Diabetes and migrants
The role of vitamin D

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Declaration

Diabetes and migrants
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By Ortillia Klinkenbijl
The Netherlands

Declaration:
The thesis Diabetes and migrants, the role of vitamin D is my own work. Where other people's work has been used (either from a printed source, internet or any other source) this has been carefully acknowledged and referenced in accordance with departmental requirements.

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Abbreviations

ADL	Activity Daily Living
BMI	Body Mass Index
HOMA-IR	Homeostasis Model Assessment- Insulin Resistance
IGT	Impaired Glucose Tolerance
IU	International Unit
MD	Medical Doctor
NHANES	National Health and Nutrition Examination Survey
NHG	Nederlands Huisartsen Genootschap (Dutch College of General Practitioners)
OGTT	Oral Glucose Tolerance Test
PCO	Polycystic Ovarian Syndrome
PTH	Parathyroid Hormone
RCT	Randomised Control Trial
RDI	Reference Daily Intake
RIVM	Rijksinstituut voor Volksgezondheid en Milieuhygiëne (Dutch National Institute for Public Health and Environmental Hygiene)
RR	Relative risk
T2DM	Type 2 Diabetes Mellitus
TURDEP	Turkish Diabetes Epidemiology Study
UK	United Kingdom
USA	United States of America
UVB	Ultraviolet B
VDR	Vitamin D receptor
VWS	Ministry of Health, Welfare and Sport (Ministerie van Volksgezondheid Welzijn en Sport)
WHO	World Health Organisation

Abstract

Migrant populations in western societies like The Netherlands have a higher prevalence of diabetes compared to the native population (Cornelisse-Vermaat et al. 2007).

The overall objective of this thesis is to find support for the hypothesis that vitamin D deficiency plays a contributing role in the high prevalence of diabetes among migrant populations in The Netherlands in order to outline possible recommendations regarding vitamin D supplementation and lifestyle-measures. In this thesis the term 'diabetes' refers to both diabetes and pre-stage diabetes unless a distinction is made.

The specific objectives of the thesis are, to:

1. appraise the relation between diabetes and vitamin D deficiency
2. find explanations for the possible existence of *interracial variation* for the relation between diabetes and vitamin D deficiency
3. find possible influences of migration and obesity as a possible confounding factor on the relation between diabetes and vitamin D deficiency
4. find support for the hypothesis that treatment of vitamin D deficiency contributes to the prevention of diabetes (either for migrants or non-migrants), and
5. find support for the hypothesis that treatment of vitamin D deficiency contributes to the management of diabetes.

Methods: Data were obtained from a literature search on Pub-Med, Embase, The Cochrane library and Picarta. Key words: diabetes (and words linked to a pre-stage diabetes: insulin resistance, glucose tolerance) vitamin D (deficiency), (im)migrants, prevalence. Forty three studies met the inclusion criteria.

Conclusions on the specific objectives:

- Studies among migrant groups (South-East Asians) consistently demonstrate the association between vitamin D deficiency and diabetes after adjustment for BMI. But studies conducted on the same ethnic groups in their native countries do not confirm a predominant relation. This leads to the conclusion that there is insufficient evidence of the existence of interracial variation
- The research results reviewed have not consistently confirmed the role of vitamin D supplementation neither in the prevention nor in the management of diabetes in non-migrant populations. Only few studies did find positive results of vitamin D supplementation on diabetes. There is a higher success rate in treatment protocols where the duration of vitamin D therapy is longer than 3 months and the dose is at least 1331IU per day.

Overall conclusion:

- Although it is a challenge to compare the research results that describe the link between diabetes and vitamin D deficiency – the study subjects differ in age, gender, nationality and the research methodology – we found support for the hypothesis
- There is little evidence that vitamin D supplementation is more effective to prevent diabetes than to improve the values of glucose metabolism in diabetic patients. This

emphasises the importance of early treatment (pre-stage diabetes) and prevention strategies

* Vitamin D supplementation of migrants in The Netherlands with vitamin D deficiency could have the following benefits on the management of diabetes:
    - direct effect on glucose regulation and insulin resistance
    - decrease in obesity with an indirect effect on diabetes (since obesity is a risk factor for diabetes)
    - increased muscle performance and therefore increased activity levels and weight loss. Greater outdoor activity results in higher vitamin d levels due to greater exposure to sunlight.
* Lifestyle advice should include recommendation on weight loss, dietary advice, physical activity and sunlight exposure.

The efficacy of vitamin D supplementation in the prevention and management of diabetes needs to be confirmed in further studies. The supplementation protocols should opt for a dosage of at least 1331IU and a treatment period of at least 3 months.

Key words: (type 2) diabetes, vitamin D (deficiency), migrants, obesity, migration
Total word count: 11.030

1. Background information on migrants in The Netherlands

Paragraph 1.1 describes the background of different groups of migrants in The Netherlands. In paragraph 1.2 information is provided about the socio-economic and health situation of this group.

1.1 History and origin of different groups of migrants in The Netherlands

"As the result of migration, The Netherlands has a sizeable minority of non-indigenous peoples" (Donner 2007). In 2011 a total of 16.3% of the Dutch population consisted of non-ethnic Dutch residents. Table 1 provides the figures.

Table 1. *Percentage of various groups of migrants in The Netherlands*

Number	Percentage	Ethnic Group
13,928,780	81%	Ethnic Dutch
387,967	2.33%	Turkish
380,047	2.28%	Indonesian
355,883	2.13%	Moroccans
344,734	2.06%	Surinam
215,000	1.29%	Indians
1,363,807	8.18%	Others
16,655,799	100%	Total
table of migrants, CBS Statline - Population; history. Statistics Netherlands. as of 2011)		

In recent history the main flows of migration were the following:

* In the 1940's people from the Indonesian Republic and The Maluku, both former Dutch colonies, sought residency in The Netherlands
* In the 1960s and 1970s people from Southern Europe (i.e. Italy, Portugal, Spain), and Turkey and Morocco came to The Netherlands as migrant workers (nowadays non-native Turkish and Moroccan people belong to the major ethnic minority groups in Europe)
* In 1975 almost half of the population of the former Dutch colony Surinam migrated to The Netherlands (Bindraban et al. 2008) – 80% of these migrants are Hindustani or African
* In the 1990s there was an increasing number of asylum seekers who came to The Netherlands as political or war refugees, originating from countries like Iraq,

Afghanistan, Iran, Chile, Argentine and African countries (source: Wikipedia (http://en.wikipedia.org/wiki/Demographics_of_the_Netherlands 2011)).

1.2 Health and socio-economic situation of migrants in The Netherlands

The majority of migrants live in urban areas in The Netherlands as well as in other western societies (Ujcic-Voortman et al. 2009). Compared to the native Dutch migrant populations in The Netherlands have a:

a) lower educational level
b) lower occupational level
c) lower household income
d) higher unemployment rates
e) underprivileged social backgrounds.

Any of these factors contributes to higher rate of mortality and morbidity (Gerritsen et al. 2009) (Reijneveld 1998). Avoidable[1] mortality is higher among migrant populations with a relative risk (RR) of 1.13. Migrants are subject to higher death rates due to several chronic conditions including diabetes (RR > 1.70) and infectious diseases (RR > 3.00) (Stirbu et al. 2006).

Adjustment to the western lifestyle is characterised by an increase in cigarette smoking, physical inactivity and being obese. Table 2 shows the prevalence of behavioural risk factors among first and second generation Turkish and Moroccan men and women in The Netherlands compared with native Dutch (Hosper et al. 2007).

[1] Definition of avoidable mortality: potentially avoidable mortality refers to premature deaths (persons aged under 75 years) that, theoretically could have been avoided given current understanding of causation and available disease prevention and health care (Tobias et al. 2001).

Table 2: *Prevalence of behavioural risk factors of Turkish and Moroccan migrants in The Netherlands compared with the native Dutch population (numbers as percentages).* ***Source:*** *Hosper et al. European J Epidemiology (Hosper et.al. 2007)*

	Turkish women n = 261		**Moroccan women n = 176**		**Dutch women[a] n=1,276**
	First generation	**Second generation**	**First generation**	**Second generation**	
Smoking	35.1	**44.4**	*2.2*	*3.2*	32.8
Alcohol intake	18.7	21.9	*5.9*	*3.4*	**86.3**
Insufficiently physically active[b]	**66.8**	58.0	**74.2**	**76.2**	53.0
Overweight	**38.9**	**25.9**	**38.9**	**26.5**	19.0
	Turkish men n = 244		**Moroccan men n = 115**		**Dutch men[a] n = 1,199**
	First generation	**Second generation**	**First generation**	**Second Generation**	
Smoking	**54.9**	**45.6**	22.0	34.8	36.2
Alcohol intake	35.0	38.9	*19.6*	*23.4*	**92.6**
Insufficiently physically active[b]	56.4	56.4	57.1	54.6	51.2
Overweight	**34.7**	**43.2**	*9.6*	22.5	21.8

All percentages were weighted for age.
[a] Data for the ethnic Dutch population were available from Statistics Netherlands: POLS-survey 2003/2004.
[b] Not meeting the guidelines of at least 30 min of moderate physical activity during 5 or more days in a week
c Marked high figures are indicated in fat, in italics the marked low figures.

2. Problem statement, justification, objectives and methodology

This chapter contains the paragraphs on the problem of global increase in diabetes prevalence and specifically focuses on migrants in The Netherlands (2.1), the justification for the subject of this thesis (2.2), the objectives of this thesis (2.3) and the methods used (2.4).

2.1 Problem statement

Sub-paragraph 2.1.1 outlines the problem of the global increase in diabetes prevalence, whereas sub-paragraph 2.1.2 focuses on this trend among Dutch ethnic minorities. Background information on vitamin D is provided in 2.1.3 and sub-paragraph 2.1.4 highlights vitamin D deficiency among Dutch ethnic minorities.

2.1.1 Diabetes – a global problem

Diabetes worldwide has reached epidemic proportions. According to the WHO:

* developing countries contribute the most to this increase
* an estimated 285 million people have diabetes – this is 6.4% of the world population
* this number is expected to grow to 438 million by 2030
* 70% of the diabetics live in low and middle income countries (WHO 2011b) (information on the exact prevalence figures id provides in annex 2).

A transition from rural to urban areas implies a decrease in physical activity and thereby leads to higher levels of obesity. Obesity is a risk factor to the development of diabetes. Research indicates that 80% of diabetes can be prevented by changes in lifestyle such as increasing physical activity and a healthier diet (Bloomgarden 1998).

2.1.2 Diabetes among ethnic minorities in The Netherlands

The prevalence of diabetes among ethnic minorities in The Netherlands (Indian, Surinam, Turks, Moroccans) is 3 - 6 times higher compared to the native Dutch population (M.C.Poortvliet 2011). This situation is not specific to The Netherlands. Similar high levels of diabetes have been identified in Turkish and Lebanese migrants in Scandinavian countries (Kristensen et al. 2007;Wandell et al. 2008) and in Arabs in the US (Jaber et al. 2003). Table 3 provides more details.

Table 3. *Diabetes prevalence figures for major groups of migrants in The Netherlands compared to native Dutch – no information on Indonesian migrants.*

Population group	**Diabetes prevalence in %**
Turkish migrants	9.9 - 12.3%
Moroccan migrants	8.0 - 12.4%
Hindustani migrants	25.6%
Surinam migrants	12.7%
Native Dutch	3.0 - 6.8%
Sources: (Dijkshoorn et al. 2003), (Kriegsman D 2003), (Ujcic-Voortman et.al. 2009), (Bindraban et.al. 2008)	

The 2007 RIVM report on diabetes (RIVM = Rijksinstituut voor Volksgezondheid en Milieuhygiëne = Dutch National Institute for Public Health and Environmental Hygiene) provides the following possible explanations for the higher prevalence of diabetes among migrants in The Netherlands and other western societies (RIVM report, 2007):

* transition from the un-industrialized to the industrialized world can be associated with a change in activity patterns to a life style with less physical activity
* lower socio economic status and a change from rural to more urban environment might influence dietary habits. This can contribute to an increase in the prevalence of obesity.

The rate of obesity solely does not explain the ethnic differences in diabetes prevalence. In the study by Ujcic et al. in 2009, 70% of the Turkish and Moroccan diabetics are obese (BMI (weight/length^2) > 30kg/m^2) compared to 48% obesity among native Dutch diabetics after correction for differences in socio economic factors. Other endogenous factors or environmental factors may be responsible for the higher frequency of diabetes among Moroccan and Turkish migrants (Dijkshoorn, 2003) (ujcic et al.2009). In the following paragraph the endogen factor vitamin D will be introduced as a possible determinant.

2.1.3 Vitamin D

"Worldwide displacement from the natural outdoor environment of human being to an indoor sedentary lifestyle along with the lack of sunlight had resulted in a global pandemic of vitamin D deficiency." (Mascitelli et al. 2010).

"It is estimated that 1 billion people worldwide are vitamin D deficient or insufficient." (Holick 2010).

Marked high prevalence levels of vitamin D deficiency (< 25nmol/l) and insufficiency (25 to 49.9nmol/l) are found among:

* African Americans in the USA
* non-western migrants in European countries
* the population of Saudi-Arabia, Iran and Tunisia due to cultural/religious habits to completely cover the skin
* Indian, Pakistani, Afghan and Bangladeshi people, especially among women, due to a pigmented skin, skin-covering clothing style and sun-avoiding behaviour
* Moroccan and Tunisian women, due to the habit of veiling (Egan et al. 2008) (Arabi et al. 2010;Lips 2010a).

Marked low prevalence levels of vitamin D deficiency and insufficiency are found among populations in (South-)East Asian countries such as Malaysia and Japan, due to dietary intake of fish and a less pigmented skin (Lips 2010b).

Three forms of vitamin D can be identified:

* vitamin D2 (Ergocalciferol) available in mushrooms
* vitamin D3 (Cholecalciferol) available in dairy products and added to margarine (300IU (International Unit) per 100 gram)[2]
* another form of vitamin D3 which is produced in the skin under influence of ultraviolet light (sunlight) (Bowerman 1 A.D.).

The most important source of vitamin D is sunlight (UV exposure). Being outside with uncovered hands and face during 15 minutes provides 100-200IU of vitamin D per day which is half of the 400IU RDI (Reference Daily Intake) (Lips 2010b).

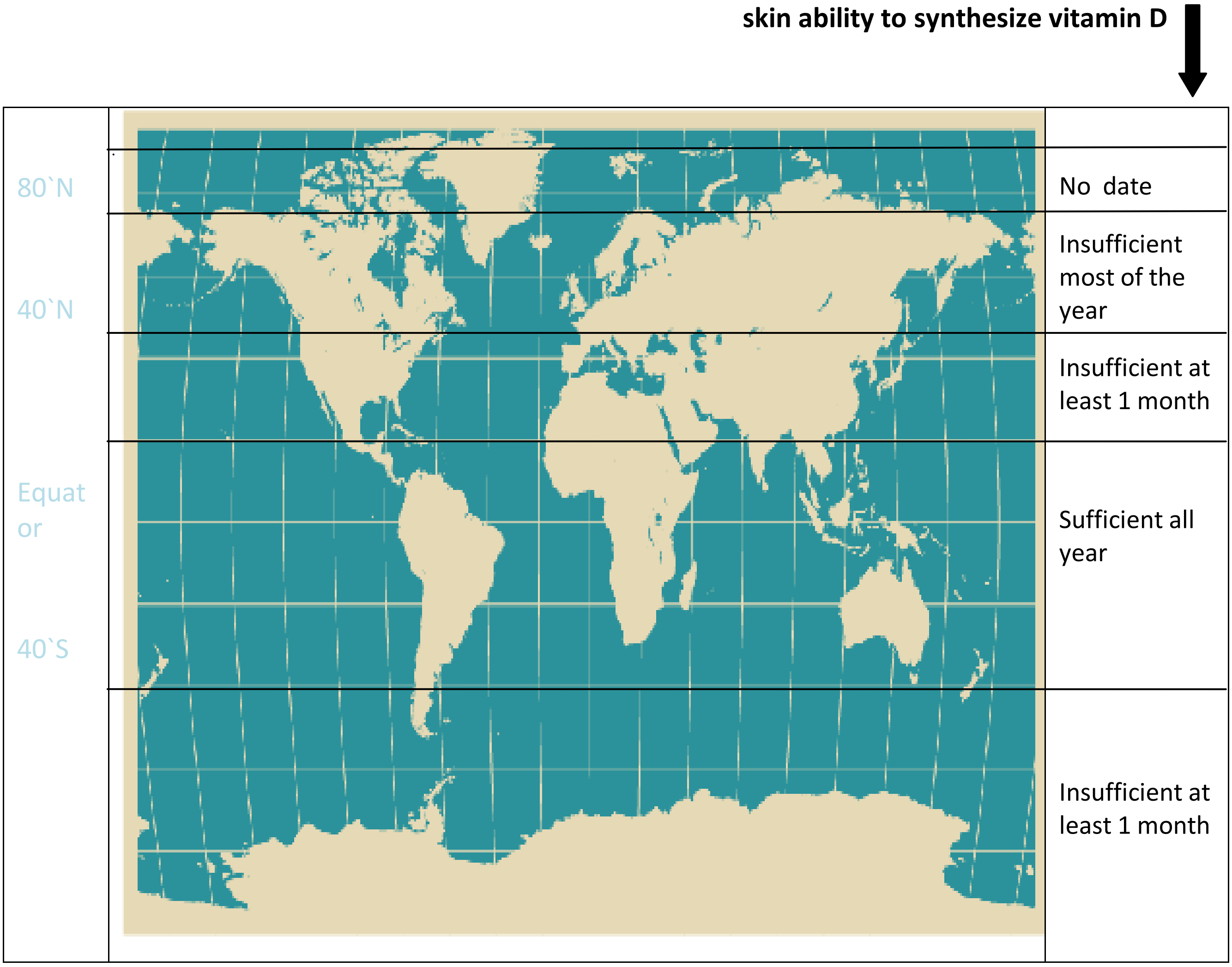
The percentage of ultraviolet light in sunlight varies with latitude, season, and time of the day, ozone amount, cloud amount, aerosol and reflectivity of the surface. The actual exposure to ultraviolet light is influenced by skin pigmentation, the use of sunscreen and clothing.

> *"Skin pigmentation shows large differences among continental populations. This can be traced back mainly because of the influence of natural selection which has shaped the distribution of pigmentation according to the latitudinal gradient."* (Lips 2010b)

In general dark-skinned migrants who have moved from the equator to the North or South are at higher risk of developing a vitamin D deficiency because a more pigmented skin absorbs less UVB radiation (Cavalier 2011).

[2] 1 IU is the biological equivalent of 0.025 µg cholecalciferol/ergocalciferol (Washington 1997)

Figure 1. *Geographical latitude related to the ability of the skin to synthesize vitamin* D *as estimated and adjusted from information provided in an article by Tavera-Mendoza and White (Arabi et.al. 2010)*



A lower presence of sunlight increases the need of fatty fish, vitamin D fortified food, vitamin D supplements (Lips 2010b), fortified margarine and on a lesser scale eggs and avocado. The consumption of vitamin D through the diet varies between countries worldwide. This is depends on the availability of types of food and food regulations. Mandatory fortification of staple food like milk and margarine is a national policy in the United States and Canada. In The Netherlands, the United kingdom, Ireland, Scotland and Australia there is no required fortification of foods, but there is optional fortification on a number of foods like margarine and breakfast cereals. Countries with limited or restricted use of fortified food are mostly European and the majority of developing countries. Countries like Japan and Norway have relatively high vitamin D intake through their high fish consumption (Calvo et al. 2005).

Table 4 provides the definition for various levels of vitamin D and related physical complaints. Annex 3 provides a Radiograph of a patient with osteomalacia as a result of severe vitamin deficiency.

Table 4. *definition of vitamin D status (Zittermann 2010)*

Vitamin D status/ definition	**25(OH)D concentration**	**Biochemical consequences or physical complaints**
Deficiency	< 25nmol/L	Rickets, osteomalacia, severe myopathy, severe hyperparathyroidism, calcium malabsorption, vascular calcification, high infection rates, low circulating calcitriol concentrations
Insufficiciency	25 – 49.9nmol/L	Osteoporosis, impaired muscle function, elevated PTH concentrations
Hypovitaminosis	50 – 99.9nmol/L	Reduced bodily store of vitamin D, slightly elevated PTH concentrations
Adequacy	100 – 500nmol/L	Adequate vitamin D stores, no disturbances in vitamin D dependent functions
Intoxication	> 500nmol/L	Calcium hyperabsorption, hypercalcemia, vascular calcification

2.1.4 Vitamin D deficiency among ethnic minorities in The Netherlands

Clinical vitamin D deficiency, manifested as rickets, was common in western countries in the early 20th century. Exposure to sunshine and the consumption of cod liver oil made it disappear. Because of the use of macrobiotic diets and the arrival of non-western immigrants after 1970 vitamin D deficiency has appeared again (Grootjans-Geerts 2001). Migrant women who wear a headscarf and mainly stay indoors are prone to develop a vitamin D deficiency. The prevalence of vitamin D deficiency among Turkish migrants is 55% which is higher in comparison to the prevalence among native Dutch which is 5% (van der Meer 2008) (Grootjans-Geerts 2001). Table 5 shows the outcomes of researches on vitamin D deficiency (25(OH)D < 25nmol/l) among migrants in The Netherlands.

Table 5. *Vitamin D deficiency prevalence among various groups of migrants in The Netherlands*

Population group	**Vitamin D deficiency prevalence in %**
Turkish migrants	41.3%
Moroccan migrants	55%
Hindustani migrants	51.4%
Surinam migrants (Creole)	45.3%
Native Dutch	5 - 6%

References: (van der Meer 2008), (Grootjans-Geerts 2001), (Wielders, van Dormael, Eskes, & Duk 2006)

2.2 Justification: the role of vitamin D

In vitro and observational studies show a link between vitamin D deficiency and diabetes, and its pre-stage symptoms insulin resistance, decrease in insulin secretion and glucose intolerance. Still studies are few and differ in set up, study population and outcome (Cavalier et al. 2007) (Chiu 2004;Kulie et al. 2009;Kumar et al. 1994). Epidemiological facts that diabetes is more common in less sunny regions again supports the hypothesis that vitamin D influences the development of diabetes (Arbor clinical Nutrition Updates 2008) (Chiu 2004).

Several mechanisms support this hypothesis – vitamin D:

* stimulates insulin secretion
* stimulates insulin release
* stimulates insulin receptor expression, and
* has a possible impact on intra-cellular insulin actions via calcium regulation
* has an antioxidant function (diabetes being a state of chronic inflammation).

Another possible influence is the genetic variation (ethnicity) in the vitamin D receptor (VDR) because different polymorphisms seem to have a varying influence on the development of diabetes (Arbor clinical Nutrition Updates 2008).

Research findings show that there is a link between obesity and vitamin D deficiency, this is partly because of a biochemical explanation that vitamin D is a fat soluble hormone which deposits in adipose tissue (Hypponen et al. 2008) (van der Meer 2008) (Wortsman et al. 2000). Other research, referring to lifestyle factors points out a stimulating effect of vitamin D on muscular performance leading to greater activity and weight loss (Sabherwal et al. 2010).

The link between obesity and diabetes is explained in sub-paragraph 2.1.1. With the above findings of a relation between obesity and vitamin D deficiency obesity could be an important confounding (risk) factor. Chapter 4 will elaborate this assumption.

2.3 Objectives

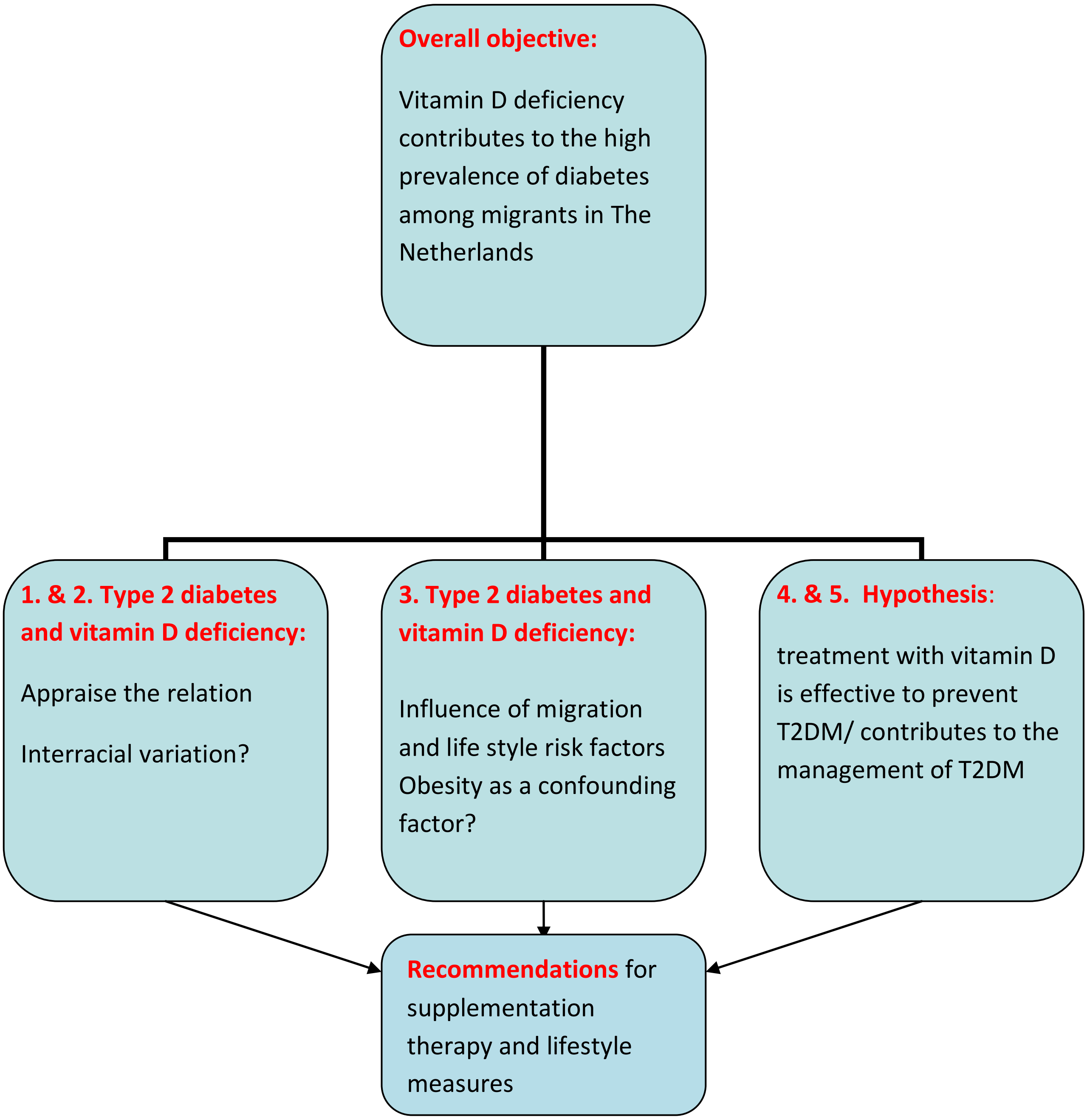
As part of a global problem, the high prevalence of (type 2) diabetes among various migrant groups in The Netherlands (as is explained in paragraph 2.1.2) is a major health concern leading to a deterioration of the health-situation resulting in higher morbidity and mortality rates. Research shows that the age of onset of diabetes is one to two decades earlier in Turks and Moroccans as compared to the native Dutch population. This early onset of diabetes increases the lifetime risk of complications. In general migrant women have a RR of 3.99 (confidence interval: 3.43 - 4.65) of death from diabetes and migrant man a RR of 3.10 (confidence interval: 2.73 - 3.53) (Stirbu et.al. 2006).

The overall objective of this thesis is to find support for the hypothesis that vitamin D deficiency plays a contributing role in the high prevalence of diabetes among migrant populations in The Netherlands in order to outline possible recommendations regarding vitamin D supplementation and lifestyle-measures to migrant populations in The Netherlands.

The specific objectives of the thesis are, to:

* appraise the relation between diabetes and vitamin D deficiency
* find possible existence of *interracial variation* for the relation between diabetes and vitamin D deficiency
* find possible influences of migration and obesity as a possible confounding factor on the relation between diabetes and vitamin D deficiency for migrants in The Netherlands
* find support for the hypothesis that treatment of vitamin D deficiency is effective to prevent diabetes (either for migrants or non-migrants), and
* find support for the hypothesis that treatment of vitamin D deficiency contributes to the management of diabetes.

Figure 2. *Objectives of the thesis*



2.4 Methods / data collection

To find support for the hypothesis that vitamin D deficiency plays a contributing role in the high prevalence of diabetes among migrant populations in The Netherlands. The existing literature is reviewed evaluating the relationship between vitamin D and diabetes. Review studies conducted on migrant and non-migrant populations with various ethnicities and from various areas over the world were included in this literature review.
Used databases include:

* PubMed
* Embase
* Cochrane, and
* Picarta.

With search profile: diabetes mellitus (MeSH terms) OR diabetes (tiab) OR diabetic (tiab) OR insulin resistance (Mesh terms) OR glucose tolerance (tiab) AND Vitamin D deficiency (Mesh) OR vitamin D (tiab) OR Vitamin D (tiab) AND deficient (tiab) combining with the terms: The Netherlands, developing countries, obesity, risk factors.

Information is extracted on:

* geographical location
* age and gender of the study population
* prevalence of diabetes
* mean vitamin D if available.

In case of correlations between vitamin D and:

* diabetes
* pre-diabetes
* glucose metabolism, and/or
* developing diabetes.

The following factors are taken into account before conclusions were drawn:

* socio economic background
* lifestyle
* influence of migration
* BMI, and
* other possible influencing aspects.

The following inclusion criteria were applied in the review:

1. cross-sectional studies, case-control studies (retrospective- prospective case control studies), cohort studies describing a correlation between vitamin D deficiency and diabetes, or
2. intervention studies – for instance randomised controlled trials (RCT’s) – on glucose, insulin resistance or other areas of glucose metabolism after treatment of vitamin D deficiency with supplements.

Studies concerning the following study subjects were excluded from the review:

* pregnant women
* participants with type 1 diabetes
* participant younger than 18 years
* participants on dialysis
* participants with hyper parathyroid disease
* participants with Crohns disease
* participants with polycystic ovarian syndrome (PCO), or
* research conducted on animals.

In addition a separate search is conducted on the prevalence of diabetes, vitamin D deficiency and obesity among the major migrant groups in The Netherlands. The related search profiles include the terms migrants, OR migration, OR diabetes prevalence, OR vitamin D deficiency. These terms were combined with specific subgroups like: Moroccan, OR Turkish, OR Surinam, OR Indian, OR Indonesian.

The prevalence of diabetes and vitamin D deficiency for the major migrant groups in The Netherlands is compared with the situation in the respective countries of origin. Further attention is given to changes in difference in prevalence figures in case these appear after migration for diabetes, vitamin D deficiency and obesity to value BMI as a confounding factor.

Limitations:

* No research has yet been conducted on the relation between diabetes and vitamin D deficiency among migrant groups in The Netherlands. The studies that have been evaluated for this research are studies conducted on migrants in various countries worldwide
* Limited information is available on prevalence figures of diabetes, vitamin D deficiency and obesity in the respective countries of origin of the major migrant groups in The Netherlands.

Intervention studies conducted on migrant and non-migrant populations are appraised and compared in terms of dose of the medication and duration of the treatment and the outcome of study results.

A positive outcome of an intervention study is defined as:

* an improvement in insulin sensitivity
* an improvement in insulin resistance
* an improvement in insulin levels
* an improved glucose tolerance
* an improvement of first phase insulin secretion
* a decrease in HbA1c.

3. Study results

Forty three studies met the inclusion criteria mentioned in 2.4 – the major findings of the review of these studies are presented in this chapter. An overview of all studies/researches and their subjects plus characteristics of the methods used are presented in the annexes 4 - 7.

Paragraph 3.1 describes the results from studies on the relation between diabetes and vitamin D conducted on non-migrants with a distinction in region of origin to distinguish racial variation. Paragraph 3.2 focuses on the influence of migration and obesity as a confounding factor on this relation. Paragraph 3.3 focuses on vitamin D supplementation studies with a distinction between migrants and non-migrants.

3.1 Studies describing the relation between vitamin D and diabetes (non-migrants)

The findings from cross-sectional studies conducted on native *Europeans* are presented below:

* Among 799 *Italians* vitamin D levels where significantly lower among diabetic patients than controls without diabetes, in this same group of diabetic patients the BMI was significantly higher (Isaia et al. 2001)
* Another study in *Italy* by Muscogiuri et al. did not demonstrate a significant correlation between 25(OH)D and insulin sensitivity in a group of non-diabetics when corrected for BMI. They did demonstrate a significant correlation between 25(OH)D and BMI
* In *Finland* a prospected study by Michos et al. demonstrated that a higher baseline 25(OH)D reduced the risk of developing diabetes – there was no correction for confounders like BMI (Michos 2009)
* Mattila et al. demonstrated a significant inverse association between 25(OH)D and the prevalence of diabetes. There was no adjustment for BMI. A significant higher 25(OH)D was identified among persons with a lower BMI (Mattila et al. 2007)
* In the same country another cross sectional study with subjects originating from 8 European countries did not associate 25(OH)D with parameters of insulin action or secretion after adjustment for confounders like BMI (Gulseth et al. 2010a)
* Hintzpeter et al. found a significant lower serum 25(OH)D in women with diabetes in a *German* national health survey; this finding was not the same for men and not adjusted for BMI. In both sexes serum 25(OH)D levels varied significantly between different BMI groups
* Kayaniyli et al. showed among 712 subjects at risk for diabetes an independent association of 25(OH)D with insulin resistance (Kayaniyil et al. 2010).

Three studies were conducted in the *United States of America*:

* Type 2 diabetes was significantly associated with hypovitaminosis among a group of 290 patients from a general ward in a hospital, there was no correction for confounders (Thomas et al. 1998)

* Melamed et al. found among 133.331 participants form the third National Health and Nutrition examination survey (NHANES III) that diabetes was independently associated with low levels op 25(OH)D and an independent association between vitamin D and BMI (Melamed et al. 2008). This study has the largest study population of all studies investigating the relation between vitamin D and diabetes
* Another study by Yoho et al. showed that vitamin D levels in a diabetic population differs significantly from the levels in non-diabetic populations (Yoho et al. 2009)
* Among 524 non-diabetics with a mean vitamin D of 64.5nmol/L for women and 57.2nmol/L for men fasting glucose and insulin resistance were inversely associated with vitamin D; this outcome was adjusted for BMI (Forouhi et al. 2008).

The research finding from studies conducted on *(South-East) Asian natives* are presented below:

* Hidayat et al. did not find a significant correlation between vitamin D deficiency and diabetes in a study in *Indonesia*. The total prevalence of vitamin D deficiency was high (78.2%). The study population was not representative for the population in *Indonesia* as a whole since it was performed in a geriatric clinic and the mean age was 71. This study showed a significant correlation between obesity and vitamin D deficiency (Hidayat et al. 2010)
* In a study in *China* vitamin D was associated with fasting insulin in people with BMI ≥ 24 (Luo et al. 2009)
* In a study in *Japan* mean vitamin D concentration did not significantly differ between the type 2 diabetic group and the non-diabetic group. In this study vitamin D deficiency was not related to BMI (Suzuki et al. 2006)
* Among three groups of *Bangladeshi* women – veiled, non-veiled and diabetic – there was no statistical difference found in prevalence of vitamin D deficiency (Islam et al. 2006).

Research finding from studies conducted on native persons in *the Middle East:*

* A study in *Iran* did not show a significant difference in vitamin D deficiency among diabetics and a control group without diabetics. This study by Bonakdaran et al. did show a significant difference in BMI between patients with and without vitamin D deficiency (Bonakdaran et al. 2009)
* Among 381 *Lebanese* students without diabetes Gannage-Yared et al. found an inverse correlation between 25(OH)D with fasting plasma glucose and 25(OH)D with insulin resistance. After correction for confounders this finding was only significant for fasting glucose (Gannage-Yared et al. 2009).

3.2 The influence of migration and obesity as possible confounding factor in the relation between diabetes and vitamin D deficiency

This chapter presents the research results on the prevalence of diabetes (paragraph 3.2.1), obesity (paragraph 3.2.2) and vitamin D deficiency (paragraph 3.2.3) among the major groups of migrants in the Netherlands in comparison with the situation among the native Dutch and the situation in their respective countries of origin. No research is conducted on the relation between diabetes and vitamin D deficiency specifically targeting migrant groups in The Netherlands. Paragraph 3.2.4 focus on studies describing the relation between vitamin D deficiency and diabetes for migrants in various countries worldwide.

3.2.1 Diabetes – prevalence comparison between migrants in The Netherlands and the situation in their respective countries of origin

This paragraph compares the diabetes prevalence among migrants in The Netherlands with the diabetes prevalence in the respective countries of origin.

Turkey

In 2002 the first population-based study of diabetes and risk characteristics was conducted in Turkey: The Turkish Diabetes Epidemiology Study (TURDEP) is a nationwide study on the prevalence of diabetes and impaired glucose tolerance (IGT). The prevalence of diabetes was 7.2% and of IGT 6.7% (age standardized to world and European populations: 7.9% and 7.0%) Both diabetes and IGT were more frequent with those living in urban rather than rural communities (Satman et al. 2002).

Morocco

In Morocco a national survey conducted in 2000 showed similar percentages of diabetes prevalence: 6.6% among both males and females. The percentages were higher in urban compared to rural areas (Tazi et al. 2003).

India

Prevalence of diabetes as presented in a survey in urban Kerala (India) is 16.3% in the 30 - 64 age group (Raman, V et al. 1999). In another Indian survey in urban Puducherry this prevalence was 8.2% in the age group from 20 years onwards and over 20% in the age group from 50 and above (Purty et al. 2009).

Suriname

Research on prevalence of diabetes in Surinam dates back to 1986. The highest prevalence rate of 12.7% was found amongst Surinam of Indian origin (Schaad et al. 1985).

Indonesia

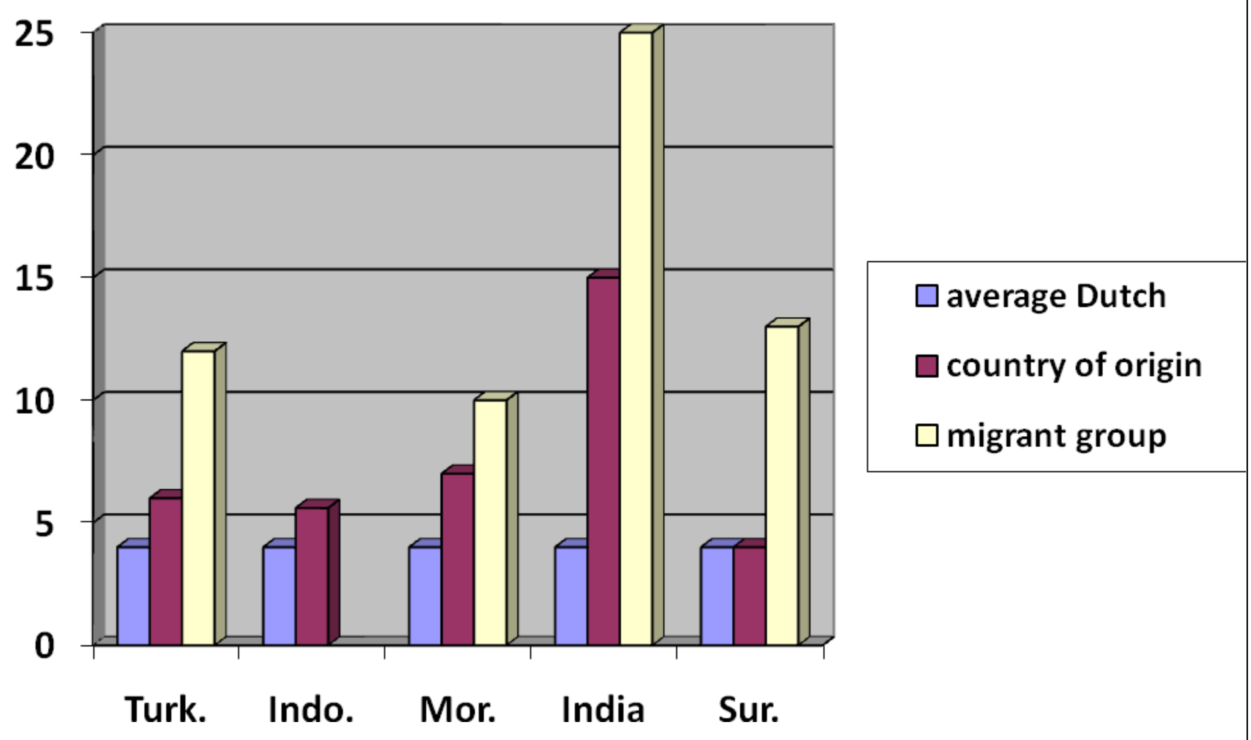
In Indonesian urban areas a diabetes prevalence of 5.7% was found (Mihardja et al. 2009). Data obtained from a surveillance in five regions in Jakarta on primary non-communicable diseases presented a diabetes prevalence of 8.4% (Soebardi et al. 2009). An Indonesian national health survey presented an overall prevalence of 5.6% (Pramono et al. 2010).

The prevalence of diabetes for various migrant groups in The Netherlands is presented in *table 6*.

Table 6 plus graph 1*. A comparison on diabetes prevalence between migrant groups in The Netherlands versus the situation in their country of origin*

Country	Diabetes prevalence in country of origin	Diabetes prevalence for migrant group in The Netherlands
Turkey	3-5%[1] 7.9%[2]	5.6%- 12.3%[3]
Indonesia	6-8%[1] 5.7%[4] 8.4%[5]	no data available
Morocco	6-8%[16]	8.0%- 12.4%[7]
Surinam	3-5%[1] 12.7%[8]	12.7%[9] Hindustani 25.6%[9]
India	6-8%[1] 8.2%-20%[10] 16.3%[11]	25.6%[9]

The average prevalence of diabetes in The Netherlands overall is 3-5%[1]



References: 1 WHO (who.int/diabetes 2011), 2 (Satman et.al. 2002), 3 (Bindraban et.al. 2008;Ujcic-Voortman et.al. 2009), 4 (Mihardja et.al. 2009), 5 (Soebardi et.al. 2009), 6 (Tazi et.al. 2003), 7 (Ujcic-Voortman et.al. 2009), 8 (Schaad et.al. 1985), 9 (Bindraban et.al. 2008), 10 (Purty et.al. 2009), 11 (Raman, V et.al. 1999)

The table compares the prevalence level in the country of origin with the prevalence among the migrant group in The Netherlands. As a reference the average Dutch diabetes prevalence figure is presented. The average diabetes prevalence in Turkey, Indonesia, Morocco, India and Surinam is higher compared to the Dutch average. The table and graph indicate that the prevalence of diabetes amongst four of the five major migrant groups even exceeds the average values in their respective countries of origin. No information on the diabetes prevalence among Indonesians in The Netherlands is available.

3.2.3 prevalence comparison between migrants in The Netherlands and the situation in their respective countries of origin

This paragraph compares the obesity prevalence among migrants in The Netherlands with the obesity prevalence in their respective countries of origin.

Morocco

El Rhazi et al. found an overall prevalence of overweight measured in reference to the obesity criterion of BMI > 25kg/m2, of 29.9% in Morocco. This percentage was higher amongst women than amongst men (32.9% versus 26.8%) and significantly higher in urban than in rural areas (Cornelisse-Vermaat et.al. 2007;El et al. 2010).

Turkey

In Turkey a cross-sectional nationwide survey was carried out on 2100 adults and showed an obesity prevalence of 34.19% among females and 20% among males (Gultekin et al. 2009).

Surinam

A survey in Surinam showed a percentage of 44.8% among men and 56.1% among women.

India

Research in 2008 in Jaipur, India, showed a difference in obesity with a prevalence varying from 8.9% in rural area and 61.5% in urban area for females. Amongst males this percentage was 9.4% in rural area and 54.0% in urban area (Gupta et al. 2008).

The prevalence of overweight in Turkey, Indonesia, Morocco, India and Surinam is higher compared to the overall Dutch average. Remarkable fact: for Turkish migrants the manifestation of overweight exceeds the value in Turkey itself. A possible explanation is that malnutrition in infancy increases the risk of obesity in later life, the so called double burden of malnutrition (The double burden of malnutrition. Case studies from six developing countries 2006). In developing countries obesity often co-exists with under nutrition whereas stunted adults in developing countries show a 1.2 times higher prevalence of overweight than non-stunted adults (Usfar et al. 2010). Because of demographic and epidemiologic transition there appears an increase in overweight among migrants from developing countries who have moved to western countries (The double burden of malnutrition. Case studies from six developing countries 2006).

The prevalence of overweight in India (in urban areas) and Surinam is higher compared to the migrants from the same ethnicity in The Netherlands and higher compared to native

Dutch. Reasons for the higher prevalence of overweight among migrants in The Netherlands compared to the native Dutch are:

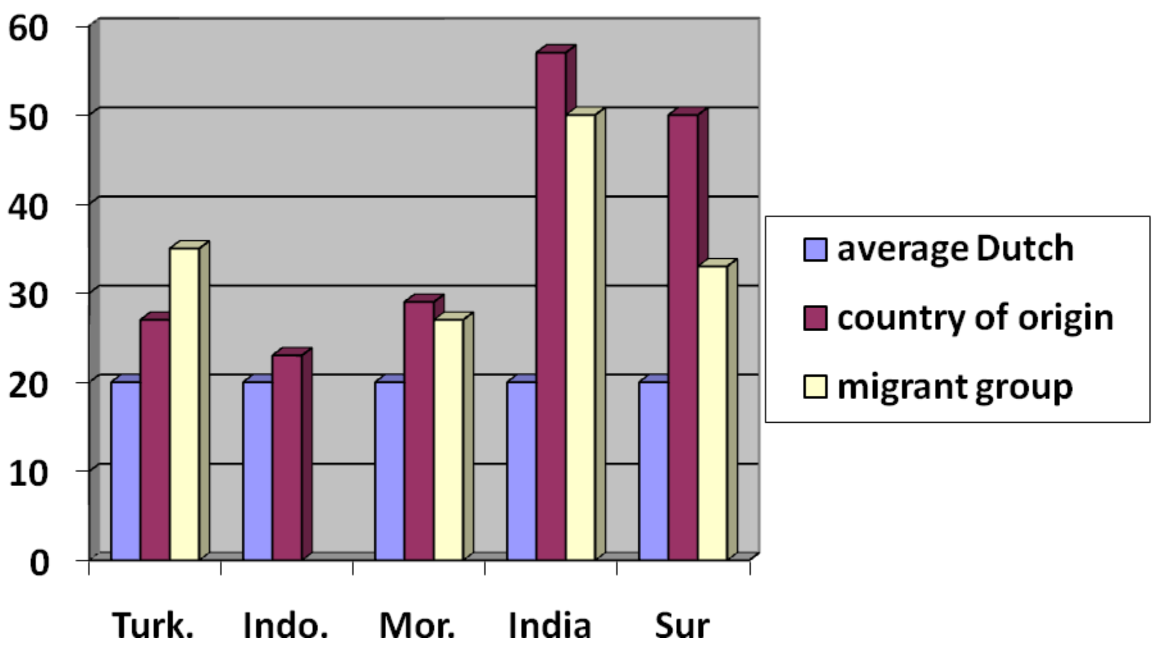
* lower physical activity levels, partly due to lesser participation in sports
* higher fast food consumption
* difference in diet (higher calorie intake, lower amount of micronutrients

(Cornelisse-Vermaat et.al. 2007) (Dijkshoorn et.al. 2003).

Table 7 plus graph 2. *A comparison on obesity prevalence (BMI > 25kg/m2) between migrant groups in The Netherlands versus the situation in their country of origin*

Country	**Obesity prevalence in country of origin**	**Obesity prevalence for migrant group in The Netherlands**
Turkey	34.1% Females 20% Males[2]	35.6%[1]
Indonesia	23.1%[4]	
Morocco	29.9%[3]	32.7% F 22.5% M[1]
Surinam	56.1 %Females[7] 44.8% Males	33%[7]
India	8.9 % rural area Females 61.5% urban area Females 9.4% rural area Males 54.0% urban area Males[6]	50%[7]

The average prevalence of obesity in The Netherlands overall is 20%[1]



References: 1 (Hosper et.al. 2007), 2 (Gultekin et.al. 2009), 3 (El et.al. 2010), 4 (Pramono et.al. 2010), 5 (who.int/infobase/Indicators), 6 (Gupta et.al. 2008), 7(Cornelisse-Vermaat et.al. 2007)

3.2.3 Vitamin D deficiency – prevalence comparison between migrants in The Netherlands

Prevalence figures on vitamin D deficiency vary widely for Turkey and Morocco. Prevalence figures on vitamin D deficiency for the countries of Indonesia, Surinam and India, are not available.

***Table 8**. Vitamin D deficiency (< 25nmol/l) prevalence for migrant groups in The Netherlands. To limited information is available on the situation in the respective countries of origin to compare with prevalence figures for the migrant groups.*

Country	**Vitamin D deficiency prevalence for migrant group in The Netherlands**
Turkey	41.3%[1]
Indonesia	no information available
Morocco	55%
Surinam	45.3%[2]
India	51.4%[2]
The average prevalence of vitamin D deficiency in The Netherlands overall is 5,9%[1]	

References: 1 (van der Meer 2008), 2 (Wielders, van Dormael, Eskes, & Duk 2006), 3 (Allali et al. 2009)

3.2.4 Studies describing the relation between vitamin D and diabetes among migrant populations

Studies describing the *relation* between vitamin D deficiency and diabetes are presented in an indented position in the following text.

South-East Asian migrants in the UK

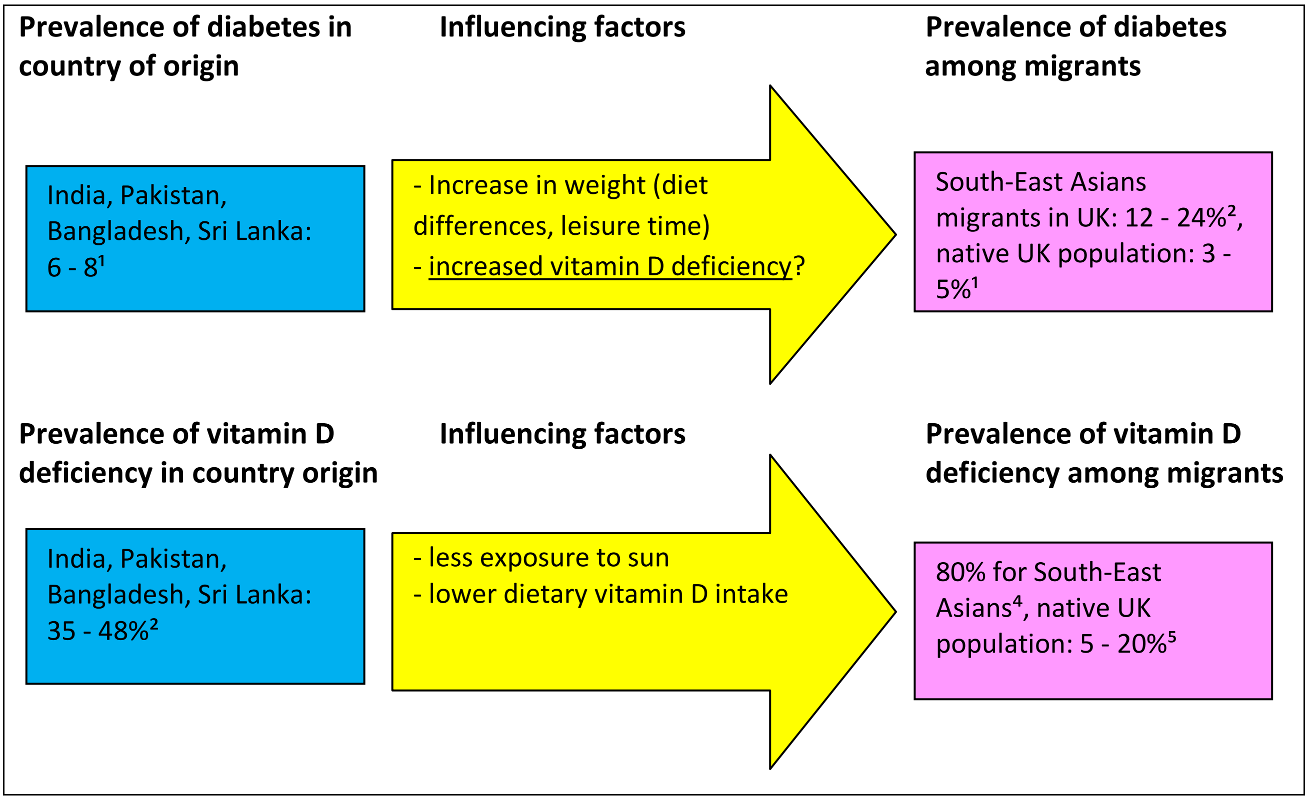
> In a study by Tahrani et al. in 2010 a significant higher prevalence of vitamin D deficiency among type 2 diabetics compared to the control group of South-East Asians in the *UK*. In this study population the prevalence of vitamin D deficiency was high (> 80%).

Asian Indians in general are prone to obesity and diabetes. According to the WHO estimates the prevalence of diabetes in *India* is 6 - 8% (age 35 - 64 years) – the prevalence of diabetes in *Pakistan*, *Bangladesh* and *Sri Lanka* is in the same range (the prevalence figures of diabetes for various countries worldwide are provided in annex 1). The above mentioned 6 – 8% prevalence is higher compared to the estimated prevalence among *UK* natives: 3 - 5%. Amongst South-East Asians in the UK diabetes is 4 - 6 times more likely to develop compared to the *UK* natives (Sabherwal et.al. 2010).

A prevalence of vitamin D deficiency is found in more than 80% of the South-East Asians living in the *UK*. This is due to a diet lacking fish and eggs and lack of exposure to sunlight, particularly among women because of skin covering behaviour (Bhopal et al. 2005) (Tahrani et al. 2010).

As *graph 3* shows that the prevalence of diabetes and vitamin D deficiency is higher amongst migrants originating from (South-East) Asia in the *UK* than the prevalence in their respective countries of origin and the prevalence among the *UK* natives. Vitamin D is presented as a possible influencing factor for a higher prevalence of diabetes amongst migrants in the UK.

Graph 3. *Comparison of the prevalence of diabetes and vitamin D deficiency for migrant groups in their country of origin and in the UK*



References: 1(WHO 2011a), 2 (Arya et al. 2004;Islam et.al. 2006;Nakamura 2006), 3 (Sabherwal et.al. 2010), 4 (Tahrani et.al. 2010), 5 (Prentice 2008)

(South-East) Asian migrants in Australia and New Zealand

The diabetes prevalence in *Australia* and *New Zealand* is comparable with the prevalence in Europe which is 3 - 5%(WHO 2011a). The *Australian/New Zealand* prevalence has increased over the last 20 years together with a clear increase in BMI (Walls et al. 2010). Lifestyle factors such as change in diet and a more sedentary life contribute to this increase in BMI and diabetes (Atlantis et al. 2009).

> Among Chinese migrants with diabetes in *Australia* a prevalence of vitamin D deficiency (< 50nmol/l) of 36% was found by Luo et al in 2009. There was no significant correlation between vitamin D deficiency and the parameters of diabetic control.

Vitamin D deficiency was not related to obesity. The BMI of this Chinese population was lower than expected compared to the native Australians. The following explanations were provided in this same study by Luo et al.:

* The *Chinese* population in *Australia* maintained an Asian lifestyle
* In *Australia* there is a reasonably high availability of Asian food (fresh fish, grains (rice), legumes (soy) as ingredients to a relatively healthy diet (Luo et.al. 2009).

In contrast to these findings South-East Asians in *New Zealand (Indians, Bangladeshi*) have a higher percentage of obesity compared to the native population in *New Zealand* and to the population in their country of origin. Posed explanations for this are:

* Adaptation to a western food pattern (increased fat and sugar intake, decreased lentils and soy) (Wahlqvist 2002)
* Lower activity levels than the Caucasians in *New Zealand* and the population in their respective countries of origin (Kolt et al. 2007).

Among this same population of South-East Asians living in New Zealand a threefold higher prevalence of diabetes is reported compared with the general population. A prevalence of 84% of 25(OH)D < 99nmol/l is reported among South-East Asian women (von Hurst et al. 2010).

As the situation in Australia for South-East Asian is different from East Asian migrants the study results are presented separately: results on East Asians (Malaysian, Chinese, Japanese) in graph 4 and the results on South-East Asians in graph 5.

As *graph 4* shows an equal prevalence of diabetes and vitamin D deficiency among migrants originating from East Asia in Australia and the prevalence in their respective countries of origin.

Graph 5 on the contrary presents a clear difference in prevalence figure between the country of origin and the Australian situation.

Graph 4. *Comparison of the prevalence of diabetes and vitamin D deficiency for migrant groups in their country of origin and in Australia*

Prevalence of diabetes in respective country of origin

China + Japan < 3%,
Malaysia 3 - 5%[1]

Influencing factors

- Continuation of Asian lifestyle[2]
- Lesser influence of overweight[3]

Prevalence of diabetes among migrants

Chinese + Malaysian migrants 3 - 5%[4],
3 - 5% native[1]

Prevalence of vitamin D deficiency in country origin

China: 20-40%[4],
Japan + Malaysia: 2 - 5%[5]

Influencing factors

- Asian diet[2]
- Fairly equal exposure to sunlight (availability + clothing style)

Prevalence of vitamin D deficiency among migrants

Chinese migrants in Australia 36%[6]

References: 1(WHO 2011a), 2 (Hsu-Hage et al. 1995), 3 (Kagawa et al. 2006), 4 (Lu et al. 2009), 5 (Rahman et al. 2004), 6 (Luo et.al. 2009)

Graph 5. *Comparison of the prevalence of diabetes and vitamin D deficiency for migrant groups in their country of origin and in New Zealand*

Prevalence of diabetes in country of origin

India, Pakistan, Bangladesh, Sri Lanka: 6 - 8[1]

Influencing factors

- Adaptation to a western diet[4]
- Lower activity levels[6]
- <u>Increased vitamin D deficiency</u>?

Prevalence of diabetes among migrants

Indian, Bangladeshi migrants in New Zealand:
9 -15%[3]
3 - 5% native[1]

Prevalence of vitamin D deficiency in country origin

India, Bangladesh,:
35 - 48%[2]

Influencing factors

- Lower dietary vitamin D intake?
- lower activity levels[6]

Prevalence of vitamin D deficiency among migrants

84% of 25(OH)D < 99nmol/l for Indians, Bangladeshi, in New Zealand[3]

References: 1(WHO 2011a), 2 (Arya et.al. 2004;Islam et.al. 2006;Nakamura 2006), 3 (von Hurst et.al. 2010) 4(Wahlqvist 2002),5(Kolt et.al. 2007)

African Americans in the United States of America

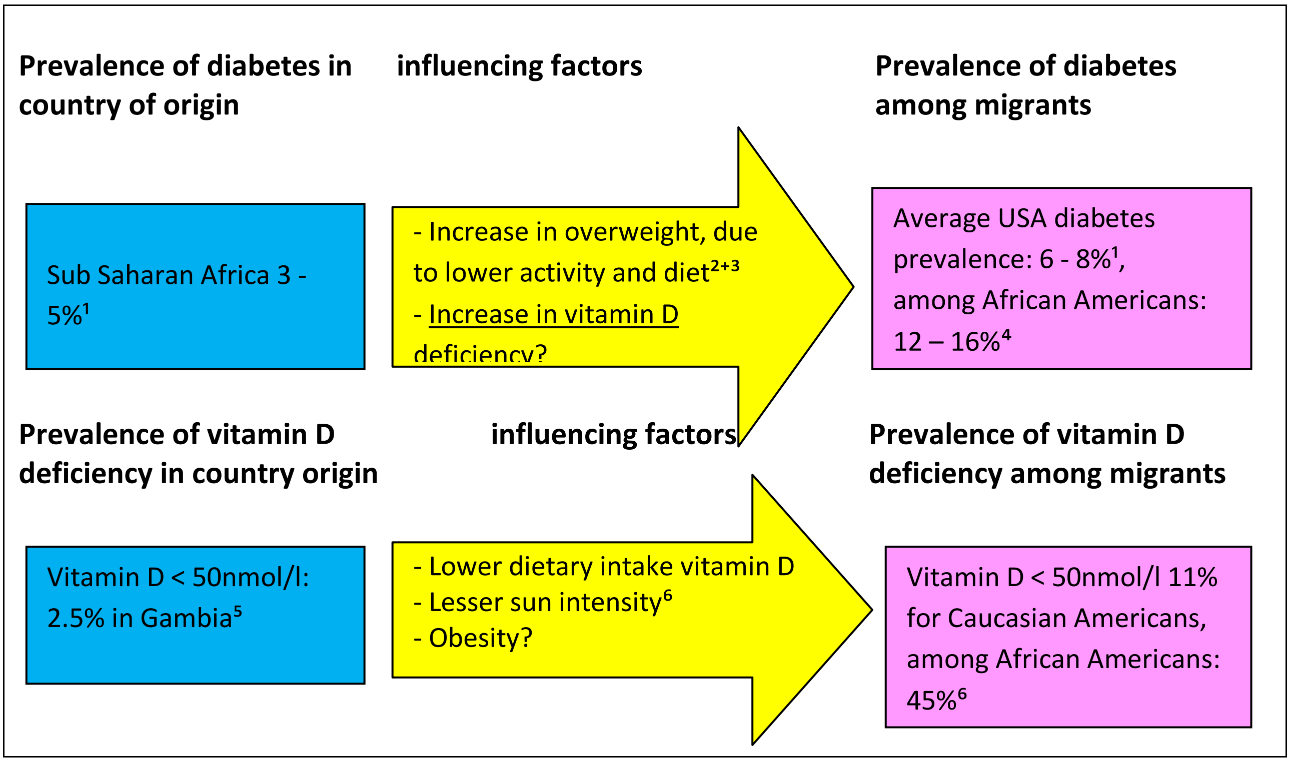
The diabetes prevalence among African Americans in the *USA* is twice as high as the prevalence among Caucasian Americans (Gorham et al. 2009). The prevalence of vitamin D deficiency among African Americans is approximately four times higher than among Caucasian Americans (Egan et.al. 2008).

The findings on the relation between diabetes and vitamin D deficiency from studies conducted on African Americans are presented below:

> Becker et al. showed a significant difference in diabetic prevalence for various levels of vitamin D deficiency among American whites and American blacks. There was no correction for BMI or other confounders. In general American blacks had higher vitamin D deficiency and a higher prevalence of diabetes (Becker et al. 2006).
>
> Alvarez et al. showed that vitamin D deficiency was correlated with insulin sensitivity among the African Americans(Alvarez et al. 2010).
>
> A correlation between vitamin D deficiency and insulin sensitivity was found by Chiu et al. among different ethnic groups in the *USA* (Asian, African, Caucasian and Mexican Americans). But after adjustment for confounders this correlation turned out not to be significant (Chiu 2004).

Graph 6 shows that the prevalence of diabetes and vitamin D deficiency is higher among African Americans in the *USA* than the prevalence among Caucasian Americans and the prevalence in their respective countries of origin. However the studies conducted on Africans in their respective countries of origin are few.

Graph 6. *Comparison of the prevalence of diabetes and vitamin D deficiency for migrant groups in their country of origin and in the USA*



References: 1(WHO 2011a), 2 (Egan et.al. 2008;Gaillard et al. 2009), 3 (Vital signs: state-specific obesity prevalence among adults --- United States, 2009 2010), 4 (Gorham et.al. 2009), 5 (Aspray et al. 2005), 6 (Egan et.al. 2008)

Arab migrants

According to the WHO the prevalence of diabetes in *Iran*, *Lebanon* and other Middle Eastern countries is amongst the highest in the world. The WHO estimates the current diabetes prevalence in *Lebanon* higher than 8%. A prevalence of even 11.3% was shown in a research among 3.000 persons from Greater Beirut, a part of *Lebanon* which represents a mixture of urban and rural areas (Hirbli et al. 2005). Only 55.5% of the Lebanese adults meet the requirements of adequate physical activity (minimum of 30 minutes a day). This can contribute to a higher level of diabetes (Al-Tannir et al. 2009).

In 2010 Estegmati et al. analysed the data of three cross-sectional national surveys on adults in *Iran*. The total prevalence of diabetes in *Iran* increased from 7.7% in 2005 to 8.7% in 2007 (Esteghamati et al. 2010). Reasons mentioned for this increase are:

* a 60% increase in the average BMI of the Iranian population
* lower physical activity – 40% of the *Iranian* adults have low physical activity and practice a sedentary lifestyle.

Only one cross-sectional study was conducted on Arabs in a western country focusing on the relation between vitamin D and diabetes:

> Among 542 Arab Americans without diabetes Pinelli et al. showed a significant correlation between both insulin resistance and fasting glucose with vitamin D levels.

3.3 Supplementation trials

There is limited research available on supplementation trials with vitamin D – available studies target both migrants and natives. The dose and duration of the supplementation therapy varies between the studies. The major findings are presented below – a summary of the dose and duration of the therapy are presented in table 11 and 12 in chapter 4.

Trials conducted on non-migrant populations

India:

* In a study conducted among native *Indians* it appeared that after administering three doses of vitamin D3 (120.000IU) there was a change in oral glucose and insulin sensitivity but no change in insulin sensitivity (Nagpal et al. 2009)
* Parekh et al. demonstrated an identical outcome: treatment with vitamin D did not improve glucose tolerance and insulin resistance in the study group consisting of Indian type 2 diabetics (Parekh et al. 2010).

USA:

* No significant improvement was demonstrated in a study by Patel et al. in fasting plasma glucose and HbA1c after treatment with 1200IU cholecalciferol for 4 months of a group of type 2 diabetics (Patel et al. 2010)
* Treatment with 1, 25-dihydroxyvitamin D (1 microgram per day for 4 consecutive days) did not demonstrate an effect on fasting plasma glucose, insulin C treatment or glucagon concentration in a group of 20 type 2 diabetics. This study demonstrated an association between vitamin D deficiency and diabetes. There was no correction for confounders (Orwoll et al. 1994).

In *Australia* one randomised controlled trial was performed:

* Among 33 participating adults with glucose intolerance and low vitamin D two doses of administered vitamin D did not demonstrate a significant effect on blood glucose or mean insulin values. The mean serum vitamin D at start was 39.0 +/- 1.5nmol/l (Tai et al. 2008a).

Supplementation trials conducted in *Europe:*

* After 7 days of oral treatment with 1.5 microgram 1.25(OH)D versus placebo among 28 *German* men no change in insulin sensitivity was found among 18 persons in the treatment group (Hintzpeter et al. 2008)
* In *Norway* a randomised controlled trial by Jorde et al. did not show a difference between fasting glucose and insulin sensitivity after supplementation with 40000IU of vitamin D for 6 weeks
* In *Denmark* by Lind et al. the same negative outcome in insulin sensitivity was demonstrated after 18 months of treatment with oral alphacalcidiol, 2microgram/day (Parekh et.al. 2010)
* The same result was presented in the research by Ljunghall et al. in a group of 65 *Swedish* men (Ljunghall et al. 1987)

* Borissova et al. found a significant increase in the first phase of insulin secretion after vitamin D supplementation. No significant change in insulin resistance was demonstrated in a small group of 10 *Bulgarian* females with diabetes compared to 17 matched controls (Borissova et al. 2003)
* No evidence was found that daily use of 800IU vitamin D was able to prevent diabetes among 5292 patients in *Scotland* (Avenell et al. 2009).

Trials conducted on migrant populations

South-East Asian migrants:

* Sabherwal et al. found a significant decrease in HbA1c among South-East Asian (*India, Sri Lanka, Pakistan, Bangladesh*) type 2 diabetics in the UK after three months of treatment with 4000IU/d vitamin D. Within this study group the body weight dropped significantly after a change in vitamin D level (Sabherwal et.al. 2010)
* A significant improvement in insulin sensitivity and insulin resistance after treatment with 4000IU/d vitamin D was also found among another group 81 women of the same ethnicity. This group contained persons with insulin resistance as a manifestation of pre-stage diabetes and vitamin D deficiency (von Hurst et.al. 2010)
* Boucher et al. found a correlation between glucose intolerance and vitamin D deficiency – a single dose of 100,000IU Cholecalciferol significantly improved insulin levels amongst again another group of the same ethnic Asians (Boucher et al. 1995).

4. Discussion

4.1 Overall discussion

Ethnic minorities in western societies have a higher prevalence of diabetes (Ujcic-Voortman et.al. 2009). Diabetes prevalence among patients in The Netherlands visiting a general practitioner varies from 5.6% among native Dutch to 12.3% among Turkish, 8.0% among Moroccan and 14% among Surinam patients. In general the diabetes prevalence among migrants in The Netherlands is higher from the diabetes prevalence in their countries of origin and is higher compared to the prevalence among native Dutch (Dijkshoorn et.al. 2003;Gorham et.al. 2009), (Dijkshoorn et.al. 2003). Graph 1 in paragraph 3.2.1. presents these figures.

The prevalence of vitamin D deficiency among migrants in The Netherlands from various ethnic backgrounds is again far higher compared to the prevalence among native Dutch. The prevalence varies from 5% among native Dutch to 55% among Turkish migrants (van der Meer 2008) (Grootjans-Geerts 2001).

The role of vitamin D in diabetes
The overall objective of this thesis is to find support for the hypothesis that vitamin D deficiency plays a contributing role in the high prevalence of diabetes among migrant populations in The Netherlands. The majority of the included studies in this review describe this link for native populations from various areas around the world, including developing countries. Other studies investigate a correlation between diabetes and vitamin D deficiency among migrant populations.

Native populations
The subjects of these studies originate from various countries around the world.

Table 9 provides the combined study results on the relation between vitamin D and (pre-stage) diabetes among native populations. From a total of 19 cross-sectional studies 14 demonstrate a relation between vitamin D deficiency and diabetes or pre-stage diabetes, which strengthens the hypothesis that a correlation exists.

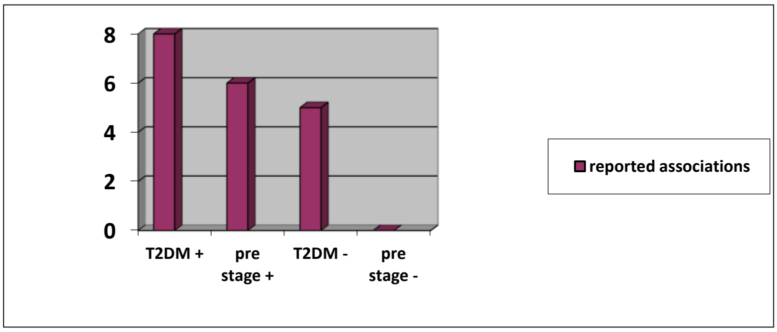
Graph 7 visualizes the predominance of the correlation between (pre-stage) diabetes and vitamin D deficiency. This predominance for studies conducted on subjects with pre-stage diabetes attenuates in comparison with manifested diabetes when we identify the maximum and the minimum number of the subjects of the study groups. As is indicated in *table 9* within the studies which demonstrate a correlation between diabetes and vitamin D deficiency the group with the maximum study subjects is fairly equal according to the study subjects in the group with the maximum study subject within studies which demonstrate a relation between (pre-stage) diabetes and vitamin d deficiency .

__Table 9.__ An overview of the research outcomes on the link between vitamin D and diabetes among native populations

native populations	**+ link vitamin D and diabetes**	**+ link vitamin D and Pre-stage diabetes**	**no link vitamin D and diabetes**	**no link vitamin D and Pre-stage diabetes**	**total number**
Reported associations	8[1]	6[2]	5[3]	0	19
Total number of participants	39 - 13331	121 - 15098	78 - 9773	0	134578

References: 1 (Hintzpeter et.al. 2008;Isaia et.al. 2001;Mattila et.al. 2007;Melamed et.al. 2008;Thomas et.al. 1998) (Kositsawat et al. 2010;Yoho et.al. 2009) (Becker et.al. 2006), 2 (Forouhi et.al. 2008;Gannage-Yared et.al. 2009;Kayaniyil et.al. 2010;Luo et.al. 2009;Michos 2009), 3 (Bonakdaran et.al. 2009;Gulseth et.al. 2010a;Hidayat et.al. 2010;Islam et.al. 2006;Muscogiuri et al. 2010)

__Graph 7.__ Comparison of the number of studies regarding research outcomes on the link between vitamin D and diabetes among native populations



↑ total number of studies

Migrant populations

The subjects of these studies are predominantly South-East Asian's who have migrated to the UK or Australia/New Zealand and studies conducted on African Americans – western countries comparable to The Netherlands (Boucher et.al. 1995;Sabherwal et.al. 2010;Von Hurst et al. 2009).

Table 10 provides the combined study results on the relation between vitamin D and (pre-stage) diabetes among migrant populations. From a total of 9 cross-sectional studies 8 demonstrate a positive correlation between vitamin D deficiency and diabetes or pre-stage diabetes, which strengthens the hypothesis that a correlation exists.

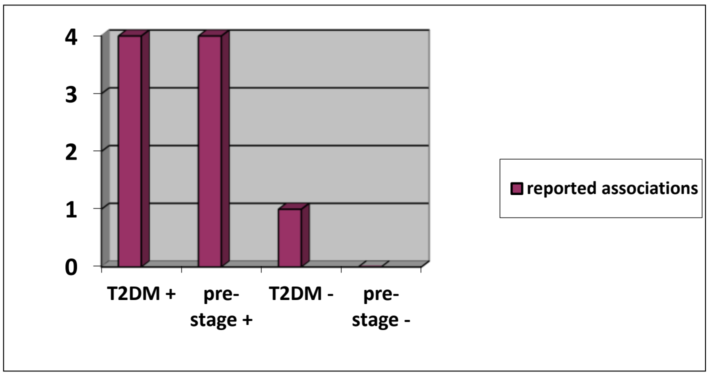
Graph 8 visualizes the predominance of the correlation between (pre-stage) diabetes and vitamin D deficiency. When we identify the maximum and the minimum number of the subjects of the study groups it is indicated that among the studies which demonstrate a correlation between diabetes and vitamin D deficiency the group with the maximum study subjects is large. As is indicated in *table 10*.

Table 10. *An overview of the research outcomes on the link between vitamin D and diabetes among migrant populations*

migrant populations	**+ link vitamin D and diabetes**	**+ link vitamin D and Pre-stage diabetes**	**no link vitamin D and diabetes**	**no link vitamin D and Pre-stage diabetes**	**Total number**
reported associations	4[1]	4[2]	1[3]	0	9
Minimum – maximum number of participants	119 - 20432156	44 - 552	109 - 109	0	20433229

References: 1 (Tahrani et.al. 2010) ((Becker et.al. 2006;Gorham et.al. 2009;McCullough et al. 2010) , 2 (Chiu 2004) (Alvarez et.al. 2010;Boucher et.al. 1995;Pinelli et al. 2010),3 (Luo et.al. 2009)

Graph 8*. Comparison of the number of studies regarding research outcomes on the link between vitamin D and diabetes among migrant populations*



↑ total number of studies

Interracial variation

The Arbor report on vitamin D and diabetes suggests a genetic variation in the vitamin D receptor since associations between vitamin D deficiency and diabetes seem stronger among various populations (Arbor clinical Nutrition Updates 2008). For South-East Asians and certain populations from the Middle East the following facts are applicable:

* There is higher genetic susceptibility to develop diabetes (Sabherwal et.al. 2010;Wandell et.al. 2008).
* They are more prone, due to genetic susceptibility, to have a greater percentage of body fat (Sabherwal et.al. 2010).

The correlation between diabetes and vitamin D deficiency observed among South-East Asian migrants seems to be consistent. Furthermore a positive outcome after supplementation therapy with vitamin D manifests in this same ethnic group. Since studies conducted on the same ethnic groups in their native countries show a contradictory result it is not likely that a genetic attribute determines the impact of vitamin D on the development of diabetes. The number of studies conducted on this ethnic group though is still low.

The influence of migration

The problem of increased prevalence of diabetes and increased prevalence of vitamin D deficiency is found among South-East Asians in the UK and Australia (Sabherwal et.al. 2010;Tahrani et.al. 2010;von Hurst et.al. 2010) among Turkish women in Sweden (Wandell et.al. 2008), migrants from Lebanon and Turkey in Denmark (Kristensen et.al. 2007) and migrants from Turkey, Morocco, Surinam and India in The Netherlands (van der Meer 2008), (Wielders, van Dormael, Eskes, & Duk 2006), (Allali et al. 2009) (Satman et.al. 2002), (Bindraban et.al. 2008; Ujcic-Voortman et.al. 2009), (Mihardja et.al. 2009), (Soebardi et.al. 2009), (Tazi et.al. 2003), (Schaad et.al. 1985), (Purty et.al. 2009), (Raman, V et.al. 1999).

The interpretation of the combined research outcome confirms the relation between diabetes and vitamin D:

* 8 from a total of 9 studies confirms this among migrant populations whereas 9 from a total of 14 studies confirms this on non-migrants
* A difference in the appearance of this relation between migrants and non-migrants is 89% versus 64%
* The outcome of the comparison though attenuates after considering the minimum and maximum number of study subjects within studies in the migrant versus the minimum and maximum number in the non-migrant group.

Other possible influencing factors on the relation between diabetes and vitamin D then genetic susceptibility, like activity levels and diet (possibly resulting in obesity), sun exposure and sun intensity, determine the level of diabetes prevalence among migrant groups.

If a link between vitamin D deficiency and diabetes is demonstrated almost equally among migrants and non-migrants (99.9% versus 99.3%) how does migration then influence the higher prevalence figure of diabetes among migrants in The Netherlands due to vitamin D deficiency?

Not all migrant groups show the same increase in vitamin D deficiency and diabetes as we have explained in sub-paragraph 3.4.2 and presented in graph 4 for Malaysian, Chinese and Japanese in Australia (Hsu-Hage et.al. 1995) (Kagawa et.al. 2006) (Lu et.al. 2009) (Rahman et.al. 2004). As we pointed out in sub-paragraph 3.4.2. these ethnic groups maintained their original (Asian) life style which implies less negative impact of the local behavioural risk factors (lower physical activity, inferior dietary intake, both presumably leading to obesity) while sun exposure and intensity is equal compared to their country of origin.

Obesity
Obesity is considered to be a confounding factor in the relation between Vitamin D and diabetes. The following is a brief explanation hereof (Tai et al. 2008b):

* Vitamin D is a fat soluble hormone which indicates a direct biochemical link with obesity
* Sun exposure generally implies outdoor physical activity which on itself has impact on BMI and glucose regulation.

From a total of 43 studies investigating the relation between diabetes and vitamin D 10 of these studies delivered data on the relation between vitamin D and BMI with the following results:

* 9 studies confirmed this relation (Muscogiuri et al., Mattila et al., Hintzpeter et al., Melamed et al., Sabherwal et.al., Bonakdaran et al., Chiu, (Lagunova et al. 2009), Hidayat et al.). These findings strengthen the assumption that obesity can be seen as an influencing factor in the correlation between diabetes and vitamin D
* 1 study did not (Suzuki et al. 2006).

Does this imply that obesity is the determinant in the link between vitamin D deficiency and diabetes? If this is the case migrants are specifically at risk since the risk of developing obesity increases as a result of migration from:

* non-industrialized to industrialized countries, and
* from rural to urban area.

In 3 of the 8 studies conducted on migrants confirming the relation between diabetes and vitamin D there was no adjustment for BMI(Becker et.al. 2006;Gorham et.al. 2009;McCullough et.al. 2010). In the remaining 5 studies this adjustment was carried out resulting in persistence of this relation (Chiu 2004),3 (Alvarez et.al. 2010;Luo et.al. 2009) (Boucher et.al. 1995;Von Hurst et.al. 2009). This weakens the assumption that obesity is the only determent in the link between vitamin D deficiency and diabetes among migrant populations.

As is illustrated in *graph 2* in paragraph 3.2.2 the prevalence of overweight is higher among the major groups of migrants in The Netherlands than among native Dutch. However it does not exceed the prevalence in the majority of the respective countries of origin – only the Turks tend to develop higher obesity levels in The Netherlands. Obesity can therefore not be presented as the only determining factor for the relation between vitamin D deficiency and diabetes.

No adjustment for the covariate BMI was made in 7 of the 14 studies conducted on non-migrants confirming the relation between diabetes and vitamin D. In the remaining 7 studies the relation maintained after correction for BMI. This affirms the assumption presented in the previous paragraph that obesity is not the only determinant in the link between vitamin D deficiency and diabetes.

Table 11 presents the combined figure regarding the total frequency of correction for BMI.

Table 11. BMI as a confounding factor on the relation between diabetes and vitamin D deficiency

	Correction for BMI	No correction for BMI	total
Relation demonstrated	12[1]	10[2]	22
Relation not demonstrated	5[3]		5

References: 1 (Alvarez et.al. 2010;Boucher et.al. 1995;Forouhi et.al. 2008;Gannage-Yared et.al. 2009;Hintzpeter et.al. 2008;Kositsawat et.al. 2010;Lu et.al. 2009;Melamed et.al. 2008;Suzuki et.al. 2006) 2 (Becker et.al. 2006;Gorham et.al. 2009;Isaia et.al. 2001;Mattila et.al. 2007;McCullough et.al. 2010;Michos 2009;Pinelli et.al. 2010;Thomas et.al. 1998;Yoho et.al. 2009), 3 (Gulseth et al. 2010b;Hidayat et.al. 2010;Luo et.al. 2009) (Chiu 2004;Islam et.al. 2006)

Treatment with vitamin D

From the total of 14 intervention studies, 5 of these studies demonstrate a positive outcome on the management of (pre-stage) diabetes. The combined study results are summarized in *table 12*.

Table 12. *An overview of research outcomes of intervention studies, both migrants and non-migrants*

Intervention studies	**+ link vitamin D and diabetes**	**+ link vitamin D and Pre-stage diabetes**	**no link vitamin D and diabetes**	**no link vitamin D and Pre-stage diabetes**	**Total number**
Studies among migrants	1[1]	2[2]	0	0	3
Studies among non-migrants	0	2[3]	4[4]	5[5]	11

References: 1 (Sabherwal et.al. 2010), 2 (von Hurst et.al. 2010) (Boucher et.al. 1995), 3(Borissova et.al. 2003;Nagpal et.al. 2009), 4 (Jorde et al. 2009) (Patel et.al. 2010) (Orwoll et.al. 1994) (Parekh et.al. 2010), 5 (Tai et.al. 2008b) (Avenell et.al. 2009) (Lind et al. 1989a) (Ljunghall et.al. 1987) (Fliser et al. 1997)

Only 3 intervention studies were conducted on migrants. Al 3 studies demonstrated a positive study outcome after supplementation with vitamin D as is indicated in *table 11.* Remarkable finding – all three studies were conducted on the same ethnic group of South-East Asians (Indians, Bangladeshi). But there are two randomised controlled trials among Indians in India which do not demonstrate a consistent positive study result.

> Nagpal et al. demonstrated a significant change in oral glucose and insulin sensitivity among 100 male after three doses of vitamin D3 of 12000IU. However there was no change in insulin secretion demonstrated (Nagpal et.al. 2009).

In both studies the intervention was relatively low compared to the intervention studies with a positive outcome as is illustrated in *table 13* (Nagpal et.al. 2009;Parekh et.al. 2010).

Out of a total of 11 intervention studies among non-migrant populations 9 studies did not demonstrate an improvement in glucose values or insulin sensitivity after vitamin D supplements – references in *table 13*.

One study demonstrated a partly positive result after supplementation:

Borissova et al. demonstrated a significant change in the first phase of insulin secretion after vitamin D supplementation of 1332IU cholecalfciferol for one month, but no significant change in insulin resistance. The study population consisted of Bulgarians with type 2 DM. The size of this study group was small: N = 27 (Borissova et.al. 2003).

As *table 13* indicates the dose and duration of the vitamin D therapy in the studies where a positive result is demonstrated varies from a minimum of 1331 IU/d for 1 month to 4000IU/d for 6 months.

Table 13. *Intervention studies with a positive outcome: dose and duration of therapy*

	Study	**Dose vitamin D**	**Time**
migrants	(von Hurst et.al. 2010)	4000IU/d	6 months
migrants	(Sabherwal et.al. 2010)	4000IU/d	3 months
migrants	(Boucher et.al. 1995)	100,000IU	Single dose
natives	(Borissova et.al. 2003)	1332IU/d	1 month
natives	(Nagpal et.al. 2009)	120.000IU/m	3 months

These dosages seem higher compared to the dose and duration of therapy in studies where a negative result is demonstrated. As *table 14* indicates the dose and duration in these studies vary from a minimum dose of 60IU cholecalciferol/day for 7 days (Fliser et.al. 1997) to a maximum dose of 1200IU cholecalcifeol/day for 4 months (Patel et.al. 2010).

Table 14. *Intervention studies with a negative outcome: dose and duration of therapy*

	Study	Dose vitamin D	Time
natives	(Tai et.al. 2008b)	100000IU/2w	2 weeks
natives	(Jorde et.al. 2009)	40000IU/w	6 months
natives	(Avenell et.al. 2009)	800IU/d	3 months
natives	(Patel et.al. 2010)	1200IU/d	4 months
natives	(Orwoll et.al. 1994)	400IU/d	4 days
natives	(Parekh et.al. 2010)	400IU/d	4 weeks
natives	(Lind et.al. 1989a)	800IU/d	18 months
natives	(Ljunghall et.al. 1987)	30IU/d	3 months
natives	(Fliser et.al. 1997)	60IU/d	7 days

Exceptional is the study by Jorde et al. with a negative effect on fasting glucose among type 2 diabetics after 6 months treatment with 40.000IU vitamin D3 per week (Jorde et.al. 2009). Intervention studies demonstrating a positive result are predominantly conducted on subjects with a pre-stage diabetes. This leads to the assumption that the stage of metabolic deregulation is of importance to the effectiveness of the therapy. Only Saberwal et al. demonstrated a significant decrease in HbA1c among type 2 diabetics after supplementation. But also body weight changed after supplementation with vitamin D

(Sabherwal et.al. 2010) – this brings us back to the question whether a change in HbA1c is caused by:

* vitamin D supplementation
* a change in bodyweight due to vitamin D supplementation
* a change in bodyweight due to other reasons.

4.2 Reaction to the vitamin D supplementation report

Since there was no clear understanding of an adequate intake of vitamin D in The Netherlands the Dutch Public Health Committee requested the Netherlands Nutrition Centre Foundation in The Hague to draw up recommendations concerning vitamin D supplementation as a preventive measure (voedingscentrum 2011b). In May 2011 a report was issued regarding the application of vitamin D – these recommendations have been adopted by the Ministry of Health, Welfare and Sport (VWS). The supplementation advice by the Nutrition Centre (voedingscentrum 2011a) concerning migrants is the following (voedingscentrum 2011b):

Target group	**Supplementation**
persons with a dark skin colour like people from Morocco, Turkey, Indonesia and Africa	microgram vitamin D per day (= 400IU)
male persons with a dark skin colour originating from the countries mentioned above 70 years of age who are not often outside	20 microgram vitamin D per day (= 800IU)
females with a dark skin colour above 50 years of age who are wearing a headscarf	20 microgram vitamin D per day (= 800IU)

Specific guidelines for non-western populations concerning the management of vitamin D still have to be drawn up: one of the problems stated in the report concerns the difficulty of bringing the issue of vitamin D deficiency to the attention of the relevant health workers due to insufficient awareness of vitamin D deficiency being a major health concern for migrants (voedingscentrum 2011a).

General practitioners, especially in urban areas with a high percentage of migrants, acknowledge the problem of vitamin D deficiency but this is barely translated into an adequate supplementation because the manifestation of vitamin D deficiency has non-specific symptoms (voedingscentrum 2011a). The supplementation advice by the Nutrition Centre though focuses more on prevention than on manifested symptoms of deficiency or insufficiency.

In the vision of the Nederlands Huisartsen Genootschap (NHG – the Dutch College of General Practitioners) collective prevention of vitamin D deficiency is not seen as a task for general practitioners. The NHG is not convincingly supporting an *active* role in neither health education or supplementation advice and provision of supplementation with regards to vitamin D – they limit their support to a *passive* advisory role regarding supplementation (voedingscentrum 2011a).

As this thesis emphasizes the problem of diabetes among migrants in The Netherlands and supports a role for vitamin D in relation to diabetes we question whether only a passive role in the management of vitamin D contributes sufficiently to the management of diabetes and whether a preventive task should be part of a guideline.

In the reviewed studies that showed a positive effect of vitamin D on diabetic or glucose regulation a predominant minimum vitamin D supplementation of 1331IU per day was applied which is higher than the by the Nutrition Centre advised dosage of 400 - 800IU. This dosage is positioned as a preventive measure which differs from supplementation treatment. Furthermore the advised duration on the preventive measure is ‘lifelong’. In case vitamin D supplementation is applied as part of the management of diabetes it is questionable whether a dose should be adjusted in case of manifested diabetes.

5. Conclusion, recommendations

Diabetes is a major health concern causing an increase in morbidity and mortality over the years. The problem rises especially among populations in developing countries and populations migrating from low or middle income countries to a western society.

First specific objective
The first specific objective of this thesis is to appraise the *relation* between diabetes and vitamin D deficiency. Although a majority of the relevant studies confirm this link it is not consistently demonstrated in all the studies.

Second specific objective
The second specific objective is to find possible existence of *interracial variation* in the relation between diabetes and vitamin D deficiency. The correlation between diabetes and vitamin D deficiency observed among South-East Asian migrants seems to be consistent as is the case with the studies that confirm a positive effect of vitamin D supplementation. But studies conducted on the same ethnic groups in their native countries do not confirm a predominant relation. This leads to the conclusion that there is insufficient evidence of the existence of interracial variation.

Third specific objective
The third specific objective is to appraise the influence of *migration and obesity as a possible confounding factor* in the relation between diabetes and vitamin D deficiency. The following statements summarize the findings:

- a link between vitamin D deficiency and obesity is demonstrated in 90% of the studies which specifically investigate this relation
- in 55% of the studies that demonstrate a relation between vitamin D and diabetes this relation persists after correction for BMI
- in 45% of the studies the relation does not persist after adjustment for BMI.

This leads to the conclusion that obesity influences vitamin D deficiency and therefore can be identified as a confounder although it is not the determent in the relation between vitamin D deficiency and diabetes.

Migration influences the risk factors regarding the relation between vitamin D deficiency and diabetes in the following ways:

- In case of migration to areas with a lower sun intensity migrants with a more pigmented skin will suffer more from vitamin D deficiency especially in case of staying indoors and skin covering behaviour
- Migrants who move to a western country and adjust to a western lifestyle including an unhealthy diet and lower physical activity are subject to developing obesity which implies a direct risk factor for diabetes
- Through biochemical interactions obesity contributes to lower vitamin D levels and thereby influences diabetes
- Physical complaints due to vitamin D deficiency like muscle weakness and pain deteriorate the activity level and decrease the outdoor activities resulting in even lower vitamin D levels.

Fourth specific objective
The fourth specific objective is to find support for the hypothesis that treatment with vitamin D is effective to prevent diabetes.
An important number of the studies conducted on non-migrants have neither demonstrated improvement of the regulation nor the prevention of diabetes after supplementation with vitamin D. For South-East Asians in the UK and native Indians though a positive effect of vitamin D supplementation is demonstrated. The overall conclusion is that the effectiveness of vitamin D supplementation depends on a minimum dose of 1332IU/d over a period of at least 3 months.

There is little evidence that vitamin D supplementation is more effective in influencing glucose metabolism among persons with pre-stage diabetics than among diabetic patients. This emphasises the importance of supplementation with vitamin D in an early stage of diabetes.

Fifth specific objective
The fifth specific objective is to find support for the hypothesis that treatment of vitamin D deficiency contributes to the management of diabetes. We found support for this – there is evidence that vitamin D is related to BMI and that therefore supplementation therapy with vitamin D deficiency has the following proven benefits in the management of diabetes:
* Direct effect on glucose regulation and insulin resistance
* Vitamin D supplementation therapy causes increased muscle performance and therefore improved activity levels leading to weight loss. A decrease of obesity diminishes the development of diabetes.

Overall objective
The overall objective of this thesis is to find support for the hypothesis that vitamin D deficiency plays a contributing role in the high prevalence of diabetes among migrant populations in The Netherlands. Two findings are of value to confirm the hypothesis:
1. A relation between vitamin D and diabetes is demonstrated in the majority of the reviewed studies as is stated in the first specific objective
2. Migrants in The Netherlands are prone to vitamin D deficiency which influences the development of diabetes although it is not clear whether the influence of vitamin D works:
    a. via the possible development of obesity, or
    b. via a direct effect on the development of diabetes.

It is clear tough that vitamin D supplementation has its own effect on the management of diabetes, that is – independent from the influence of obesity on diabetes.

This thesis therefore emphasizes the importance of optimizing vitamin D levels among migrants in The Netherlands by supplementation of vitamin D.

To be able to bring the role of vitamin D treatment on a higher level as a way to manage diabetes among migrants in The Netherlands a number of recommendations have been defined. These recommendations are listed under the following three categories – lifestyle advises, supplementation advises and recommendations for further studies.

Lifestyle advises:

* Since obesity is a risk factor for developing diabetes and an important number of studies are demonstrating a correlation between vitamin D deficiency and obesity controlling weight among migrants is of important value – the advice is the following:
  Increase attention to weight control among migrants in The Netherlands.
  Stakeholders for his advice are: general practitioners, Nutrition Centre, VWS, migrants
* Higher physical activity levels and increased sun exposure need to be stimulated with migrants since: 30 minutes/day outside with uncovered hands and face.
  Stakeholders: general practitioners, Nutrition Centre, VWS, migrants

Vitamin D supplementation advises:

In order for the advice as defined by the Nutrition Centre regarding the supplementation of vitamin D for migrants in The Netherlands to be more effective the following is recommended:

* Adopt vitamin D deficiency in the priority list of health key issues for migrants by the ministry of VWS.
  Stakeholders: VWS, Nutrition Centre
* Guidelines need to be defined by the NHG, translating the follow-up of the Nutrition Centre's supplementation advice, in order for general practitioners to manage the vitamin D deficiency among migrants effectively.
  Stakeholders: NHG, general practitioners, Nutrition Centre.

Recommendations for further studies:

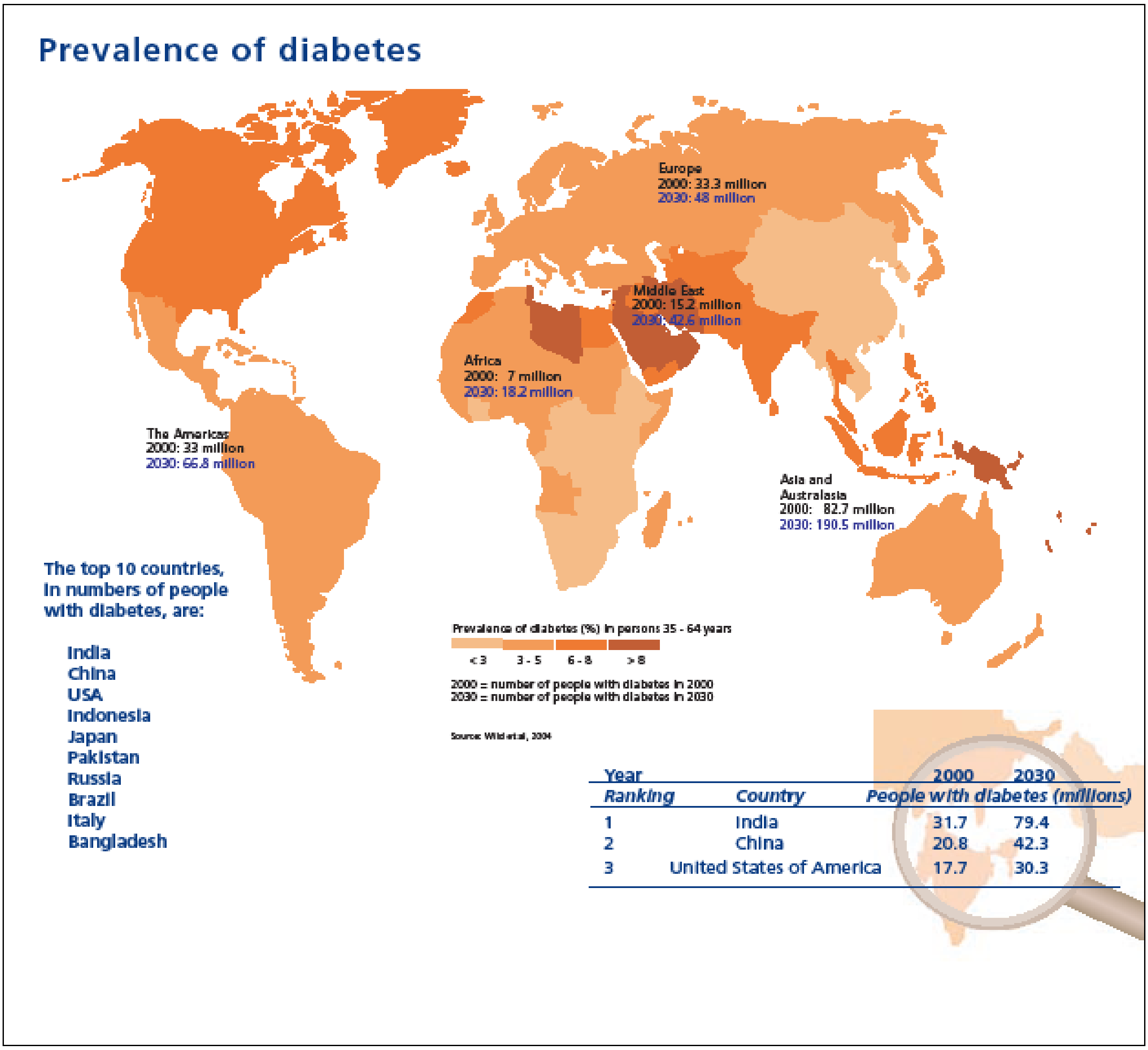
Because the number of studies on the effect of vitamin D on the prevention and regulation of diabetes are few a further investigation into this matter is suggested – a randomised controlled trial in which the effect of vitamin D supplementation therapy is evaluated for various groups of migrants in The Netherlands. The trial should include:

* Study subjects in a pre-stage of diabetes to assess the efficacy of supplementation in the management of diabetes
* Genetic variation among the different groups of migrants in The Netherlands
* The applicable dosage and duration of the vitamin D supplementation therapy with regards to the different stages in diabetes should further be researched. A minimum dose of 1332IU is recommended.
  Stakeholders: VWS, academic research institutions, general practitioners.

The outcome of the trial will lead to the further understanding on the improvement of diabetes prevention and management strategies directed on migrants in The Netherlands.

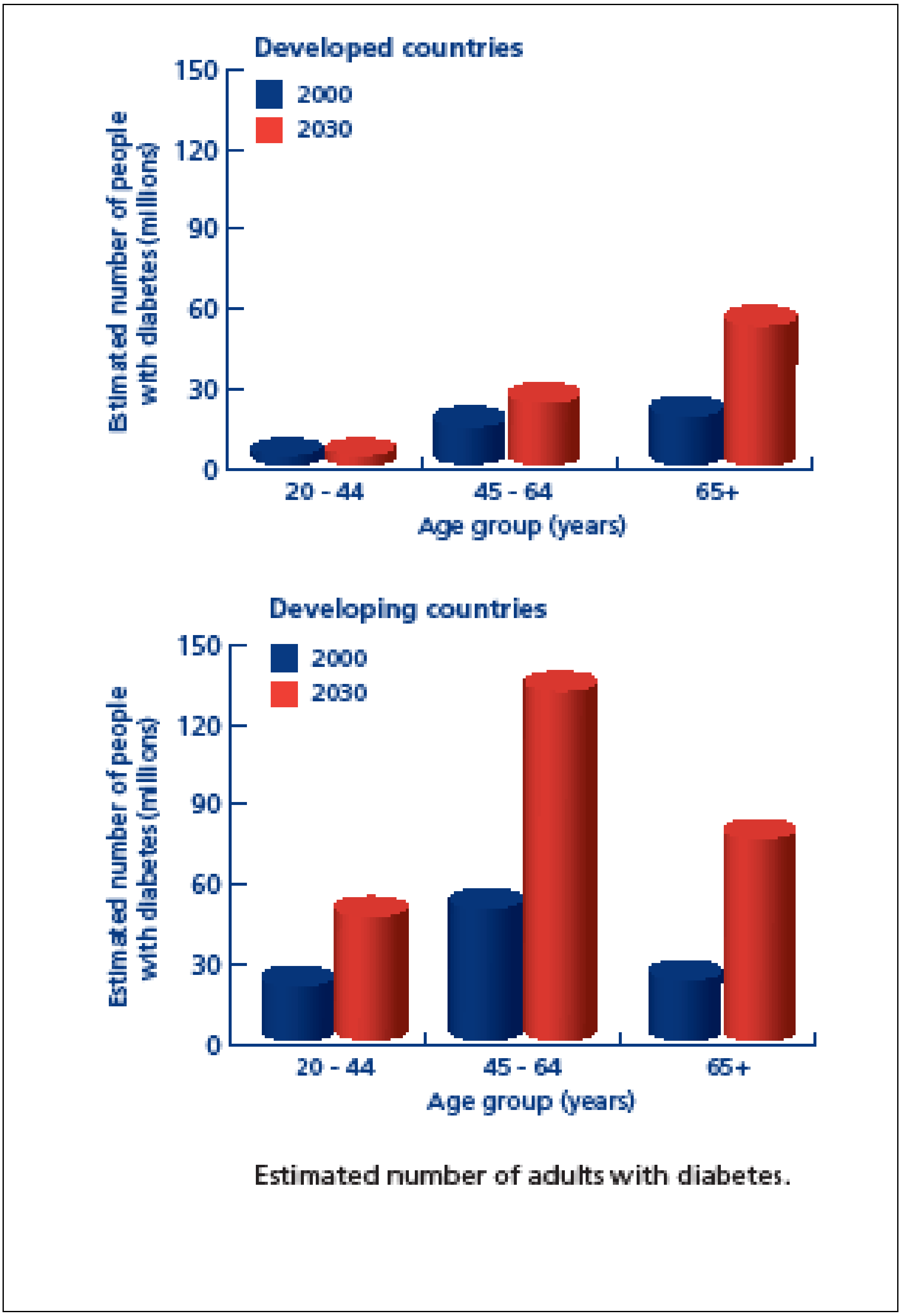
6. Annexes

Annex 1. *Prevalence of diabetes for various countries worldwide*
source: *http://www.who.int/diabetes/actionnow/en/mapdiabprev.pdf*



Year		2000	2030
Ranking	*Country*	*People with diabetes (millions)*	
1	India	31.7	79.4
2	China	20.8	42.3
3	United States of America	17.7	30.3

Annex 2. *Estimated number of people with diabetes indicated per age-group for developed and developing countries*



Source: worldwidehttp://www.who.int/diabetes/actionnow/en/mapdiabprev.pdf

Annex 3. *Radiograph of a patient with osteomalacia (arrows indicating multiple pseudo fractures) (Akkus et al. 2001)*

Annex 4. *Reported CROSS-SECTIONAL associations in studies among native populations*

study characteristics	**measure**	**population**	**outcome**	**additional comments**
China (Beijing, Shanghai), cross-sectional study (Lu et.al. 2009)	Fasting Insulin and glucose (HOMA-IR)	M 1443, F 1819, age 50 - 70	Mean 25 (OH)D 40.4nmol/L. Significant inverse association between 25(OH)D, fasting glucose and fasting insulin (P = 0.0114)	25(OH)D was negatively associated with fasting insulin only when BMI ≥ 24 kg/m^2 (p = 0.0001) but not in those with BMI < 24 kg/m^2 (p = 0.5948 and 0.5874 for insulin. Adjusted for covariates: age, sex, physical activity, BMI
USA, cross-sectional study (Thomas et.al. 1998)	Fasting glucose	290 patients from a general ward in hospital, mean age 44 ± 14, M: 48%, F: 38%	Type 2 diabetes (p = 0.04) was significantly associated with hypovitaminosis D. (< 37nmol/L, Mean serum 25 hydroxyvitamin D 15 ± 9ng/L	No correction for covariates
Italy, cross-sectional study (Isaia et.al. 2001)	Fasting glucose	799 Italian women	25(OH)D levels (means 6 SD) were significantly lower in diabetic patients than in control subjects (1169.8 vs. 9611.3ng/ml (p < 0.008), prevalence of 25(OH)D deficiency (< 5ng/ml) was significantly higher in diabetic patients than in control subject (39 vs. 25%)	The ADL score was significantly worse in diabetic patients than in control subjects (p < 0.01). BMI significantly higher in diabetic patients. No adjustment for covariates
US, cross sectional study (Becker et.al. 2006)	Patient records	155 women and 30 man with acute fragility fractures	38% of diabetes prevalence in group of vitamin D < 13, 15% in group: 13 - 19, 18% in group > 20 (p = 0.009)	Higher prevalence of diabetes among American black then whites. Not corrected for covariates like BMI

Japan, cross-sectional study (Suzuki et.al. 2006)	HbA1c	581 Japanese patients with diabetes and 51 without, F: 342, F: 290, mean age 61.6	Mean serum 25(OH)D 17.0 +/- 7.1ng/ml. Serum D not significantly different from normal population. Hypovitaminosis (25(OH)D < 20ng/ml) associated with HbA1c ($p = 0.013$)	Hypovitaminosis not Related to BMI. Adjusted for covariates: age, BMI
Indonesia, geriatric clinic, age > 60, cross-sectional study (Hidayat et.al. 2010)	History of diabetes	Indonesian F (66.7%), mean age 71 years (SD ± 6.0). N = 78, 40 in diabetes group and 38 in non-DM group	no significant correlation between vitamin D deficiency and diabetes ($p = 0.456$). Total prevalence of vitamin D deficiency 78.2% (50nmol/L)	Female sex, obesity and sunscreen application positive correlation with vitamin D deficiency. Adjusted for covariates: BMI, sex, age, outdoor activities
UK, systematic review + meta-analysis (Parker et al. 2010)	NI	28 studies that met inclusion criteria, 99,745 participants	High levels of vitamin D among middle age elderly populations associated with decrease in diabetes	
Oslo, cross-sectional study (Lagunova et al. 2009)		2126 patients registered in Metabolic clinic in Oslo	Significant decrease of serum 25(OH)D3 with increasing BMI	Prevalence of vitamin D deficiency was highest in individuals with BMI > 40, 32% among women and 46% among men
Finland, prospective study (Michos 2009)	Patient records	412 incident diabetes cases and 986 controls, total 7503, age 40 years	Higher baseline 25(OH)D reduced the risk of diabetes with 72%	Only in men, not in women

Iran, cross-sectional study (Bonakdaran et.al. 2009)	Fasting glucose	119 diabetes patients	Prevalence of low Vitamin D 26.1% among diabetic patients, not significant with control group (p = 0,12)	Patients with vitamin D deficiency had significant differences in BMI (p = 0.003)
USA, cross-sectional study (Yoho et.al. 2009)	Patient records	41 participants with diabetes	Vitamin D levels in diabetic population significantly lower (p < 0.05) then in non-diabetic population	
USA, cross-sectional study (Melamed et.al. 2008)	Fasting glucose	13331 participants from the Third National Health and Nutrition Examination Survey (NHANES III) > 20 years	Diabetes independently associated with low level of 25(OH)D (17.8ng/mL)	Higher BMI also independently associated with low 25(OH)D (17.8ng/mL), physical activity inversely associated. Adjusted for covariates: age, sex, race, season, BMI
Germany, national health survey, cross-sectional study (Hintzpeter et.al. 2008)		1763 men and 2267 women, age 18 - 79 year	Significantly lower serum 25(OH)D observed in women with diabetes type 2, Median serum 25OHD 45.2nmol/L for men and 44.7nmol/L for women	Independent determinant of 25(OH)D was physical activity, BMI inversely correlated with 25 OHD. Adjusted for age, sex, season
Bangladesh, cross-sectional study (Islam et.al. 2006)	Patient history	Non-veiled women: 36, veiled women: 30, non-veiled diabetic women: 55	No statistical difference between Vitamin D deficiency within three groups	General hypovitaminosis common among Bangladeshi women

US, meta-analysis of systematic reviews (Pittas et al. 2007)		Observatio-nal studies and clinical trials	Observational studies: relatively consistent inverse association with diabetes and Vitamin D deficiency 0.36 (0.16 - 0.80) among non-Blacks for highest versus lowest 25(OH)D	Most studies no adjustment for confounders
USA, cross-sectional study (Kositsawat et.al. 2010)	HbA1c	9,773 adults age > or = 18 years old, participating in the 2003 - 2006 National Health and Nutrition examination Survey	Serum 25(OH)D levels were inversely associated with HbA1C levels. In subjects age 35 - 74 years ($p = 0.0045$), not reported with diabetes ($p = 0.0282$)	Accounted for covariates: race, ethnicity, sex, BMI, physical activity.
USA, prospective study (10 years) (Forouhi et.al. 2008)	Fasting glucose, fasting insulin and HOMA-IR	524 Non diabetic F and M. Age 40 - 69 years	Mean vitamin D: M: 64.5nmol/L, F: 57.2nmol/L. Fasting glucose ($p = 0.019$) insulin resistance ($p = 0.010$) inversely associated with vitamin D	Adjusted for age, sex, BMI
Italy, cross-sectional study (Muscogiuri et.al. 2010)	Hyperglycae mic clamp	39 non diabetics, mean age: 41.4 ± 12,4, F: 54%, M: 46%	No significant correlation between 25(OH)D and insulin sensitivity ($p < 0.01$) when corrected for BMI. Mean 25(OH)D 40.4 ± 18.3	Significant correlation between 25(OH)D and BMI. Adjusted for cofounders like BMI

Middle East, cross-sectional study (Gannage-Yared et.al. 2009)	Fasting insulin and glucose (HOMA-IR)	381 Lebanese students, mean age 23.9 ± 3.9, 201 males, 180 females	Mean 25(OH)D: 77.4 ± 31.2nmol/L. Inverse correlation between 25(OH)D fasting plasma glucose and insulin resistance. After adjustment for confounders only significant for fasting glucose	Adjusted for covariates sex, physical activity and BMI
Europe, cross-sectional study (Gulseth et.al. 2010)	HOMA, Glucose Tolerance test	446 subjects from 8 European countries, age 35 - 70 years with metabolic syndrome	Mean 25(OH)D 57.1 ± 26.0nmol/L. Multiple linear analysis not associated with parameters of insulin action or secretion after adjustment for BMI + covariates	Adjusted for covariates: BMI
UK, cohort study (Kayaniyil et.al. 2010)	HOMA-IR, OGTT	712 subjects at risk for diabetes, mean age 49.0 ± 10 years, F: 69,9%	Independent associations of 25(OH)D with insulin resistance and insulin sensitivity	Adjusted for covariates: BMI, physical activity
Finland, longitudinal, multivariate (Mattila et.al. 2007)	Fasting glucose	4097 adults, age 40 - 69, M: 47%, F: 53%	Significant inverse association between 25(OH)D and incidence diabetes. Mean serum 25(OH)D 43.6 ± 19.5nmol/L	Significant higher 25(OH)D with a lower BMI. When correction of correlation for BMI and leisure time correlation attenuated (p = 0.07). Covariates: BMI, leisure-time exercise, smoking and education

Annex 5. *Intervention studies among native populations*

study characteristics	measure	population	outcome	additional comments
Australia, intervention study (Tai et.al. 2008a)	OGTT, fasting insulin and glucose	33 adults with vitamin D insufficiency (< 50nmol/L) and impaired glucose tolerance test. Mean age 55 years	No significant effect on blood glucose ($p = 0.63$) or insulin mean ($p = 0.67$) or sensitivity ($p = 0.74$) after two dose of 100000IU of Cholecalciferol, mean serum vitamin D at start 39.9 ± 8.5	No association between glucose/insulin homeostasis and vitamin D, short term measures
Norway, RCT (Jorde et.al. 2009)	Fasting insulin, glucose and c -peptide	36 patients with diabetes, age 21 - 75, M: 56%, F: 44%, mean serum 25(OH)D 60 ± 40 in vitamin D group and 58.5 ± 21 in placebo group	No difference in Vitamin D supplementation group (40,000IU/week for 6 months) and placebo group between fasting glucose, insulin ($p = 0.90$)	No difference in baseline BMI between two groups
Scotland, RCT (Avenell et.al. 2009)	Patient history	5292 patients, age > 70 years, mean age 77 years, 85% female, baseline Vitamin D <44nmol/L	No evidence that vitamin D in daily use of 800IU was able to prevent diabetes	No data on BMI or glycaemic control
USA, pilot prospective randomized trial (Patel et.al. 2010)	Fasting glucose and insulin sensitivity, HbA1c	24 patients with diabetes and serum 25(OH)D < 25ng/ml	Mean 25(OH)D 17.6 ± 1.5. No significant improvement of fasting plasma glucose, HbA1c after 1200IU Cholecalciferol for 4 months	No change in BMI after vitamin D treatment

US, RCT (Orwoll et.al. 1994)	Meal challenge	35 diabetic patients (23 males), mean age: 61 ± 8, vitamin D concentra-tion 35 ± 7nmol/L	In 20 subjects, a double blind, placebo controlled trial of treatment with 1, 25(OH)D (400IUp/d for 4 days), no effect fasting glucose, Insulin C treatment or glucagon concentrations	No adjustment for confounders
Bulgaria, intervention study (Borissova et.al. 2003)	Glucose tolerance test	10 females with diabetes, matched group of 17 females with normal glucose tolerance	Mean 25 (OH)D levels 35.3 ± 15.1nmol. 70% deficient. Significant change in first phase of insulin secretion after Vitamin D supplementation 1332IU cholecalciferol/d for one month ($p < 0.018$)	No significant change in insulin resistance
India, RCT (Nagpal et.al. 2009)	OGTT	100 Asian Indian male, age > 35 years	Three doses of vitamin D3 120.000IU in treatment group and placebo in control group. Age and baseline adjusted 25 hydroxyvitamin D difference in change in oral glucose insulin sensitivity. No change in insulin secretion. Mean 25(OH)D: 34.44 ± 5.02	Adjusted for covariate: BMI
India, RCT (Parekh et.al. 2010)	OGTT, fasting glucose + insulin	28 Asian Indians with diabetes	No association with treatment with 25(OH)D glucose tolerance and insulin resistance	

Denmark, RCT (Lind et al. 1989b)	Glucose tolerance test	10 Danish men with impaired glucose tolerance. Age 60 - 63 years	No change in insulin sensitivity after 18 months of treatment with oral alphacalcidiol, 800IU/day	No correction for BMI
Sweden, RCT (Ljunghall et.al. 1987)	Glucose tolerance test	65 Caucasian men, age 61-65 years with impaired glucose tolerance	Non change in insulin sensitivity after three months treatment with oral 0.75 microgram. Day alphacalcidiol. Mean vit D: 92.4 ± 23.5nmol/L in treatment group and 97.3 ± 72.4 in placebo group	No correction for BMI
Germany, RCT (Fliser et.al. 1997)	Euglycemic clamp	18 German males, age 26 years	No change in insulin sensitivity after 7 days of oral 1.5 microgram 1.25(OH)D versus placebo	No correction for BMI

Annex 6. *Reported CROSS-SECTIONAL associations between vitamin D deficiency and Diabetes among migrant populations*

study characteristics	measure	population	outcome	additional comments
10 cohorts from worldwide geographic area, cross sectional study (McCullough et.al. 2010)	Patient history of diabetes	N = 4,723, F: 53%, M: 47%, worldwide geographic area, age > 50 years	Significant negative correlation with history of diabetes and low vitamin D < 50nmol/L)	Other significant inverse correlates body mass index, sedentary behaviour, smoking and black race/ethnicity
Australia, cross-sectional study (Luo et.al. 2009)	HbA1c	109 Chinese patients > 50 years with diabetes	Prevalence Vitamin D deficiency (< 50nmol/L) 36%, no relation found between low Vitamin D and metabolic control	Study suggests that low vitamin D has no clinical impact on metabolic control and correction doesn't have therapeutic implications. Adjusted for BMI
UK, cross-sectional study (Tahrani et.al. 2010)	HbA1c	210 Asian patients (85.9% Muslims), 170 with and 40 without diabetes	Vitamin D deficiency more common in diabetics: 83% versus 70%; ($p = 0.07$,) HbA1c higher in women with vitamin D deficiency (< 50nmol/L)	High prevalence of vitamin D deficiency as a whole (> 80%) Adjustment for age, sex, not for BMI
Multi-ethnic, cross-sectional study (Gorham et.al. 2009)	Patient records	20.427038 persons age 18-44	2,918 new cases of insulin-requiring diabetes, incidence rates twice as high in black as in white ($p < 0.001$) and with a peak in winter season ($p < 0.01$)	Since race and seasonal differences persisted in multivariate analysis suggest contribution from Vitamin D deficiency. Adjusted for covariates: age, sex, and race. No information on BMI

USA, cross-sectional study (Chiu 2004)	Hyper-Glycemic Clamp/ OGTT	126 healthy glucose tolerant people (34 Asian, 54 white, 27 Mexican American) living in California. 73 women and 53 men. Mean age 26 ± 6 years	Positive correlation of 25(OH)D with insulin sensitivity ($p < 0.0001$). Hypovitaminosis D (< 20ng/ml), mean vitamin D: 46.9nmol/L. Not significant after adjustment for covariates	25(OH)D concentration determined by ethnicity ($p = 0.0086$) and BMI ($p = 0.0033$) Prevalence of Vitamin D < 20ng/mL: Asian; 47%, African: 54%, White: 26%, Mexican: 41%. Adjusted for covariates: age, sex, BMI
London, cross-sectional study (Boucher et.al. 1995)	OGTT	44 glucose intolerant Asians living in UK. Mean age 44.9 years	Mean 25(OH)D 9.0 ± 4.5nmol/l. Correlation between vitamin D deficiency and high blood sugar, ($p = 0.04$,) mean serum 25(OH)D	Corrected for confounders: age, sex, BMI
USA, cross sectional study (Alvarez et.al. 2010)	HOMA-IR, fasting insulin, fasting glucose	115 African American, 137 European American women	Vitamin D positively associated with insulin sensitivity and resistance among African Americans	Adjusted for covariates: age, BMI, ethnic group
USA, cross-sectional study (Becker et.al. 2006)	Patient records	155 women and 30 man with acute fragility fractures	38% of diabetes prevalence in group of vitamin D < 13, 15% in group: 13 - 19, 18 % in group > 20 ($p = 0.009$)	Higher prevalence of diabetes among American black then whites. Not corrected for covariates like BMI
USA, cross-sectional study (Pinelli et.al. 2010)	Fasting glucose, HbA1c, OGTT	542 Arab Americans, mean age 38 ± 13	Mean serum 25(OH)D in men: 18 ± 6.4, females: 14.1 ± 7.1. In male 25(OH)D negatively correlated with insulin resistance ($p = 0.0043$), fasting glucose ($p = 0.027$) and A1C $p = 0.038$	No adjustment for covariates like BMI

Annex 7. *Intervention studies among migrant populations*

study characteristics	measure	population	outcome	additional comments
South Asian women living in New Zealand, RCT (von Hurst et.al. 2010),	HOMA-IR, fasting glucose and insulin	81 South Asian women (India, Pakistan, Sri Lanka), aged 23 - 68 with insulin resistance, vitamin D levels < 50nmol/L	Significant improvements in insulin sensitivity (p = 0.003) and insulin resistance (p = 0.02) after treatment with 4000IU vitamin D3/day for 6 months	Adjusted for covariates: BMI
UK, retrospective study (Sabherwal et.al. 2010)	HbA1c	South-East Asians (India, Sri Lanka, Pakistan, Bangladesh) N = 52, mean age 59.33 ± 7.98. Diagnosis of diabetes + vitamin D deficiency (< 50nmol/L)	Significant decrease in HbA1c after treatment with 4000IU vitamin D3 (p < 0.05) for three months	Significant negative correlations with changes in HbA1c and weight after change in vitamin D (p = 0.044)
London, cross-sectional study (Boucher et.al. 1995)	OGTT	44 glucose intolerant Asians living in UK. Mean age 44.9 years	Significant increase in insulin sensitivity after single dose of IV 100,000IU cholecalciferol	Corrected for confounders: age, sex, BMI

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