advanced search of all databases in the Web of Knowledge citation and journal database covering all document statuses via <http://wok.mimas.ac.uk/>.

Database host – Scientific Electronic Library Online (SciELO)

Date of search – June 30th 2013

Years covered – All years.

Search terms:

Free text terms:

(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM)

AND

(metformin OR metformin hydrochloride OR biguanides OR biguanide)

AND

(B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)

There were 123 results identified and 46 remained following title and abstract screening.

Included within this search were all of the following databases in Web of Knowledge: Web of Science, MEDLINE, BIOSIS Citation Index and Previews and Current Contents Connect.

Database – JSTOR - this was an advanced search covering all document statuses in the English language via <http://www.jstor.org/>.

Database host – EBSCO

Date of search – June 30th 2013

Years covered – All years.

Search terms:

Free text terms:

diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM AND

metformin OR metformin hydrochloride OR biguanides OR biguanide AND

B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency

There were 43 results identified and 3 remained following title and abstract screening.

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Database – LILACS - this was an advanced search using the Interface for Access on Health Information (iAH) form covering all document statuses in the English language via <http://lilacs.bvsalud.org/en/>.

Database host – CDS/ISIS Win/ISIS – VHL (Virtual Health Library)

Date of search – June 18th 2013

Years covered – 1986-2013

Search terms:

Free text terms:

(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM)
AND

(metformin OR metformin hydrochloride OR biguanides OR biguanide)

AND

(B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)

There was 1 result identified and this remained following title and abstract review for duplicate analysis.

LILACS – Latin American and Caribbean Studies/Health Sciences Literature

Database – MEDLINE - this was an advanced search using Boolean logic covering all document statuses in the English language for humans via
<http://search.proquest.com/medline/advanced?accountid=17256>
Database host – Proquest
Date of search – June 30th 2013
Years covered – 1950-2013

Search terms:

Free text terms:

(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM)
AND

(metformin OR metformin hydrochloride OR biguanides OR biguanide)

AND

(B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)

There were 65 records of which 5 were relevant following title, abstract and duplicate screening.

Database – National Institute for Health Research (NIHR) Clinical Research Network Study Portfolio (CRN) - this was a basic and advanced search covering all document statuses of this UK based database of clinical studies being undertaken in the National Health Service (NHS) via <http://public.ukcrn.org.uk/search/>.

Database host – National Institute for Health Research (NIHR)

Date of search – June 16th 2013

Years covered – 2010 to the present day.

Search terms via the Portfolio:

Search Box – Topic – *Diabetes*

There were no subtopic categories for (*metformin OR metformin hydrochloride OR biguanides OR biguanide*) and so all trials on the topic of diabetes were searched.

There were no subtopic categories for (*B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency*) and so all trials on the topic of diabetes were searched.

There were a total of 680 results identified. None were relevant for inclusion.

Contact was made with the Study Delivery Manager for the Diabetes Research Network Co-ordinating Centre. She ran an internal search on all trials and there were no trials identified covering the search phrase relevant for the Systematic Review under question.

In addition a NIHR search was carried out via the Network and 1 study on B vitamins was identified, 60 on diabetes via the Published Findings and Case studies. There were no trials identified covering the search phrase relevant for the Systematic Review under question.

Database – National Research Register - this was a basic and advanced archive search covering all document statuses of this public database of recently published and ongoing research projects funded by, or relevant to the National Health Service (NHS) up to 2007 via <http://www.nihr.ac.uk/Pages/NRRArchiveSearch.aspx>.

Database host – National Institute for Health Research (NIHR)

Date of search – June 30th 2013

Years covered – 1990-2007.

Search terms:

Metformin (164)

Biguanide(s) (2)

B12/Vitamin B12 (171)

Cobalamin/Cyanocobalamin/Transcobalamin/Hydroxocobalamin (13)

In order to search then the whole database was obtained from the Department of Health. The register contained 170,454 research projects. Results generated from the above search terms in the ‘Published Projects’, ‘Any part of the field’, were 352.

From the 352 reports identified, none were relevant for inclusion.

Database – Neurosciences Abstracts - this was an advanced search covering all document statuses via <http://search.proquest.com/neurosciabstracts?accountid=28159> (<http://search.proquest.com/neurosciabstracts/advanced?accountid=17256>).
Database host – ProQuest
Date of search – June 30th 2013
Years covered – All years.

Search terms:

Free text terms:

(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM)

AND

(metformin OR metformin hydrochloride OR biguanides OR biguanide)

AND

(B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)

There were 2 results identified and none were relevant for inclusion.

Database – NEXIS - this was a search looking at studies in the English language news covering all document statuses via:

<http://www.lexisnexis.com/uk/nexis/auth/checkbrowser.do?t=1371558671957&bhcp=1>.

Database host – LexisNexis

Date of search – June 30th 2013

Years covered – 1950 -2013

Search terms:

Free text terms:

(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM)
AND

(metformin OR metformin hydrochloride OR biguanides OR biguanide)

AND

(B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)

There were 146 results of which 13 were relevant for inclusion to duplicate analysis.

Database – NHS Evidence - this was an advanced search looking at studies covering all document statuses via <https://www.evidence.nhs.uk/>. This provides access to the most important medicine and prescribing sources of information. NHS Evidence search is the National Institute for Health and Care Excellence (NICE) search and includes the previously titled National electronic Library for Medicines (NeLM).

Database host – NICE

Date of search – June 24th 2013

Years covered – All years

Search terms:

Databases:

1. (*diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM*) (796481)

2. (*metformin OR metformin hydrochloride OR biguanides OR biguanide*) (6872)

3. (*B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency*) (12007)

4. *1+2+3* (37)

Journals:

Free text term:

Diabetes – generated 29 journals

1. British Journal of Diabetes and Vascular Disease – *metformin AND B12 AND deficiency* (Aug 2001-present day) (8)

2. American Diabetes Association Diabetic Journals - Clinical Diabetes, Diabetes Care, Diabetes, Diabetes Spectrum – *metformin* OR biguanide* AND B12 OR cobalamin* (Jan 1978 – present day) (99)

3. Diabetes and Vascular Disease Research – (*diabet* OR Type 1 OR Type 2 OR insulin dependent diabet* OR non-insulin dependent diabet* OR non insulin dependent diabet* OR IDDM OR NIDDM*) AND (*metformin* OR biguanide**) AND (*B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cobalamin deficiency*) (May 2004-present day) (0)

4. Journal of Diabetes and Metabolic Disorders – (*diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM*) AND (*metformin OR biguanides OR biguanide*) AND (*B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency*) (Boolean Search – all years) (1)

Other Journals were already searched for articles in other database searches carried out as part of this review, within Journals@Ovid, Proquest, Pub Med and CINAHL.

There were 37 combined results for the databases and 108 results for the journals. In total 30 reports were carried forward to duplicate and full text review.

NHS Evidence healthcare databases included in the advanced database search included: Allied and Complementary Medicine (AMED) (1985 to the present day - Ovid), British Nursing Index (BNI) (1992 to the present day - Ovid), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981 to the present day - EBSCO), Excerpta Medica Database (EMBASE) (1980 to the present day - Ovid), Health Management Information Consortium (HMIC): Department of Health (DH) -Data and Kings Fund (1979 to the present day - Ovid), Medline (1950 to the present day - Ovid) and PsycInfo (1806 to the present day - Ovid)

NHS Evidence healthcare journals included in the advanced and Boolean searches included:

British Medical Journal (BMJ) and their journals, Journal of American Medical Association (JAMA) and their archive journals, CINAHL, and Health Business Elite.

Database – ProQuest Nursing and Allied Health Source - this was an advanced search covering all document statuses in the English language via http://www.proquest.com/en-US/catalogs/databases/detail/pq_nursingahs.shtml

(<http://search.proquest.com/nursing/advanced?accountid=17256>)

Database host – ProQuest

Date of search – June 30th 2013

Years covered – All years.

Search terms:

Free text terms:

(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM)
AND

(metformin OR metformin hydrochloride OR biguanides OR biguanide)

AND

(B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)

There were 107 results identified of which 6 were relevant for inclusion to duplicate analysis and full text review.

.

Database – PubMed - this was an advanced search of all fields looking at human studies in the English language covering all reviews, journal articles and clinical trials via <http://www.ncbi.nlm.nih.gov/pubmed>.

Database host – National Centre for Biotechnology Information (NCBI), National Library of Medicine (US)

Date of search – June 30th 2013

Years covered – All years

Search terms:

((diabetics[All Fields] OR ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) OR (Type[All Fields] AND 1[All Fields]) OR (Type[All Fields] AND 2[All Fields]) OR (("insulin"[MeSH Terms] OR "insulin"[All Fields]) AND dependent[All Fields] AND diabetics[All Fields]) OR (non-insulin[All Fields] AND dependent[All Fields] AND diabetics[All Fields]) OR ("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields] OR ("insulin"[All Fields] AND "dependent"[All Fields] AND "diabetes"[All Fields]) OR "insulin dependent diabetes"[All Fields]) OR ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR ("non"[All Fields] AND "insulin"[All Fields] AND "dependent"[All Fields] AND "diabetes"[All Fields]) OR "non insulin dependent diabetes"[All Fields]) OR (non[All Fields] AND ("insulin"[MeSH Terms] OR "insulin"[All Fields]) AND dependent[All Fields] AND diabetics[All Fields]) OR ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR ("non"[All Fields] AND "insulin"[All Fields] AND "dependent"[All Fields] AND "diabetes"[All Fields]) OR "non insulin dependent diabetes"[All Fields]) OR ("diabetes mellitus, type 1"[MeSH Terms] OR "type 1 diabetes mellitus"[All Fields] OR "idm"[All Fields]) OR ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "niddm"[All Fields])) AND (("metformin"[MeSH Terms] OR "metformin"[All Fields]) OR ("metformin"[MeSH Terms] OR "metformin"[All Fields]) AND hydrochloride[All Fields]) OR ("biguanides"[MeSH Terms] OR "biguanides"[All Fields] OR ("biguanides"[MeSH Terms] OR "biguanides"[All Fields] OR "biguanide"[All Fields]))) AND (B12[All Fields] OR (B12[All Fields] AND ("deficiency"[Subheading] OR "deficiency"[All Fields])) OR ("vitamin b 12"[MeSH Terms] OR "vitamin b 12"[All Fields] OR ("vitamin"[All Fields] AND "b12"[All Fields]) OR "vitamin b12"[All Fields]) OR ("vitamin b 12 deficiency"[MeSH Terms] OR "vitamin b 12 deficiency"[All Fields] OR ("vitamin"[All Fields] AND "b12"[All Fields] AND "deficiency"[All Fields]) OR "vitamin b12 deficiency"[All Fields]) OR ("vitamin b 12"[MeSH Terms] OR "vitamin b 12"[All Fields] OR "cobalamin"[All Fields]) OR ("vitamin b 12"[MeSH Terms] OR "vitamin b 12"[All Fields] OR "cyanocobalamin"[All Fields]) OR ("vitamin b 12 deficiency"[MeSH Terms] OR "vitamin b 12 deficiency"[All Fields] OR ("cobalamin"[All Fields] AND "deficiency"[All Fields]) OR "cobalamin deficiency"[All Fields]) OR ("vitamin b 12 deficiency"[MeSH Terms] OR "vitamin b 12 deficiency"[All Fields] OR ("cyanocobalamin"[All Fields] AND "deficiency"[All Fields]) OR "cyanocobalamin deficiency"[All Fields]) OR ("hydroxocobalamin"[MeSH Terms] OR "hydroxocobalamin"[All Fields] OR "hydroxycobalamin"[All Fields]) OR ("hydroxocobalamin"[MeSH Terms] OR "hydroxocobalamin"[All Fields]) OR ("hydroxocobalamin"[MeSH Terms] OR "hydroxocobalamin"[All Fields] OR "hydroxycobalamin"[All Fields]) AND ("deficiency"[Subheading] OR "deficiency"[All Fields])) OR ("hydroxocobalamin"[MeSH Terms] OR "hydroxocobalamin"[All Fields])

AND ("deficiency"[Subheading] OR "deficiency"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang])

Free text terms:

(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM)
AND

(metformin OR metformin hydrochloride OR biguanides OR biguanide)
AND

(B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)

There were 71 records identified of which 33 were relevant for inclusion to duplicate analysis.

Database – Research Councils UK, Gateway to Research - this was a search looking at data from the seven research councils in the UK and Medical Research Council (MRC) host institutes and covered all document statuses via <http://gtr.rcuk.ac.uk/>.

Database host – EBSCO

Date of search – June 30th 2013

Years covered – All years

Search terms:

Free text terms:

1. *(B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)* (740)

2. *(metformin OR metformin hydrochloride OR biguanides OR biguanide)* (31)

There were 771 records identified of which none were relevant for inclusion to duplicate analysis and full text review.

The Research Councils included in this gateway are the Medical Research Council, Engineering and Physical Sciences Research Council, Arts and Humanities Research Council, Science and Technology Facilities Council, Biotechnology and Biosciences Research Council, Natural Environmental Research Council and the Economic and Social Research Council.

Database – Science Direct - this was an advanced search covering all document statuses via <http://www.sciencedirect.com/>.

Database host – Elsevier B.V.

Date of search – June 30th 2013

Years covered – All years.

Search terms:

Free text terms:

(metformin OR metformin hydrochloride OR biguanides OR biguanide)

AND

(B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)

There were 204 records were identified. 3 were relevant for inclusion to duplicate analysis.

Database – Scopus - this was an advanced search covering all document statuses via <http://www.scopus.com/home.url>.

Database host – Elsevier B.V.

Date of search – June 30th 2013

Years covered – All years.

Search terms:

Free text terms:

(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM) AND (metformin OR biguanides OR biguanide) AND (B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)

There were 208 results identified. 33 were relevant for inclusion to duplicate analysis and full text review.

Database – Turning Research into Practice (TRIP) - this was an advanced search covering all document statuses. A PICO search was carried out via <http://www.tripdatabase.com/>.

Database host – Trip Database/Lucene

Date of search – June 30th 2013

Years covered – All years.

Search terms:

PICO Search:

Population - *diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM*

Intervention - *metformin OR metformin hydrochloride OR biguanides OR biguanide*

Comparisons - *none*

Outcome - *B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency*

The PICO search gave 11 results identified. 4 were relevant for inclusion to duplicate.

Database – UK Clinical Trials Gateway (UKCTG) - this was an advanced search looking at studies covering all document statuses via <http://www.ukctg.nihr.ac.uk/default.aspx>.

Database host – National Institute for Health Research (NIHR)

Date of search – July 1st 2013

Years covered – 2006 to the date of search

Keywords/Search terms – the search option with the maximum number of hits was used:

- 1 *metformin (keyword) (104)*
 - 2 *biguanide (intervention) (2)*
 - 3 *biguanides (intervention) (1)*
 - 4 *B12 (keyword) (20)*
 - 5 *b12 deficiency (health condition) (71)*
 - 6 *vitamin b12 (intervention) (142)*
 - 7 *vitamin b12 deficiency (health condition) (81)*
 - 8 *cobalamin (keyword/intervention) (0)*
 - 9 *cobalamin deficiency (keyword/intervention) (0)*
 - 10 *cyanocobalamin (keyword/intervention) (0)*
 - 11 *cyanocobalamin deficiency (keyword/intervention) (0)*
 - 12 *hydroxocobalamin (keyword/intervention) (0)*
 - 13 *hydroxocobalamin deficiency (keyword/intervention) (0)*
 - 14 *hydroxycobalamin (keyword/intervention) (0)*
 - 15 *hydroxycobalamin deficiency (keyword/intervention) (0)*
 - 16 *(diabetics OR diabetes OR Type 1 OR Type 2 OR insulin dependent diabetics OR non-insulin dependent diabetics OR insulin dependent diabetes OR non-insulin dependent diabetes OR non insulin dependent diabetics OR non-insulin dependent diabetes OR IDDM OR NIDDM) (keyword), (metformin OR metformin hydrochloride OR biguanides OR biguanide) (intervention), (B12 OR B12 deficiency OR Vitamin B12 OR Vitamin B12 deficiency OR cobalamin OR cyanocobalamin OR cobalamin deficiency OR cyanocobalamin deficiency OR hydroxycobalamin OR hydroxocobalamin OR hydroxycobalamin deficiency OR hydroxocobalamin deficiency)(health condition) (0) – any combination of the individual terms above in search 16 generated no responses in the search.*
-

There were 421 records identified of which 0 were relevant for inclusion to duplicate analysis and full text review.

Its data sources of clinical trials include the Current Controlled Trials (CCT), the US National Institute of Health (NIH, clinicaltrials.gov), International Standard Randomized Controlled Trial Number (ISRCTN), the Database of Uncertainties about the Effects of Treatments (DUETs), Medical Research Council (MRC), Medicines and Healthcare Products Agency (MHRA), NHS Evidence, National Institute for Health Research, PROSPERO, UK Clinical Research Collaboration, UK PubMed Central, World Health Organisation (WHO) and the Association of the British Pharmaceutical Industry (ABPI).

Database – UpToDate - this was a search looking at studies covering all document statuses via <http://www.uptodate.com/home>.

Database host – UpToDate - OvidSP

Date of search – June 30th 2013

Years covered – All years

Search terms:

Free text terms:

DM metformin Vitamin B12 (150)

There were 150 records. 1 was relevant for inclusion to duplicate analysis and full text review.

Database – YourJournals@Ovid - this was an advanced search looking at studies covering all document statuses via <http://ovidsp.ovid.com>

(<https://shibboleth.ovid.com/WAYF/ovid/en?shire=https%3A%2F%2Fshibboleth.ovid.com%2FShibboleth.sso%2FSAML%2FPOST&time=1371559306&target=https%3A%2F%2Fshibboleth.ovid.com%2Fsecure&providerId=https%3A%2F%2Fshibboleth.ovid.com%2Fentity>).

Database host – OvidSP

Date of search – June 30th 2013

Years covered – All years

Free text terms:

*((diabetics or diabetes or Type 1 or Type 2 or insulin dependent diabetics or non-insulin dependent diabetics or insulin dependent diabetes or non-insulin dependent diabetes or non insulin dependent diabetics or non-insulin dependent diabetes or IDDM or NIDDM on metformin or metformin hydrochloride OR biguanides or biguanide) and (B12 or B12 deficiency or Vitamin B12 or Vitamin B12 deficiency or cobalamin or cyanocobalamin or cobalamin deficiency or cyanocobalamin deficiency or hydroxycobalamin or hydroxocobalamin or hydroxycobalamin deficiency or hydroxocobalamin deficiency)).mp.
[mp=ti, ab, tx, ct, hw, ar, ax, bx, cx, ft, fd, ad, jh, jx, fi, ca, pa, pu, pc, it, st, sp]*

Search terms used:

1. 1
2. 2
3. b12
4. b12 deficiency
5. biguanide
6. biguanides
7. cobalamin
8. cobalamin deficiency
9. cyanocobalamin
10. cyanocobalamin deficiency
11. deficiency
12. dependent
13. diabetes
14. diabetics
15. hydroxocobalamin
16. hydroxocobalamin deficiency
17. hydroxycobalamin
18. hydroxycobalamin deficiency
19. iddm
20. insulin
21. insulin dependent diabetes
22. insulin dependent diabetics
23. metformin
24. niddm
25. niddm on metformin
26. non
27. non insulin dependent diabetics
28. non-insulin

29. *non-insulin dependent diabetes*
30. *non-insulin dependent diabetics*
31. *on*
32. *type*
33. *type 1*
34. *type 2*
35. *vitamin*
36. *vitamin b12*
37. *vitamin b12 deficiency*

There were 272 records identified of which none were relevant for inclusion to duplicate analysis and full text review.

Included within this search were all of the following databases in addition to YourJournals@Ovid:

Maternity and Infant Care (1971-2013), International Index to Film Periodicals (1972-2013), FIAF Databases (International Index to Film/TV Periodicals, Periodicals Indexed, Treasures, Affiliates, Publications and Film/TV Documentation Collections, International Index to TV Periodicals (1979-2006), List of Periodicals Indexed, Treasures from the Film Archives, FIAF Affiliates Publications (1966-2010) and Film/TV Documentation Collections.

Database – Zetoc - this was an advanced search covering all document statuses on the General search field which covers both Journal and Conference searches via <http://zetoc.mimas.ac.uk/>.

Database host – Manchester Information and Associated Services (MIMAS), University of Manchester, for the British Library

Date of search – June 17th 2013

Years covered – 1993 to the date of the search.

Search terms: the only Boolean operators allowed are AND and the truncation symbol*.

1. *B12 B12 deficiency metformin** (19)
2. *B12 B12 deficiency biguanide** (2)
3. *B12 B12 deficiency metformin hydrochloride* (0)
4. *cobalamin metformin** (5)
5. *cobalamin metformin hydrochloride* (0)
6. *cobalamin biguanide** (3)
7. *cobalamin deficiency metformin** (4)
8. *cobalamin deficiency metformin hydrochloride* (0)
9. *cobalamin deficiency biguanide** (3)
10. *cyanocobalamin metformin** (1)
11. *cyanocobalamin metformin hydrochloride* (0)
12. *cyanocobalamin biguanide** (0)
13. *cyanocobalamin deficiency metformin** (1)
14. *cyanocobalamin deficiency metformin hydrochloride* (0)
15. *cyanocobalamin deficiency biguanide** (0)
16. *hydroxocobalamin metformin** (0)
17. *hydroxocobalamin metformin hydrochloride* (0)
18. *hydroxocobalamin biguanide** (0)
19. *hydroxocobalamin deficiency metformin** (0)
20. *hydroxocobalamin deficiency metformin hydrochloride* (0)
21. *hydroxocobalamin deficiency biguanide** (0)
22. *hydroxycobalamin metformin** (0)
23. *hydroxycobalamin metformin hydrochloride* (0)
24. *hydroxycobalamin biguanide** (0)
25. *hydroxycobalamin deficiency metformin** (0)
26. *hydroxycobalamin deficiency metformin hydrochloride* (0)
27. *hydroxycobalamin deficiency biguanide** (0)

There were 38 records identified of which 20 were relevant for inclusion to duplicate analysis.

Table A.1 Results summary for the systematic review

<p style="text-align: center;">Cochrane Library</p> <p style="text-align: center;">Records identified - 166 Records excluded (e.g. titles and abstracts) – 161 Records remaining - 5 Duplicates removed - 5 Full text retrieved - 0 Full text excluded - 0 Records included - 0</p>
<p style="text-align: center;">CRD</p> <p style="text-align: center;">Records identified - 1 Records excluded (e.g. titles and abstracts) – 1 Records remaining - 0 Duplicates removed - 0 Full text retrieved - 0 Full text excluded - 0 Records included - 0</p>
<p style="text-align: center;">CINALH</p> <p style="text-align: center;">Records identified - 31 Records excluded (e.g. titles and abstracts) – 8 Records remaining - 23 Duplicates removed - 19 Full text retrieved - 4 Full text excluded - 4 Records included - 0</p>
<p style="text-align: center;">EMBASE</p> <p style="text-align: center;">Records identified – 2056 Records excluded (e.g. titles and abstracts) – 1962 Records remaining - 94 Duplicates removed - 93 Full text retrieved - 1 Full text excluded - 1 Records included - 0</p>
<p style="text-align: center;">Google Scholar</p> <p style="text-align: center;">Records identified - 694 Records excluded (e.g. titles and abstracts) – 668 Records remaining - 26 Duplicates removed - 22 Full text retrieved - 4 Full text excluded - 3 Records included – 1</p>

Index to Thesis

Records identified - 421
Records excluded (e.g. titles and abstracts) – 421
Records remaining - 0
Duplicates removed - 0
Full text retrieved - 0
Full text excluded - 0
Records included – 0

Ingenta Connect

Records identified - 65
Records excluded (e.g. titles and abstracts) – 53
Records remaining - 12
Duplicates removed - 11
Full text retrieved - 1
Full text excluded - 1
Records included - 0

JCR

Records identified - 123
Records excluded (e.g. titles and abstracts) – 77
Records remaining - 46
Duplicates removed - 37
Full text retrieved - 9
Full text excluded – 4
Records included - 5

JSTOR

Records identified - 43
Records excluded (e.g. titles and abstracts) – 40
Records remaining - 3
Duplicates removed - 3
Full text retrieved - 0
Full text excluded - 0
Records included – 0

LILACS

Records identified - 1
Records excluded (e.g. titles and abstracts) – 0
Records remaining - 1
Duplicates removed - 1
Full text retrieved - 0
Full text excluded - 0
Records included - 0

MEDLINE

Records identified - 65
Records excluded (e.g. titles and abstracts) – 31
Records remaining - 34
Duplicates removed - 28
Full text retrieved – 6
Full text excluded - 4
Records included - 2

NIHR CRN

Records identified - 680
Records excluded (e.g. titles and abstracts) – 680
Records remaining - 0
Duplicates removed - 0
Full text retrieved - 0
Full text excluded - 0
Records included - 0

NRR

Records identified - 352
Records excluded (e.g. titles and abstracts) – 352
Records remaining - 0
Duplicates removed - 0
Full text retrieved - 0
Full text excluded - 0
Records included - 0

Neurosciences abstracts

Records identified - 2
Records excluded (e.g. titles and abstracts) – 2
Records remaining - 0
Duplicates removed - 0
Full text retrieved - 0
Full text excluded - 0
Records included - 0

NEXIS

Records identified - 146
Records excluded (e.g. titles and abstracts) – 133
Records remaining - 13
Duplicates removed - 13
Full text retrieved - 0
Full text excluded - 0
Records included - 0

NHS Evidence

Records identified - 145
Records excluded (e.g. titles and abstracts) – 116
Records remaining - 29
Duplicates removed - 24
Full text retrieved - 5
Full text excluded - 3
Records included - 2

Proquest NAHS

Records identified - 107
Records excluded (e.g. titles and abstracts) – 101
Records remaining - 6
Duplicates removed - 4
Full text retrieved - 2
Full text excluded - 1
Records included - 1

Pub Med

Records identified - 71
Records excluded (e.g. titles and abstracts) – 39
Records remaining - 32
Duplicates removed - 17
Full text retrieved - 15
Full text excluded - 7
Records included - 8

RCUK GTR

Records identified - 771
Records excluded (e.g. titles and abstracts) – 771
Records remaining - 0
Duplicates removed - 0
Full text retrieved - 0
Full text excluded - 0
Records included - 0

Science Direct

Records identified - 204
Records excluded (e.g. titles and abstracts) – 201
Records remaining - 3
Duplicates removed - 2
Full text retrieved - 1
Full text excluded - 1
Records included - 0

Scopus

Records identified - 208
Records excluded (e.g. titles and abstracts) – 175
Records remaining - 33
Duplicates removed - 33
Full text retrieved - 0
Full text excluded - 0
Records included - 0

TRIP

Records identified - 11
Records excluded (e.g. titles and abstracts) – 7
Records remaining - 4
Duplicates removed - 4
Full text retrieved - 0
Full text excluded - 0
Records included - 0

UKCTG

Records identified - 421
Records excluded (e.g. titles and abstracts) – 421
Records remaining - 0
Duplicates removed - 0
Full text retrieved - 0
Full text excluded - 0
Records included - 0

UpToDate

Records identified - 150
Records excluded (e.g. titles and abstracts) – 149
Records remaining - 1
Duplicates removed - 0
Full text retrieved - 1
Full text excluded - 1
Records included - 0

YJ@Ovid

Records identified - 272
Records excluded (e.g. titles and abstracts) – 272
Records remaining - 0
Duplicates removed - 0
Full text retrieved - 0
Full text excluded - 0
Records included - 0

Zetoc

Records identified - 38
Records excluded (e.g. titles and abstracts) – 18
Records remaining - 20
Duplicates removed - 14
Full text retrieved - 6
Full text excluded - 2
Records included - 4

Reference Lists

Records identified - 13
Records excluded (e.g. titles and abstracts) – 6
Records remaining - 7
Duplicates removed - 0
Full text retrieved - 7
Full text excluded – 3
Unobtainable - 1

Table A.2 Summary- Database searches

<i>Database</i>	<i>Host</i>	<i>Search Date</i>	<i>Search Period</i>	<i>Records identified</i>	<i>Records excluded (e.g. titles and abstracts)</i>	<i>Duplicates removed</i>	<i>Full text retrieved</i>	<i>Full text excluded</i>	<i>Records included</i>
Cochrane Library	Cochrane	30.6.13	All	166	161	5	0	0	0
CRD	CRD	29.6.13	All	1	1	0	0	0	0
CINALH	EBSCO	29.6.13	1981-2013	31	8	19	4	4	0
EMBASE	Elsevier	29.6.13	1974-2013	2056	1962	93	1	1	0
Google scholar	Google	17.6.13	All	694	668	22	4	3	1
Index to Thesis	Proquest	30.6.13	All	421	421	0	0	0	0
Ingenta connect	Publishing Technology	30.6.13	All	65	53	11	1	1	0
JCR	SciELO	30.6.13	All	123	77	37	9	4	5
JSTOR	EBSCO	30.6.13	All	43	40	3	0	0	0
LILACS	ISIS	30.6.13	1986-2013	1	0	1	0	0	0
MEDLINE	EBSCO	30.6.13	1950-2013	65	31	28	6	4	2
NIHR CRN	NIHR	16.6.13	2010-2013	680	680	0	0	0	0

<i>Database</i>	<i>Host</i>	<i>Search Date</i>	<i>Search Period</i>	<i>Records identified</i>	<i>Records excluded (e.g. titles and abstracts)</i>	<i>Duplicates removed</i>	<i>Full text retrieved</i>	<i>Full text excluded</i>	<i>Records included</i>
NRR	NIHR	27.6.13	1990-2007	352	352	0	0	0	0
Neurosciences abstracts	Proquest	30.6.13	All	2	2	0	0	0	0
NEXIS	LexisNexis	30.6.13	1950-2013	146	133	13	0	0	0
NHS Evidence	NICE	30.6.13	All	145	116	24	5	3	2
Proquest NAHS	Proquest	30.6.13	All	107	101	4	2	1	1
Pub Med	NCBI NLM	30.6.13	All	71	39	17	15	7	8
RCUK GTR	EBSCO	30.6.13	All	771	771	0	0	0	0
Science Direct	Elsevier BV	30.6.13	All	204	201	2	1	1	0
Scopus	Elsevier BV	30.6.13	All	208	175	33	0	0	0
TRIP	TRIP - Lucene	30.6.13	All	11	7	4	0	0	0
UKCTG	NIHR	1.7.13	2006-2013	421	421	0	0	0	0
UpToDate	OvidSP	30.6.13	All	150	149	0	1	1	0
YJ@Ovid	OvidSP	30.6.13	All	272	272	0	0	0	0

<i>Database</i>	<i>Host</i>	<i>Search Date</i>	<i>Search Period</i>	<i>Records identified</i>	<i>Records excluded (e.g. titles and abstracts)</i>	<i>Duplicates removed</i>	<i>Full text retrieved</i>	<i>Full text excluded</i>	<i>Records included</i>
Zetoc	MIMAS	30.6.13	1993-2013	38	18	14	6	2	4

Table A.3 Summary table totals-Database searches

<i>Database</i>	<i>Host</i>	<i>Search Date</i>	<i>Search Period</i>	<i>Records identified</i>	<i>Records excluded (e.g. titles and abstracts)</i>	<i>Duplicates removed</i>	<i>Full text retrieved</i>	<i>Full text excluded</i>	<i>Records included</i>
26 different databases	16 different database hosts	From the 16.6.13 to 1.7.13	1950 to 2013 where the years have been specified	7257	6865	330	62	36 ¹	26

¹Unobtainable – one study was unobtainable and excluded.

Appendix B: Excluded Studies

Table B.1 Characteristics of all excluded studies upon full-text review – with the major reference studies referred to.

Study	Reason for exclusion	Study	Reason for exclusion
Adams 1983[1]	RCT – looking at absorption of B ₁₂ and not B ₁₂ levels	Langan 2011[2]	Not a study - review article on B ₁₂ only
Andres 2002[3]	Not a study - Editorial	Lev 2007[4]	Not a study – letter of correspondence
Andres 2004[5]	Not a study – letter of correspondence	Xu 2013[6]	Preliminary study – awaiting an upcoming clinical trial
Andres 2007[7]	Not a study – correspondence	Lin 2007[8]	Case report – invalid as a relevant study for the review
Bailey 1996[9]	Not a study – review article	Liu 2006[10]	Case report – invalid as a relevant study for the review
Bell 2010[11]	Case report – invalid as a relevant study for the review	Mahajan 2010[12]	Not a study – review article
Bloomgarden 2007[13]	Not a study – review article	Mazopakis 2012[14]	Not a study – review article
Buvat 2004[15]	Not a study – letter of correspondence	McCulloch 2013[16]	Not a study - review article
Callaghan 1980[17]	Case report – invalid as a relevant study for the review	Mohamed 2004[18]	Case report – invalid as a relevant study for the review

Study	Reason for exclusion	Study	Reason for exclusion
Caspary 1977[19]	Clinical Trial – looking at absorption of B ₁₂ and not B ₁₂ levels	O’Connell 2011[20]	Not a study - review <i>article</i> – not specific B ₁₂ /metformin
Defonseka 2008[21]	Case report – invalid as a relevant study for the review	Parikh 2010[22]	Not a study – review article
Diggle 2012[23]	Not a study – response to a review	Reactions Weekly 2010[24]	Case report – invalid as a relevant study for the review
Drug and Therapeutics bulletin	Not a study - review article	Stowers 1971[26]	Study on phenformin
Fujita 2003[27]	Case report – invalid as a relevant study for the review	Tomkin 1973[28]	Study on phenformin
Gilligan 2002[29]	Case report – invalid as a relevant study for the review	Tsaglis 1999[30]	Conference abstract
Holt 2012[31]	Not a study - review article	Varughese 2007[32]	Not a study - response to a review article
Home 2012[33]	Not a study – review article	Varughese 2007[34]	Case report – invalid as a relevant study for the review
Kumethekar 2012[35]	Case report – invalid as a relevant study for the review		

Table B.2 Characteristics of excluded studies – Case reports (Summary table)

Study	Main topic and relevant findings
Bell 2010[11]	Link between vitamin B ₁₂ deficiency and cognitive and neurological symptoms with improvement in response to vitamin B ₁₂ supplementation and stopping metformin.
Callaghan 1980[17]	Link between vitamin B ₁₂ deficiency and megaloblastic anaemia in a metformin treated diabetic which resolved upon vitamin B ₁₂ supplementation, whilst continuing metformin
Defonseka 2008[21]	Link between vitamin B ₁₂ deficiency and peripheral neuropathy with resolution upon initiating vitamin B ₁₂ supplementation
Fujita 2003[27]	Link between vitamin B ₁₂ deficiency post gastrectomy which resolved upon stopping metformin and initiating vitamin B ₁₂ supplementation
Gilligan 2002[29]	Link between vitamin B ₁₂ deficiency and poor absorption as measured by the Schilling test, which returned to normal upon stopping the metformin and receiving vitamin B ₁₂ supplementation
Kumethekar 2012[35]	Link between vitamin B ₁₂ deficiency and peripheral neuropathy with resolution upon stopping metformin and initiating vitamin B ₁₂ supplementation
Lin 2007[8]	Link between vitamin B ₁₂ deficiency and Hcy with particular reference to the methylenetetrahydrofolate reductase (<i>MTHFR</i>) gene. Possible association with venous thrombosis
Liu 2006[20]	Link between vitamin B ₁₂ deficiency and cognitive and neurological symptoms with improvement in response to vitamin B ₁₂ supplementation and stopping metformin.
Mohamed 2004[18]	Link between vitamin B ₁₂ deficiency and myelopathy with minimal clinical response or elevation in vitamin B ₁₂ levels whilst metformin was continued
Reactions weekly 2010[24]	Link between vitamin B ₁₂ deficiency and myelitis
Varughese 2007	Link between vitamin B ₁₂ deficiency and peripheral neuropathy without resolution upon continuing metformin and initiating vitamin B ₁₂ supplementation

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