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Leiden  
The Netherlands

**Travel medicine : knowledge, attitude, practice and immunisation**  
Roukens, A.H.E.

**Citation**

Roukens, A. H. E. (2010, March 4). *Travel medicine : knowledge, attitude, practice and immunisation*. Retrieved from <https://hdl.handle.net/1887/15037>

Version: Corrected Publisher's Version

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Downloaded from: <https://hdl.handle.net/1887/15037>

**Note:** To cite this publication please use the final published version (if applicable).

## Symptoms of Infectious Diseases in Travellers with Diabetes: a Prospective Study with Matched Controls

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*Submitted for publication*

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## **Abstract**

### **Background**

Diabetic travellers to the (sub)tropics are thought to have symptomatic infectious diseases more often and longer than non-diabetics. Evidence for this is needed. This study evaluates whether diabetic travellers are at increased risk of symptomatic infectious diseases.

### **Methods**

A prospective study was performed between October 2003 and February 2008 among adult medication-dependent diabetic travellers, with their non-diabetic, non-immune-suppressed travel companions serving as matched controls. Thus, diabetics and controls were assumed to have comparable exposure to infection. Data on symptoms of infectious diseases were recorded by using a structured diary.

### **Results**

Among 70 insulin-dependent diabetics, the incidence of travel-related diarrhea was 0.99 per person-month, and the median number of symptomatic days 1.54 per month. For their 70 controls, figures were 0.74, and 1.57, respectively ( $p>0.05$ ). Among 82 non-insulin-dependent diabetics, incidence was 0.75, and the median number of symptomatic days was 1.68. For their 82 controls, figures were 0.70, and 1.68, respectively ( $p>0.05$ ). As for other symptoms, no significant travel-related differences were found between diabetics and controls.

Only 17% of diabetic travellers with diarrhea used their standby-antibiotics.

### **Conclusions**

Medication-dependent diabetic travellers to (sub)tropical destinations do not have symptomatic infectious diseases more often or longer than non-diabetics. Although the incidence of metabolic dysregulation among diabetic travellers should be assessed in more detail, routine prescription of stand-by antibiotics against uncomplicated travellers' diarrhea is probably not useful, in particular not for NIDD. Self-treatment should be reserved for more complicated diarrhea.

## Introduction

In recent years, the number of travellers to (sub)tropical countries has increased dramatically [1], including those with pre-existing medical conditions such as diabetes. Due to improved awareness and support for diabetic travellers, their number probably will continue to rise [2,3].

Travelling to the (sub)tropics may complicate an underlying medical condition and may require special considerations and advice. For example, it has been suggested that diabetic travellers have a higher risk of metabolic dysregulation and symptomatic infectious diseases [4-6]. Dutch travel guidelines thus recommend that diabetics taking insulin or oral anti-diabetic medication should be prescribed stand-by antibiotics for treatment of diarrhea while in the (sub)tropics [7]. British guidelines likewise advise to consider prescribing a course of antibiotics for diabetic travellers [8]. However, data on the association of diabetes mellitus with tropical infections, and on the benefits of preventive and therapeutic measures are lacking. Even evidence for a causal relation between diabetes and domestic infections is limited and inconsistent [9].

The exact number of diabetics who visit the (sub)tropics is not known. In a study published in 1991, 0.4% of 2445 travellers to a developing country who visited a travel clinic had insulin-dependent diabetes mellitus [10]. Since then, the prevalence of diabetes, both insulin-dependent and non-insulin-dependent, has increased. Annually, about ninety million persons travel to the (sub)tropics from North America and Europe [11], where diabetes prevalence is about 2.8% [12]. Assuming that diabetics travel as frequently as non-diabetics, an estimated 2.5 million diabetics travel annually from North America and Europe to (sub)tropical destinations.

In order to improve travel advice for this substantial group, we conducted a prospective study with matched controls to see if diabetics are more susceptible to symptomatic infectious diseases than non-diabetics. We also studied the usage of antibiotics for stand-by treatment of diarrhea among diabetics.

## Methods

### Study population

A prospective study with matched controls was performed among travellers who attended the travel clinics of the Public Health Service Amsterdam or the Leiden University Medical Centre between October 2003 and February 2008. All medication-dependent diabetics 18 years or older were eligible if planning to travel to one or more (sub)tropical countries together with a non-diabetic, non-immune-suppressed travel

companion, who was within 10 years of their own age. Thus, the control group was comparable for travel destination, travel duration, and exposure. Tropical or subtropical destinations were defined as those with moderate to high risk on hepatitis A according to the World Health Organization [13].

Insulin-dependent diabetes (IDD) was defined as diabetes mellitus requiring daily insulin treatment, with or without additional oral anti-diabetics. Non-insulin-dependent diabetes (NIDD) was defined as diabetes mellitus requiring only oral anti-diabetics.

### **Survey methods and definition of symptoms**

A standard questionnaire was used to collect data on socio-demographics and medical history. Diabetics and controls were asked to fill out a structured diary about symptoms of infectious diseases, from the day they visited the travel clinic (up to 4 weeks before departure), until 2 weeks after return from travel. Data were collected before departure to gain information about baseline symptoms, and for 2 weeks after return to encompass incubation periods of the most (acute) travel-related infectious diseases. In the results section, the term 'travel-related' refers to the period of travel itself and the two weeks thereafter.

Recorded in the diary were any episodes of fever, diarrhea, vomiting, rhinitis, cough, and signs of skin infection; consultation with a doctor; and whether the diabetics used the stand-by antibiotics or other medication. Fever was defined as a self-measured body temperature of 38.5 degrees Celsius or more. Diarrhea was defined as loose or watery stools. Rhinitis was defined as nasal discharge or congestion. Cough could be dry or productive. Signs of skin infection included redness or (itching) rash, swelling, tenderness, and/or pus-like drainage. The diary also provided for recording non-infectious symptoms and signs, such as dysregulation of blood glucose level. Diabetics monitored blood glucose levels at their own discretion.

All diabetics were prescribed ciprofloxacin (500 mg 2 times a day for 3 days), to be used as immediate self-treatment in case of traveller's diarrhea, according to the Dutch national guidelines on travel advice [7].

Power-analysis showed that 70 pairs were needed to prove a diarrhea outcome ratio of 2 or more, with  $\alpha = 0.05$  and power = 80%.

This study was approved by a medical ethics committee. All participants gave their informed consent.

### **Statistical Analysis**

For non-independent, non-matched characteristics, McNemar's statistic testing was performed (SPSS for Windows release 15.0, SPSS Inc., Chicago, USA). A p-value < 0.05 was considered to be statistically significant.

A random effects Poisson regression model was used to calculate incidence rates and accompanying incidence rate ratios (IRR). Incidence rate was defined as the number of symptom onsets divided by the sum of symptom-free days for all individuals during a specific time period. A random effects logistic regression model was used to calculate median number of symptomatic days and accompanying odds ratios. Median number of symptomatic days equals an individual's probability to have a symptom per day. It was calculated to compare the disease burden between the diabetics and non-diabetic controls. In order to express results in units per month, numbers per day were multiplied by 30.

The random effects model takes into account two levels of correlation: 1) diabetics and their travel companions had more or less the same exposure, and thus are not independent; 2) for incidences, there may be repeated episodes of a symptom within an individual; for numbers of symptomatic days, presence of symptoms over the days within an individual are correlated. IDD and NIDD were analyzed separately.

For estimation of the parameters, a Bayesian approach was used, starting with non-informative priors. Posterior distributions were obtained by Markov Chain Monte Carlo methods, using the WinBUGS program [14,15]. Three chains were generated, based on different sets of baseline values. Parameter estimates are the medians of the posterior distributions. The range from the 2.5% to the 97.5% quantile is used to quantify the uncertainty in the parameter estimates. This range can be interpreted as a 95% confidence interval and will be referred to as such. If 1 is not included in the 95% confidence interval of a ratio, the ratio can be considered statistically significant ( $p < 0.05$ ).

## Results

During the study period, 210 diabetics planning to travel with a non-diabetic, non-immune-suppressed companion were eligible for inclusion: 93 IDD, and 117 NIDD. Of these 210 eligible pairs, 58 (28%) did not participate, citing lack of time (34%), lack of interest (57%) or reasons unspecified (9%). The remaining participants all provided a completed diary.

### Characteristics of the study sample

The study sample comprised 70 IDD and their 70 controls, plus 82 NIDD and their 82 controls. Of these 152 pairs, 137 (90%) were included at the Public Health Service Amsterdam, and 15 (10%) at the University Medical Centre Leiden. Table 1 shows the characteristics per type of diabetes.

Sixty-four IDD (91%) and 70 NIDD pairs (85%) matched for country of birth; only 8 IDD (11%), and 12 NIDD pairs (15%) matched for gender (data not shown). The IDD more often had cardiovascular disease and dyslipidemia than their controls ( $p < 0.05$ ). There was no difference in the use of gastric acid inhibitors. The NIDD more often had non-ischemic cardiovascular disease and dyslipidemia than their controls ( $p < 0.05$ ). Their use of gastric acid inhibitors seemed more frequent, but not significantly.

### **Incidence rates and number of symptomatic days between diabetics and their controls**

Table 2 shows the travel-related symptoms by prevalence, incidence rate, mean duration among symptomatics, and median number of symptomatic days per symptom for IDD and their travel companions. The figure in Table 2 shows the accompanying incidence rate ratios (IRR) and odds ratios (OR) on a logarithmic scale. Likewise, table 3 shows the results for NIDD and their controls.

#### **IDD and controls**

The prevalence of travel-related diarrhea was 44% among IDD and 41% among controls. The incidence rate of travel-related diarrhea was 0.99 per person-month versus 0.74; the IRR showed no significant difference. The median number of days with diarrhea was 1.54 per month among IDD, comparable to controls.

Diarrhea outcome measures before travel showed no significant differences between IDD and controls ( $p > 0.05$ ) (data not shown).

Diarrhea incidence rate and median number of symptomatic days were higher during travel than before travel, for both IDD and their controls ( $p < 0.05$ ) (data not shown).

The IDD and controls did not significantly differ in travel-related incidence rates and median number of symptomatic days for vomiting, fever, cough, rhinitis, and signs of skin infection. Nor did they differ pre-travel, except that the median number of days with cough was lower among IDD ( $p < 0.05$ ) (data not shown).

Travel-related and pre-travel outcome measures did not differ significantly, except that cough among IDD increased after departure in incidence rate and median number of symptomatic days ( $p < 0.05$ ), although confidence intervals approximated 1 (data not shown).

#### **NIDD and controls**

The prevalence of travel-related diarrhea was 39% among NIDD and 43% among controls. The incidence rate was 0.75 per person-month versus 0.70; the IRR showed no significant difference. The median number of days with diarrhea was 1.57 per month among NIDD, comparable to controls.

Pre-travel diarrhea incidence rate and median number of symptomatic days were higher for NIDD than controls ( $p < 0.05$ ) (data not shown).

Diarrhea incidence rate and median number of symptomatic days were higher during travel than before travel for both NIDD and controls ( $p < 0.05$ ) (data not shown).

Travel-related incidence rates and median number of symptomatic days for vomiting, fever, cough, and rhinitis were comparable between both groups. The travel-related incidence rate and median number of days for signs of skin infection were higher among NIDD than among controls. However, these measures also differed before travel (data not shown) and showed no significant increase after departure (data not shown).

Before travel, incidence rate and median number of symptomatic days for vomiting were higher for NIDD than controls ( $p < 0.05$ ) (data not shown).

Travel-related and pre-travel outcome measures did not differ significantly, except that rhinitis and vomiting among controls increased after departure in both incidence rate and median number of symptomatic days ( $p < 0.05$ ) (data not shown).

#### **Treatment and doctor consultation**

Only 6 out of 31 IDD with diarrhea (19%) used the stand-by antibiotics. Effect on the duration of diarrhea was unclear due to small numbers. Seven (23%) used loperamide or activated carbon, and 3 (10%) used oral rehydration solution. Of 29 controls with diarrhea, 10 (34%) used loperamide or activated carbon, and 1 (3%) used oral rehydration solution (not statistically different from IDD).

Only 5 out of 32 NIDD with diarrhea (16%) used the standby antibiotics. Effect on the duration of diarrhea was unclear due to small numbers. Nine diabetics (28%) used loperamide or activated carbon, and 1 (3%) used oral rehydration solution. Of the 35 controls with diarrhea, 12 (34%) used loperamide or activated carbon, and 1 (3%) used oral rehydration solution (not statistically different from NIDDs).

As to the use of other medication (antibiotics, antipyretics, and anti-inflammatory drugs) and doctor consultations, both IDD and NIDD were comparable to their controls.

#### **Dysregulation of blood glucose**

Of 70 IDD, 3 (4.3%) reported dysregulation of blood glucose levels during travel. A 69-year old woman had two hypoglycemic episodes, of which one coincided with non-febrile diarrhea, for which she took stand-by antibiotics. A 47-year old man had a 2-day episode of hyperglycemia without fever or diarrhea. A 25-year old woman had 2 alternating hypo- and hyperglycemic episodes, of which one coincided with non-febrile diarrhea, for which she took no stand-by antibiotics.



**Table 1** Characteristics of the insulin-dependent and non-insulin-dependent diabetics, and their controls

	IDD	Controls	Odds ratio (p-value)	IDD	Controls	Odds ratio (p-value)
Number of participants	70	70		82	82	
Sex						
Male	41	59%	25	36%	41	50%
Female	29	41%	45	64%	41	50%
Median age in years °	48	(34-59)	46	(33-59)	60	(53-67)
Country of birth						
Western country	57	81%	59	84%	51	62%
Non-western country	13	19%	11	16%	31	38%
Travel destination						
Middle East and North Africa	19	27%	Idem		12	15%
Sub-Saharan Africa	15	21%	Idem		18	22%
Asia	19	27%	Idem		31	38%
Latin America	17	24%	Idem		21	26%
Median travel duration in days °	21	(13-27)	Idem		20	(15-23)
Median duration data collection in days						
Before departure °	16	(10-21)	Idem		15	(11-28)
After departure °	34	(27-39)	Idem		33	(28-38)

Anti-diabetic treatment										
Metformin	18	26%	0			67	82%	0		
Sulfonylurea / thiazolidinedione drug	9	13%	0			50	61%	0		
Only short-acting insulin	5	7%	0							
Only intermediate-acting insulin	12	17%	0							
Only long-acting insulin	4	6%	0							
Intermediate- and short-acting insulin	11	16%	0						Long- and Continuous	
short-acting insulin	30	43%	0							
insulin infusion	8	11%	0							
Comorbidity										
Ischemic cardiovascular disease	9	13%	2	3%	4.5 (0.028)*	11	13%	8	10%	1.4 (0.63)
Other cardiovascular disease	17	24%	8	11%	2.8 (0.047)*	33	40%	19	23%	2.2 (0.035)*
Dyslipidemia	19	27%	1	1%	∞ (0.0001)*	39	48%	9	11%	11.0 (0.0001)*
Asthma/ COPD	2	3%	4	6%	0.5 (0.69)	4	5%	4	5%	1.0 (1.0)
Hypothyroidism	5	7%	1	1%	5.0 (0.22)	2	2%	2	2%	1.0 (1.0)
Gastric acid inhibitor medication	4	6%	6	9%	0.6 (0.73)	10	12%	4	5%	3.0 (0.15)

IDD = insulin dependent diabetics.

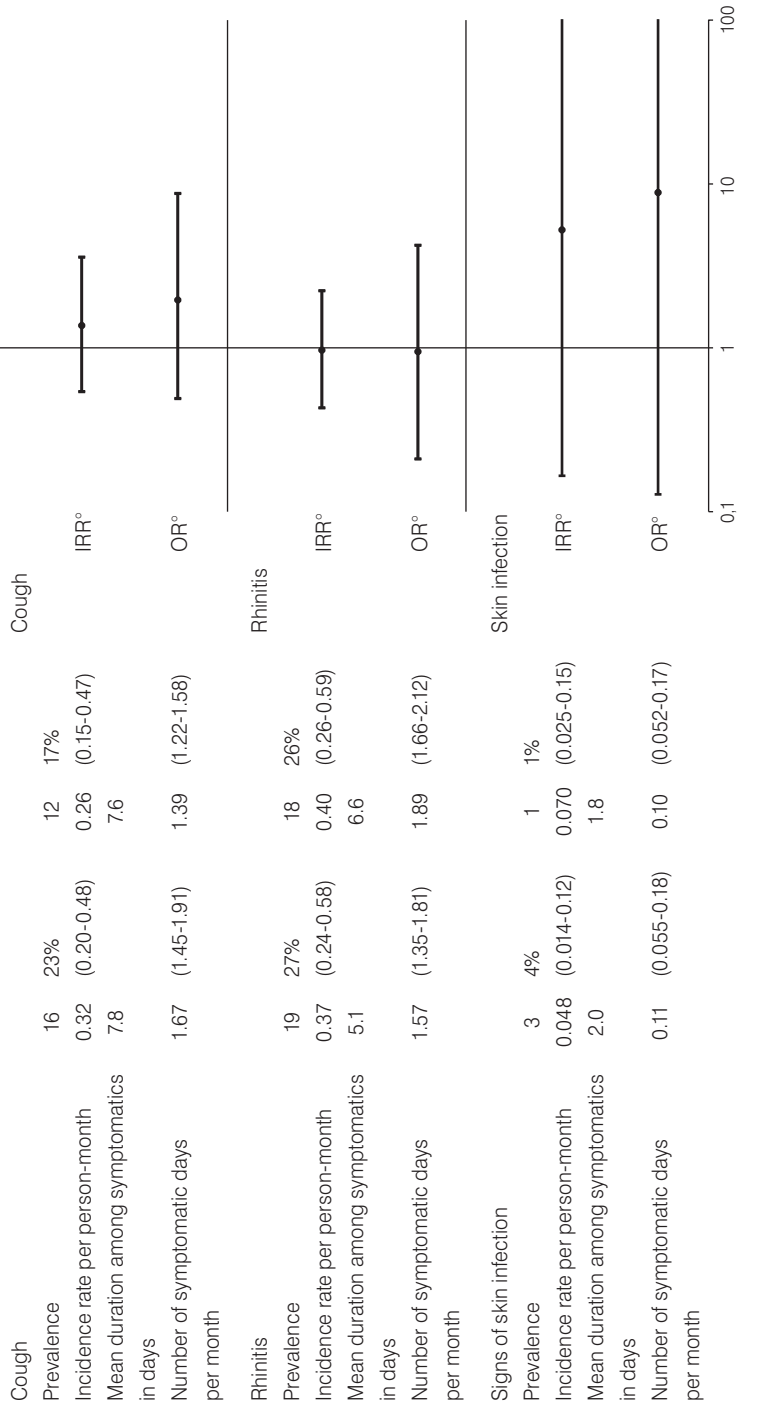
NIDD = non-insulin dependent diabetics.

° Interquartile range between brackets.

\* p-value < 0.05

**Table 2** Travel-related symptoms of infectious diseases among insulin-dependent diabetics and their non-diabetic controls

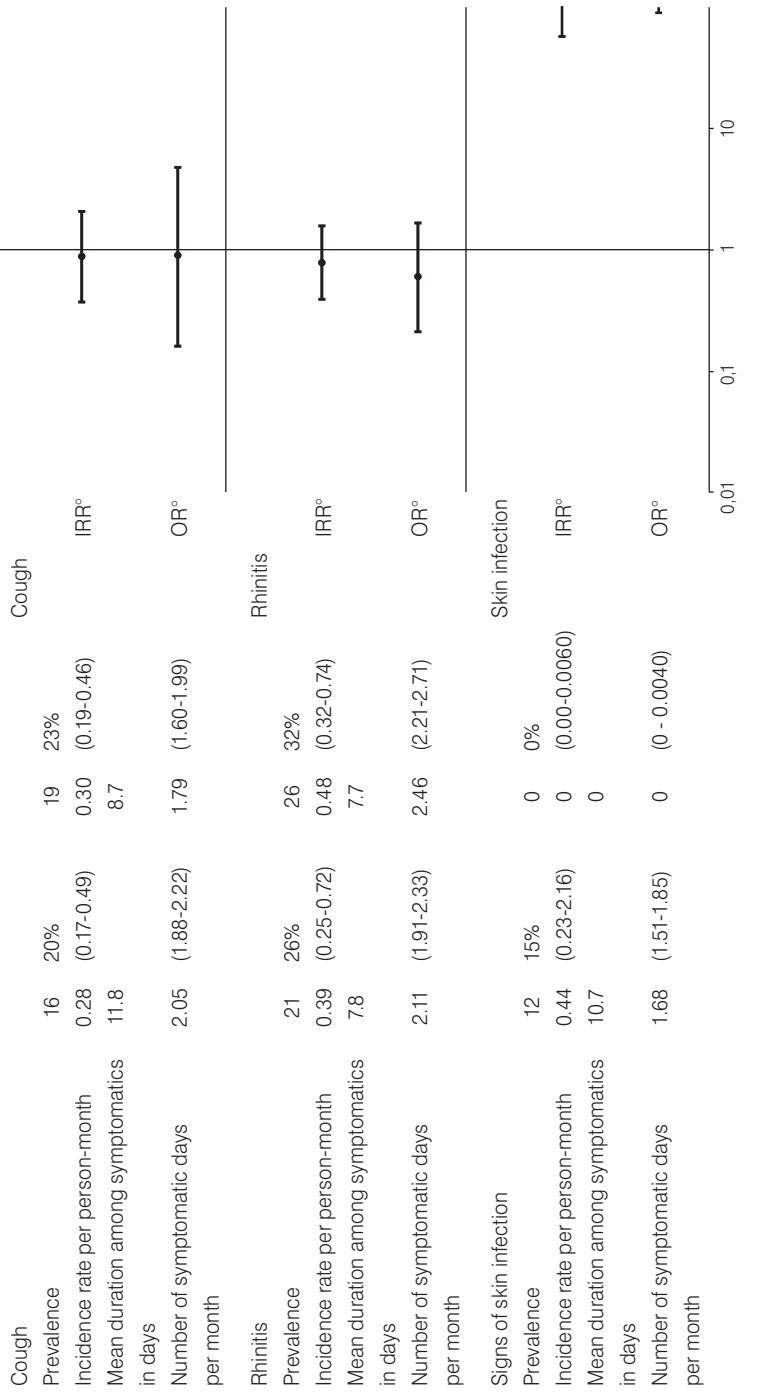
	IDD	Controls	Ratios with 95% confidence intervals, for IDD versus controls	
Number of participants	70	70		
<b>Diarrhea</b>				
Prevalence	31	29	41%	
Incidence rate per person-month	0.99	0.74	(0.75-1.28)	IRR°
Mean duration among symptomatics in days	1.9	2.5		
Number of symptomatic days per month	1.54	1.57	(1.30-1.82)	OR°
<b>Vomiting</b>				
Prevalence	4	2	3%	
Incidence rate per person-month	0.049	0.022	(0.014-0.12)	IRR°
Mean duration among symptomatics in days	1.0	2.0		
Number of symptomatic days per month	0.049	0.051	(0.015-0.12)	OR°
<b>Fever</b>				
Prevalence	9	7	10%	
Incidence rate per person-month	0.16	0.11	(0.084-0.27)	IRR°
Mean duration among symptomatics in days	2.4	1.7		
Number of symptomatic days per month	0.37	0.18	(0.25-0.52)	OR°



IDD = insulin-dependent diabetics, Numbers between brackets are 95% confidence intervals, IRR: Incidence rate ratio, IDD versus controls, with 95% confidence interval, OR: Odds ratio for the number of symptomatic days, NIDD versus controls, with 95% confidence interval, ° p>0.05, \* p<0.05

**Table 3** Travel-related symptoms of infectious diseases among non-insulin-dependent diabetics and their non-diabetic controls

	NIDD		Controls		Ratios with 95% confidence intervals, for NIDD versus controls	
Number of participants	82		82			
Diarrhea						
Prevalence	32	39%	35	43%		
Incidence rate per person-month	0.75	(0.56-1.00)	0.70	(0.52-0.91)	IRR°	
Mean duration among symptomatics in days	2.4		3.0			
Number of symptomatic days per month	1.57	(1.35-1.82)	1.69	(1.45-1.94)	OR°	
Vomiting						
Prevalence	3	4%	5	6%		
Incidence rate per person-month	0.049	(0.017-0.11)	0.051	(0.018-0.11)	IRR°	
Mean duration among symptomatics in days	2.0		1.2			
Number of symptomatic days per month	0.097	(0.044-0.18)	0.060	(0.023-0.12)	OR°	
Fever						
Prevalence	5	6%	6	7%		
Incidence rate per person-month	0.051	(0.018-0.11)	0.073	(0.031-0.14)	IRR°	
Mean duration among symptomatics in days	2.2		2.7			
Number of symptomatic days per month	0.12	(0.060-0.20)	0.20	(0.13-0.30)	OR°	



NIDD = non-insulin-dependent diabetics. Numbers between brackets are 95% confidence intervals. IRR: Incidence rate ratio, NIDD versus controls, with 95% confidence interval, OR: Odds ratio of the number of symptomatic days, NIDD versus controls, with 95% confidence interval, ° p>0.05, \* p<0.05

Of 82 NIDD, 2 (2.4%) reported dysregulation of blood glucose levels during travel. A 63-year old woman had one hyperglycemic episode, coinciding with non-febrile diarrhea, for which she did not take stand-by antibiotics. A 47-year old woman had a 4-day episode of hyperglycemia without fever or diarrhea.

## Discussion

This is the first prospective study evaluating whether medication-dependent diabetic travellers to the (sub)tropics are at increased risk for developing symptomatic infectious diseases. Although we hypothesized that they would have symptoms more often and longer than non-immune-suppressed non-diabetics, no differences in travel-related diarrhea, vomiting, fever, cough, or rhinitis were found. The NIDD had signs of skin infection more often than controls, unrelated to travel. A higher incidence rate and burden of non-travel-related signs of skin infection among type 1 and 2 diabetics has been reported before, irrespective of insulin use [9,16]. Why we found increased risk for skin infection only among NIDD and not IDD, may reflect differences in age, exposure, or unknown co-morbidity, such as pre-existing skin disease, carriage of *Staphylococcus aureus*, peripheral neuropathy, or microvascular disease [9,17].

Before travel, disease burden of cough seemed to be lower among IDD than controls. This coincided with a higher prevalence of asthma or chronic obstructive pulmonary disease among the controls, although the difference was not statistically significant ( $p > 0.05$ ).

Before travel, outcome measures for diarrhea and vomiting were higher among NIDD than controls. The increased diarrhea might be explained by medication, as the oral anti-diabetic metformin is known for such gastro-intestinal side effects [18]. Also, diarrhea has been associated with metabolic dysregulation. In a retrospective population-based survey including 423 IDD and NIDD and more than 8000 controls, non-travel-related diarrhea was more prevalent among diabetics than controls, with an OR of 2.06 (95% confidence interval 1.56 - 2.74) after adjusting for age and sex [19]. That study linked poorer levels of self-reported glycemic control with a higher prevalence rate of diarrhea.

Our study design had distinctive strengths. Structurally specified data were obtained prospectively and on a daily basis. Data collection started before departure (median 15 days) to gain insight into pre-existing symptoms. It continued until 2 weeks after return from travel to encompass incubation periods of the most (acute) travel-related infectious diseases. With a travel companion serving as a matched control, situational

specifics for diabetics and non-diabetics were comparable, which minimized any differences in exposure to infectious agents between the two groups. Diabetics and controls also matched in age and country of birth. They did not match for gender or for cardiovascular disease and dyslipidemia. However, prospective studies on travel-related infectious diseases found no association of symptoms of infectious diseases and gender [20,21], and we are not aware of any association with cardiovascular disease or dyslipidemia.

The prevalence of diabetes among visitors of our clinic was 3.1%, comparable with the general population [12]. Also, age and male-female ratio of our diabetic subjects were comparable with the general diabetic population. Participants' travel destinations were equally distributed across the four (sub)tropical regions. Their median travel duration of 20 days corresponded well with the median travel duration of the average traveller [22,23]. Thus, the study sample can be considered representative, and results can reasonably be applied to the average diabetic traveller to a (sub)tropical country.

This study has some limitations. Sample size may not have been large enough to detect small differences. Secondly, although the diary provided information on symptom duration, it did not distinguish mild symptomatology from severe. For example, diabetics could have had more bowel movements or more water loss. Thirdly, diabetics and controls differed in counseling and prescription; some diabetics did use the stand-by antibiotics. Therefore, the data may be skewed toward seeing less differences in outcome measures between both groups.

Metabolic dysregulation was minimal among our diabetics: 4.3% among IDD and 2.4% among NIDD. A retrospective, descriptive cohort study among IDD performed in 1996-1997 reported that 68% of 19 IDD travellers to tropical destinations had metabolic dysregulation [4]. Moreover, it found that 55% of those IDD reported dysregulations more frequently during travel than at home. This suggested that travel to the tropics is a risk factor for metabolic dysregulation. However, data were collected retrospectively, by telephone interviewing, and the study size was small and comprised only IDD. Finally, with improvements in the quality and use of insulin preparations and treatment schedules [5,24,25], diabetics might now be more aware and more compliant with anti-diabetic therapy, including its adjustments to travel-related alterations in eating habits, physical exertion, climate, and circadian rhythm.

Nevertheless, the prevalence of metabolic dysregulation in our subjects, may be underestimated, because regular testing of blood glucose levels during travel was not part of the study protocol. The diabetics monitored blood sugar at their own discretion.



Aside from such limitations, our findings represent diabetics who sought pre-travel health advice. One may assume that they had a more than average health awareness, particularly having received travel advice and knowing the objectives of the study. As to usage of stand-by antibiotics, it was carefully explained to all diabetics. Its importance was emphasized by an experienced travel health expert, and by means of information leaflets. Nevertheless, 83% of all diabetics with diarrhea did not use this treatment, even in the case of metabolic dysregulation. Of 152 stand-by antibiotic courses provided, 141 (92.8%) were not used. Moreover, NIDD did not experience hypoglycemias, only hyperglycemias. Indeed, hypoglycemia is uncommon when using only oral anti-diabetics [26]. Thus, routine prescription of stand-by antibiotics to prevent hypoglycemia during uncomplicated diarrhea is probably not useful. For IDD, monitoring blood glucose more frequently, and adjusting insulin dosage and diet accordingly, are probably more helpful in minimizing the impact of diarrhea or fever on metabolic dysregulation. Stand-by antibiotics may be useful for diabetic travellers to areas where health facilities are lacking or for complicated cases, for example 3 or more unformed stools per 24 hours with accompanying symptoms such as fever, or blood in stools. The merits of this definition could not be assessed in this study.

In conclusion, this study showed that medication-dependent diabetic travellers to (sub)tropical destinations do not have travel-related symptoms of diarrhea, vomiting, fever, cough, rhinitis, and signs of skin infection more often or longer than non-diabetics.

The incidence of metabolic dysregulation among diabetic travellers should be assessed in more detail, but our findings indicate that routine prescription of stand-by antibiotics against mild, uncomplicated travellers' diarrhea is probably not useful, in particular not for NIDD. Self-treatment could be of value for travellers to remote areas or for cases of complicated diarrhea.

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