## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | A prospective observational study of quality of diabetes care in a shared care setting: trends and age differences (ZODIAC-19) |
| **AUTHORS** | van Hateren, Kornelis ; Drion, Iefke; Kleefstra, Nanne; Groenier, Klaas; Houweling, Sebastiaan; van der Meer, Klaas; Bilo, Henk |

## VERSION 1 - REVIEW

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| **REVIEWER** | Goderis, Geert<br><br>competing interests: none to declare |
| **REVIEW RETURNED** | 28-May-2012 |

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| **THE STUDY** | The study is in general well performed with only few flaws in the description. There is a lack of clarity for some aspects;<br>- how were data collected, especially how happened the assessment of process parameters?<br>- in table 1: % of patients measured (eg HbA1c): is this at least once a year? What about 'optimal' follow-up (4 times a year)?<br>It would be better to explain how process and outcomes were collected instead of giving the definition (p. 8, line 1-11 is superfluous)<br><br>Statistical methods: what was performed in SPSS and what in SAS?<br>Statistical description of linear mixed models is very brief. What about assumption testing, outliers,...?<br>Interaction term of which main effects? (time*age I suppose)<br><br>a linear mixed model for binary outcomes is not possible PROC GLIMMIX is generalized linear mixed model with link function (and thus here a hierarchical logistic regression). |
| **RESULTS & CONCLUSIONS** | - There is first a problem of internal validity of the results. I think it is not possible to make a comparison of 4508 patients in 2005 and 18469 patients in 2006. This 'sudden explosion' in patients is also not explained.<br>- It is absolutely not clear to me how the "p for trend" (table 2) is related to the linear mixed models described in the method section. Time Trends in longitudinal analyses should analyse the timely evolution of individuals and thus take into account significance of the interaction term. This is important since the authors mention an improvement of diabetes care, which means a change (improvement) over time. The mere results do not allow this conclusion because they compare outcomes in different populations. (see remark above). In the interpretation, the authors insinuate that improvement is due to shared care. However, there is a general tendency in almost all Western countries of improved diabetes care (e.g. Germany, Belgium, France,....) with several publications |

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| | (e.g.Exp Clin Endocrinol Diabetes. 2009 Feb;117(2):88-94. Epub 2008 Aug 25). Improvement can be explained by organisational initiaves (CCM, shared care), but also by greater awareness since 2010 AND better medication (new OAD, antihypertensive drugs, widely use of statins,....) The authors should nuance their conclusions and place them in an international perspective referring to other articles describing time trends.<br>- In this perspective, the conclusions are somewhat trivial.<br>- The authors emphasize the importance of the study for older people ('first study...', p.13,line15). But what are then the conclusions, the lessons learned of this study about older people? Older people follow the same trend? Yes, and so?<br>- I do not agree that these results in this study (with a year by year change of included patients and a 'sudden explosion' of included patients in the year 2006 allow to conclude on a timely IMPROVEMENT. Outcomes are better, but this can be the result of other factors (eg. changing selection bias over the years). |
| **GENERAL COMMENTS** | - The Title is somewhat confusing: "shared care prospective observational study": a study cannot be "shared care". Better would be: Prospective (observational) study of quality of diabetes care in a shared care setting: trends and age differences.<br>- There are two major methodological limitations in this study:<br>1. No control group<br>2. no defined cohort<br>Every interpretation of the results should take into account these limitations and should compell to prudent, nuanced statements. |

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| **REVIEWER** | David C. Aron, MD, MS<br>Associate Chief of Staff/Education<br>Louis Stokes Cleveland Dept. of Veterans Affairs Medical Center<br>10701 East Blvd.<br>Cleveland, OH 44106<br>and<br>Professor of Medicine and Epidemiology and Biostatistics, School of Medicine, and<br>Professor of Organizational Behavior, Weatherhead School of Management,<br>Case Western Reserve University |
| **REVIEW RETURNED** | 14-Jun-2012 |

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| **THE STUDY** | First, let it be said that the questions above force dichotomous answers when the reality is that there is a continuum so that my responses seem harsher than they are. Second, this is a very interesting paper that represents the best in linking research and practice.<br><br>There is some lack of clarity regarding patients initially including in the standard care group. Were they switched to shared care when that became the standard for the Zwolle region? Were they not included in the analysis?<br><br>Another issue is A1c measurement. Were A1c measurements made using the same technology for the entire study. Did coefficients of variation for the assay vary among sites?<br><br>I have inferred that the analytic approach is that of serial cross sections. This should be explicitly stated. Assuming this is the approach used, it is far from ideal and ignores the differences |

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| | observed between serial cross sections and panel data. The latter approach has been reported but not cited: see Miller DR and Pogach. J Diabetes Sci Technol 2008;2:24-32 and Thompson W et al. HSR 2005;40:1818. |
| **RESULTS & CONCLUSIONS** | Two major concerns:<br>1. One major concern relates to conclusions drawn from serial cross sections. This approach does not account for secular changes in the extent to which diabetes is screened for and for "admixture" of less seriously ill patients. Although the relatively constant median duration of disease is somewhat reassuring, the determination of duration is fraught with difficulties. This is also not much of an issue for process measures of care, but for outcomes, especially A1c which, as shown in UKPDS, deteriorate over time, it is important. Changes in the nature of the population are suggested by the decreasing proportion of patients on insulin. (See work by Pogach and Miller)<br>2. Another concern is the issue of secular trends. That process measures of care improved is clear; that they resulted from shared care is not. This limitation is mentioned in the discussion. The temporary decreases in process measure adherence observed as large numbers of new sites were added could as easily be attributed to the effects of data reporting as to the mode of care delivery. |
| **GENERAL COMMENTS** | It might be worth mentioning the arbitrary nature of the thresholds for intermendiate outcome measures, especially as the importance of individualizing care is gaining greater recognition. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer: Geert Goderis
competing interests: none to declare

The study is in general well performed with only few flaws in the description. There is a lack of clarity for some aspects;
- how were data collected, especially how happened the assessment of process parameters?
- in table 1: % of patients measured (eg HbA1c): is this at least once a year? What about 'optimal' follow-up (4 times a year)? It would be better to explain how process and outcomes were collected instead of giving the definition (p. 8, line 1-11 is superfluous)

Response of authors: The quality measures are collected in the general practitioners' patients information systems during the yearly diabetic check-ups, and each year the relevant data are uploaded and sent to our diabetes centre for benchmarking and research purposes. The participating practices were instructed to use the guidelines of the Royal College of General Practitioners for blood pressure measurement. Laboratory data were determined using standard hospital procedures. We included the following passage to the methods section:

Participating practices were instructed to perform blood pressure measurements in supine position after at least 5 min of rest, and to calculate the mean blood pressure of two recording for each visit. Laboratory data (HbA1c, serum creatinine and lipid profile) were determined using standard hospital procedures. Until 2005, all procedures were performed in the clinical chemistry laboratory of the Isala Clinics (Zwolle region). Because of the expansion of the project in 2005-2006 to the northeast region of the Netherlands, laboratories of other regions started participating. HbA1c was measured using

affinity chromatography high-performance liquid chromatography (HPLC, Ultra 2, Trinity Biotech, Kansas City, MO) in the Zwolle region (coefficient of variation approximately 1.5%) [1]. There are differences in the methods used in the various laboratories in the northeast region of the Netherlands. Generally speaking, the variation coefficient has decreased in the study period due to the worldwide standardization of HbA1c measurements and improved techniques. Because of the high number of patients in the last years of the project, it is not likely that differences in the coefficient of variation coefficient have influenced the results.

In our opinion it is not superfluous to explain the definition of process and outcome measures, since many health care providers do not exactly know the differences between them.

It is correct that the % of patients measured indicates a measurement at least once a year. We opted not to investigate how many patients had their HbA1c measured 4 times a year since this follow-up is not advised in the Netherlands.

Statistical methods: what was performed in SPSS and what in SAS? Statistical description of linear mixed models is very brief. What about assumption testing, outliers,...? Interaction term of which main effects? (time*age I suppose). A linear mixed model for binary outcomes is not possible PROC GLIMMIX is generalized linear mixed model with link function (and thus here a hierarchical logistic regression).

Response of authors: We used SPSS for the descriptive statistics, and SAS was used for all other analyses. We inspected the residuals of the regression analyses for possible violations of the assumptions and outliers. Two interaction terms were added to the models: time* age and time*sex. We improved the statistical methods section on this issue.

We do not quite understand the reviewer’s remark considering the use of PROC GLIMMIX in the case of binary responses. PROC GLIMMIX is a realization of the generalized linear model as was introduced by John Nelder and Robert Wedderburn in their 1972 article: "Generalized Linear Models" (Journal of the royal statistical society) [2]. An important difference between the general linear model and the generalized linear model is that in the former only continuous variables with normally distributed errors can be modeled, while in the latter also other types of responses and error distributions can be modeled (among others binary and count data). In the case of binary data the binomial distribution is used and the logit is the link function used in this case (the link function provides the relationship between the linear predictor and the mean of the distribution function. In the case of normally distributed error the identity function is used). As a consequence, the general linear model is a special case of the generalized linear model (in the case of continuous variables PROC MIXED and PROC GLIMMIX give the same results).

Furthermore, in the literature the terms “multilevel models”, “hierarchical multilevel models”, “mixed models”, “nested models” are often used exchangeable. In our case the repeated measures are nested within the patients, so that is why we used the term “mixed models”. In our analyses we used the variables “time”, “age” and “sex” as fixed variables. We added this to the statistical methods section.

There is first a problem of internal validity of the results. I think it is not possible to make a comparison of 4508 patients in 2005 and 18469 patients in 2006. This 'sudden explosion' in patients is also not explained.

It is absolutely not clear to me how the "p for trend" (table 2) is related to the linear mixed models described in the method section. Time Trends in longitudinal analyses should analyse the timely evolution of individuals and thus take into account significance of the interaction term. This is

important since the authors mention an improvement of diabetes care, which means a change (improvement) over time. The mere results do not allow this conclusion because they compare outcomes in different populations. (see remark above).

Response of authors: We thank the reviewer for his comments regarding the methods we used in our study. We acknowledge that the statistical design is rather complex and that our description in the methods section was too brief. Although the presented data for each year are cross-sectional data (table 2), the time trend analyses were longitudinal.

It is not clear to us which interaction term the reviewer is referring to. Since the analyses were of a longitudinal nature the variable “time” is the within person effect of time. Introduced in the model as a continuous variable, this is the linear component (“linear time trend”). The interaction terms time*age and time*sex indicate to what extent this linear trend is different for the three age groups and/or different for men and women. When the graphs of the changes over time clearly showed a non-linear trend, a quadratic time*time term was incorporated in the model (or higher order polynomials).

We will use the HbA1c analyses as an example (please find the SAS output below). Our database consists of 37320 unique patients and 92340 unique yearly check-ups. For some patients we have 11 years of follow-up data: they started in the first year of the project and data were collected for all yearly check-ups. As a number of patients died or moved away during the course of the follow-up, not all patients starting in the first year of the project completed all 11 measurements. On the other hand, during the course of the project new patients were also included. The majority of patients that were included in our analyses, started to participate in 2006-2008. As a results, we only have data of a few yearly check-ups for the majority of patients. Obviously, we do not have follow-up data of patients that started to participate in 2008.

Our conclusions on timely improvements are not based on the cross-sectional data, but on the time trend analyses. We acknowledge that cross-sectional outcomes are influenced by changes in population (in- and outmigration) besides possible changes in the quality of care that the participants received [3]. Cross-sectional outcomes tend to overestimate time trends when compared to longitudinal analyses [3]. However, longitudinal analyses with complete data for all patients are also not possible because of the in- and outmigration of participants (death, moving away, new participants). We could present strictly longitudinal data for all patients that started in year 1 of the shared care project and completed 11 years of follow-up. However, trends based on these data will also be biased since many patients will have died before the end of the follow-up. Therefore, we have opted to present the cross-sectional data and perform longitudinal trend analysis in which we included all patients with at least two visits. Since our trend analyses are based on the individual changes, we do think it is possible to conclude that there is a timely improvement. However, it remains a point of debate whether the improvements are exactly of the same magnitude as the cross-sectional data (presented in table 2 and figure 2) suggest. Because of the overestimation that is associated with cross-sectional analyses, the true improvements are probably smaller. We made several changes to the methods section and included some comments in the discussion section with respect to the design of our study.

With respect to the question about the ‘sudden explosion’ of participants. This is explained in the first paragraph of the methods section: “In the first years of ZODIAC, only patients in the surrounding area of the city of Zwolle participated in the study. Because of the improvements in the quality of diabetes care in the two intervention groups, the shared care project has expanded gradually in the past decade. Firstly, the shared care project became the standard for diabetes care in the entire Zwolle region (2002-2003), and in 2005-2006 the project expanded to the northeast region of the Netherlands. The number of participating general practitioners (GPs) has increased from 53 in 1998 to 459 in 2008. Patient numbers increased from 1622 to 27.438 in this time frame, and nowadays

even more than 60.000 patients are participating."

In the interpretation, the authors insinuate that improvement is due to shared care. However, there is a general tendency in almost all Western countries of improved diabetes care (e.g. Germany, Belgium, France,....) with several publications (e.g.Exp Clin Endocrinol Diabetes. 2009 Feb;117(2):88-94. Epub 2008 Aug 25). Improvement can be explained by organisational initiaves (CCM, shared care), but also by greater awareness since 2010 AND better medication (new OAD, antihypertensive drugs, widely use of statins,....) The authors should nuance their conclusions and place them in an international perspective referring to other articles describing time trends.
- In this perspective, the conclusions are somewhat trivial.

Response of authors: We fully agree with the reviewer that causality cannot be proven in our study. We acknowledge that we insinuate that the improvements in our study are caused by shared care. Several changes have been made to the discussion section. We included the reference about the time trends on diabetes care in Germany to the other references about improvements in diabetes care.

The authors emphasize the importance of the study for older people ('first study...', p.13,line15). But what are then the conclusions, the lessons learned of this study about older people? Older people follow the same trend? Yes, and so?

Response of authors: The lessons learned from this study is indeed that elderly patients follow the same trends as younger patients with diabetes. Since the evidence for strict cardiovascular risk control in old age is low, old age is characterized by a high prevalence of complications and comorbidities, and elderly patients are at increased risk for possible adverse events, less strict treatment targets for elderly patients with T2DM have been advocated in literature. Nevertheless, we observed large improvements in old age during the past decade. Although we cannot answer the question whether the improvements in old age are a 'good' or a 'bad' thing, it is important to become aware of these trends. We made a few changes to the paragraph in which we explain the importance of these findings in old age.

I do not agree that these results in this study (with a year by year change of included patients and a 'sudden explosion' of included patients in the year 2006 allow to conclude on a timely IMPROVEMENT. Outcomes are better, but this can be the result of other factors (eg. changing selection bias over the years).

Response of authors: Our conclusions on timely improvements are not based on the cross-sectional data, but on the time trend analyses. We acknowledge that cross-sectional outcomes are influenced by changes in population (in- and outmigration) besides possible changes in the quality of care that the participants received [3]. Cross-sectional outcomes tend to overestimate time trends when compared to longitudinal analyses [3]. However, in our opinion strictly longitudinal analyses are also not possible because of the same in- and outmigration of participants (death, moving away, new participants). We could present strictly longitudinal data for all patients that started in year 1 of the shared care project and completed 11 years of follow-up. However, trends based on these data will also be biased since many patients will have died before the end of the follow-up. Therefore, we have opted to present the cross-sectional data and perform longitudinal trend analysis in which we included all patients with at least two visits. Since our trend analyses are based on the individual changes, we do think it is possible to conclude that there is a timely improvement. However, it remains a point of debate whether the improvements are exactly of the same magnitude as the cross-sectional data (presented in table 2 and figure 2) suggest. Because of the overestimation that is associated with cross-sectional analyses, the true improvements are probably smaller. We made several changes to the methods section and included some comments in the discussion section with respect to the

design of our study.

The Title is somewhat confusing: "shared care prospective observational study": a study cannot be "shared care". Better would be: Prospective (observational) study of quality of diabetes care in a shared care setting: trends and age differences.

Response of authors: We thank the reviewer for his suggestion. We have changed the title.

There are two major methodological limitations in this study:
1. No control group
2. no defined cohort

Response of authors: We thank the reviewer for his interesting comments. It is correct that our study had no control group. Although are observational study is not able to prove a causal relationship between shared care and the observed improvements, a control group of patients with diabetes receiving standard care would have led to more insight.

The reviewer also mentions that there is no defined cohort. We interpreted this remark as that he is referring to the absence of many inclusion criteria. We respectfully disagree with his statement for two reasons. Firstly, we have described in the methods section how the study population was defined: “The patients participating in the ZODIAC study are known with T2DM and exclusively treated in primary care. Patients who were already treated in secondary care for their diabetes, patients with a very short life expectancy (including patients with active cancer) and patients with insufficient cognitive abilities were excluded from participation.” Secondly, if the reviewer indeed refers to the absence of many inclusion criteria, this is not a methodological limitation in our opinion. We aimed to include a population that would be representative of the population in daily practice. Therefore, we see it as a strength that we have included as many patients as possible.

Every interpretation of the results should take into account these limitations and should compell to prudent, nuanced statements.

Response of authors: We made various changes throughout the manuscript. The methods have been described more elaborately and the limitations are discussed in more detail now.

Reviewer 2

Reviewer: David C. Aron, MD, MS
Associate Chief of Staff/Education
Louis Stokes Cleveland Dept. of Veterans Affairs Medical Center and Professor of Medicine and Epidemiology and Biostatistics, School of Medicine, and Professor of Organizational Behavior, Weatherhead School of Management, Case Western Reserve University

This is a very interesting paper that represents the best in linking research and practice.

There is some lack of clarity regarding patients initially including in the standard care group. Were they switched to shared care when that became the standard for the Zwolle region? Were they not included in the analysis?

Response of authors: We thank the reviewer for this comment. Patients who were received standard care in the beginning of the project, switched to shared care in 2002-2003 when the shared care

project became the standard for the entire Zwolle region. These patients were included in the current analyses from the moment they switched to shared care. We have changed this in the methods section of the manuscript.

Another issue is A1c measurement. Were A1c measurements made using the same technology for the entire study. Did coefficients of variation for the assay vary among sites?

Response of authors: Laboratory data (HbA1c, serum creatinine and lipid profile) were determined using standard hospital procedures. Until 2005, all procedures were performed in the clinical chemistry laboratory of the Isala Clinics (Zwolle region). Because of the expansion of the project in 2005-2006 to the northeast region of the Netherlands, laboratories of other regions started participating. HbA1c was measured using affinity chromatography high-performance liquid chromatography (HPLC, Ultra 2, Trinity Biotech, Kansas City, MO) in the Zwolle region (coefficient of variation approximately 1.5%) [1]. There are differences in the methods (HPLCs and immune-assays) used in the various laboratories in the northeast region of the Netherlands. Unfortunately, we do not have the coefficients of variation for all laboratories. We have asked all clinical chemists to send us these data. If necessary, it is possible to include these data in the final manuscript. Generally speaking, the variation coefficient has decreased in the study period due to the worldwide standardization of HbA1c measurements and improved techniques. Because of the high number of patients in the last years of the project, it is not likely that differences in the coefficient of variation coefficient will influence the overall conclusion. Especially since the same method has been used for all patients until 2005.

I have inferred that the analytic approach is that of serial cross sections. This should be explicitly stated. Assuming this is the approach used, it is far from ideal and ignores the differences observed between serial cross sections and panel data. The latter approach has been reported but not cited: see Miller DR and Pogach. J Diabetes Sci Technol 2008;2:24-32 and Thompson W et al. HSR 2005;40:1818.

Response of authors: We thank the reviewer for his comments regarding the methods we used in our study. We acknowledge that the statistical design is rather complex and that our description in the methods section was too brief. Although the presented data for each year are cross-sectional data (table 2), the time trend analyses were longitudinal.

We will use the HbA1c analyses as an example (please find the SAS output below). Our database consists of 37320 unique patients and 92340 unique yearly check-ups. For some patients we have 11 years of follow-up data: they started in the first year of the project and data were collected for all yearly check-ups. The majority of patients that were included in our analyses, started to participate in 2006-2008. As a results, we only have data of a few yearly check-ups for the majority of patients. Obviously, we do not have follow-up data of patients that started to participate in 2008. The analysis presented below are the trend analyses for HbA1c as a continuous variable (SAS PROC MIXED for continuous variables). SAS used 83061 observations of 92340 observations in total. 9279 observations were not used, because this is the number of patients of which we have no follow-up data. The estimated linear time trends are based on individual changes over time; therefore, these analyses are longitudinal.

Our conclusions on timely improvements are not based on the cross-sectional data, but on the time trend analyses. We acknowledge that cross-sectional outcomes are influenced by changes in population (in- and outmigration) besides possible changes in the quality of care that the participants received [3]. Cross-sectional outcomes tend to overestimate time trends when compared to longitudinal analyses [3]. However, in our opinion strictly longitudinal analyses are also not possible because of the in- and outmigration of participants (death, moving away, new participants). We could

present strictly longitudinal data for all patients that started in year 1 of the shared care project. However, trends based on these data will also be biased since many patients will have died after 10 years of follow-up. Therefore, we have opted to present the cross-sectional data and perform longitudinal trend analysis in which we included all patients with at least two visits. Since our trend analyses are based on the individual changes, we do think it is possible to conclude that there is a timely improvement. However, it remains a point of debate whether the improvements are exactly of the same magnitude as the cross-sectional data (presented in table 2 and figure 2) suggest. Because of the overestimation that is associated with cross-sectional analyses, the true improvements are probably smaller. We made several changes to the methods section and included some comments in the discussion section with respect to the design of our study.

Two major concerns:
1. One major concern relates to conclusions drawn from serial cross sections. This approach does not account for secular changes in the extent to which diabetes is screened for and for "admixture" of less seriously ill patients. Although the relatively constant median duration of disease is somewhat reassuring, the determination of duration is fraught with difficulties. This is also not much of an issue for process measures of care, but for outcomes, especially A1c which, as shown in UKPDS, deteriorate over time, it is important. Changes in the nature of the population are suggested by the decreasing proportion of patients on insulin. (See work by Pogach and Miller)

Response of authors: We would like refer to our previous answer. In short, since our conclusions are based on the longitudinal trend analyses, we are able to draw conclusions on timely improvements. However, the magnitude of these improvements is not exactly known. The cross-sectional outcomes probably overestimate the true longitudinal improvements.

2. Another concern is the issue of secular trends. That process measures of care improved is clear; that they resulted from shared care is not. This limitation is mentioned in the discussion. The temporary decreases in process measure adherence observed as large numbers of new sites were added could as easily be attributed to the effects of data reporting as to the mode of care delivery.

Response of authors: We fully agree with the reviewer that causality cannot be proved in our study. Although we mention that causality cannot be proved in our study, we acknowledge that we insinuate that the improvements in our study are caused by shared care. Several changes have been made to the discussion section.

It might be worth mentioning the arbitrary nature of the thresholds for intermendiate outcome measures, especially as the importance of individualizing care is gaining greater recognition.

Response of authors:
We thank the reviewer for this important comment. We underline that the importance of individualizing care is gaining greater recognition. Especially in old age, health status is very heterogeneous and therefore it is essential to individualise treatment strategies. Nevertheless, quality indicators are commonly used in daily practice and therefore this seems the most appropriate method to describe quality of diabetes care. We added a few sentences with respect to the importance of individualizing treatment targets in the discussion section.

References

1. Lenters-Westra E, Slingerland RJ. Hemoglobin A1c determination in the A1c-derived average glucose (ADAG)-study. Clin Chem Lab Med 2008;46:1617-23.

2. Nelder JA, Wedderburn RW. Generalized linear models. Journal of the royal statistical society, Serias A. 1972;135:370-84.
3. Miller DR, Pogach L. Longitudinal approaches to evaluate health care quality and outcomes: the veterans health administration diabetes epidemiology cohorts. J Diabetes Sci Technol 2008;2:24-32.

The Mixed Procedure

Model Information

Data Set SYS.ZODIAC19_SEP2011
Dependent Variable HBA1C
Covariance Structure Compound Symmetry
Subject Effect PATIENTID
Estimation Method REML
Residual Variance Method Profile
Fixed Effects SE Method Model-Based
Degrees of Freedom Method Between-Within

Class Level Information

Class Levels Values

SEX2 2 0 1
PATIENTID 37320 not printed
LFT_3CAT 3 1 2 3

Dimensions

Covariance Parameters 2
Columns in X 12
Columns in Z 0
Subjects 37320
Max Obs Per Subject 11

Number of Observations

Number of Observations Read 92340
Number of Observations Used 83061
Number of Observations Not Used 9279

Iteration History

Iteration Evaluations -2 Res Log Like Criterion

0 1 233709.97027529
1 2 213508.96028423 0.00000398
2 1 213508.83869140 0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm Subject Estimate

CS PATIENTID 0.5399
Residual 0.4523

The SAS System 13:55 Tuesday, December 6, 2011 2

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood 213508.8
AIC (smaller is better) 213512.8
AICC (smaller is better) 213512.8
BIC (smaller is better) 213529.9

Null Model Likelihood Ratio Test

DF Chi-Square Pr > ChiSq

1 20201.13 <.0001

Type 3 Tests of Fixed Effects

Num Den
Effect DF DF F Value Pr > F

LFT_3CAT 2 3122 11.61 <.0001
SEX2 1 35E3 5.78 0.0162
JAAR2 1 48E3 789.74 <.0001
JAAR2*LFT_3CAT 2 48E3 13.83 <.0001

Definition of the variables used in our analysis:

jaar2: this variable defines the year of the check-up.
sex2: gender.
lft_cat: this variable defines to which age category the patient belongs.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Goderis, Geert<br><br>Competing interests: none |

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| **REVIEW RETURNED** | 21-Jul-2012 |

- The reviewer completed the checklist but made no further comments.

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| **REVIEWER** | David C. Aron, MD, MS<br>Associate Chief of Staff/Education<br>Louis Stokes Cleveland Dept. of Veterans Affairs Medical Center<br>10701 East Blvd.<br>Cleveland, OH 44106 USA<br>and<br>Professor of Medicine and Epidemiology and Biostatistics, School of Medicine, and<br>Professor of Organizational Behavior, Weatherhead School of Management,<br>Case Western Reserve University |
| **REVIEW RETURNED** | 25-Jul-2012 |

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| **GENERAL COMMENTS** | The authors have satisfactorily responded to the reviews. |