Geographic variation in diagnostic and treatment interval, cancer stage and mortality among colorectal patients – an international comparison between Denmark and Scotland using data-linked cohorts

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CONTRIBUTORSHIP STATEMENT
PM, LV and PV conceived the study. PM and LV wrote the protocol, secured approvals for data sharing and collaborated in establishing the combined dataset within Statistics Denmark. LV and AF conducted the analysis with support from MT. LV prepared the tables and figures for the manuscript which was written by PM and LV with comments on drafts from AF, MT and PV.

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Peter Murchie: Conceptualization, Methodology, Project Administration, Writing – Original Draft. **Alina Zalounina Falborg:** Formal analysis, Data Curation, Writing – Review & Editing. **Melanie Turner:** Methodology, Data Curation, Writing – Review & Editing. **Peter Vedsted:** Conceptualization, Writing – Review & Editing. **Line F. Virgilsen:** Conceptualization, Methodology, Project Administration, Data Curation, Visualization, Writing – Original Draft.

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Abstract

Background

Rural dwellers with colorectal cancer have poorer outcomes than their urban counterparts. The reasons why are not known but are likely to be complex and be determined by an interplay between geography and health service organization. By comparing the associations related to travel-time to primary and secondary healthcare facilities in two neighbouring countries, Denmark and Scotland, we aimed to shed light on potential mechanisms.

Methods

Analysis was based on two comprehensive cohorts of patients diagnosed with colorectal cancer in Denmark (2010-16) and Scotland (2007-14). Associations between travel-time and cancer pathway intervals, tumour stage at diagnosis and one-year mortality were analysed using generalised linear models. Travel-time was modelled using restricted cubic splines for each country and combined. Adjustments were made for key confounders.

Results

Travel-time to key healthcare facilities influenced the diagnostic experience and outcomes of CRC patients from Scotland and Denmark to some extent differently. The longest travel-times to a specialised hospital appeared to afford the most rapid secondary care interval, whereas moderate travel-times to hospital (about 20-60 minutes) appeared to impact on later stage and greater one-year mortality in Scotland, but not in Denmark. A U-shaped association was seen between travel-time to the GP and one year-mortality.

Conclusions

This is the first international data-linkage study to explore how different national geographies and health service structures may determine cancer outcomes. Future research should compare more countries and more cancer sites and evaluate the impact and implications of differences in national health service organisation.

Keywords: Colorectal Neoplasms; Travel; Diagnosis; Primary Health Care; Time-to-Treatment; Neoplasm Staging; Mortality

Introduction

Throughout the developed world rural-dwellers diagnosed with cancer have higher mortality than urban counterparts, but underlying mechanisms are poorly understood.[1,2] This is intriguing, since rurality and health service organization differ markedly between countries.[1] Several explanatory mechanisms for poorer rural cancer survival have been proposed, at the levels of patient and practitioner behaviour; service organization, and wider health policy.[2] Studies exploring travel burden, an obvious aspect of rurality, and cancer outcomes vary in findings between countries, suggesting mechanisms could operate differently between countries and cancer sites.[1,3-8]

In Europe the impact of travel burden on colorectal cancer (CRC) diagnosis and survival has received particular attention.[9-12] This includes Denmark and the UK where CRC survival has historically lagged behind other developed nations, prompting effective health service changes.[13-15]

Studies with CRC patients diagnosed in Northeast Scotland between 1997 and 1998 found rural patients and those travelling furthest to their general practitioner (GP) were more likely to have alarm symptoms and advanced stage at diagnosis, more likely to experience difficulties in accessing health services, but also more likely to survive for at least three years.[4,9,16] In England, routes to diagnosis of CRC have been linked to travel burden with higher likelihood of emergency presentation and lower rates of urgent referral and screen-detection among patients with more than 30 minutes' travel to their GP.[Murage et al, 2018] In Denmark, increased travelling distance to hospital was associated with later stage at diagnosis for rectal but not colon cancer.[17]

Considered in the context of geography and health service organization, these studies suggest geography could impact rural CRC patients and pathways to diagnosis differently in different countries. This study aimed to compare Denmark vs Scotland in the association between travel burden to healthcare, CRC pathway intervals, tumor stage at diagnosis and mortality.

Methods

Study design and population

Cohort study of individuals diagnosed with CRC (ICD-10 code: C18-C20) from 2010 onwards and recorded in national cancer registers of Denmark and Scotland.

Setting

Scotland and Denmark are neighbouring Northern European Countries sharing similar latitude and similarly age-structured populations of 5.5 and 5.8 million respectively.[18,19] Scotland's population is more dispersed giving relative population densities of 69 people km^2 in Scotland compared to 138 people km^2 in Denmark.[19] This reflects classifications placing 17% of Scots as rural compared to 12% of Danes.[20,21] Denmark has higher GDP than Scotland, with a correspondingly higher per capita healthcare spend.[22,23] Both countries have primary care-led healthcare systems where GPs are usually first contact point for symptomatic patients and gatekeepers to secondary care, although have diverged in cancer referral pathways in recent years.[3,24] Both countries have current CRC screening programmes for 50-74 year olds, national rollout occurring in Scotland in 2009 and Denmark in 2014.[25,26]

Data sources

Colorectal cancer data - Scotland

The NASCAR cohort has been fully described.[3] Briefly, cancer patients diagnosed in North Scotland (approximately 11% of Scotland's population) between 2007 and 2014 were identified using the NHS Grampian Cancer Care Pathway database collecting data from several sources to form a complete record of individual cancer cases from GP referral onward.[3]. Further linkages were made to the Scottish Cancer Registry (SMR06) to provide further details of individuals' cancers, Scottish Hospital Episode databases (SMR00 and SMR01) and the National Records of Scotland Death Registry.[27-29] For this study 1,184 patients from 112 GP practices diagnosed with CRC between 2010 and 2014 were included.

Colorectal cancer data -Denmark

CRC patients were identified through the Danish National Patient Registry,[30] and included for the Danish Cancer in Primary Care (CAP) Cohorts in 2010 and 2016, if the following criteria were fulfilled : >=18 years of age at CRC diagnosis, registered with a GP and eligible for research contact. Diagnosis date and tumour stage was obtained from the Danish Cancer Registry and date of death from the Danish Register of Causes of Death.[31,32] Eligible patients were sent a questionnaire asking about the pathway followed to cancer diagnosis. Overall patient response rate was 61%. GPs of included patients were sent a questionnaire about their view of the diagnostic process.[33] GPs of patients who died shortly after diagnosis were also sent a questionnaire. Overall GP response rate was 76%. In total 4,714 CRC patients were included.

Main variables

Exposure: burden of travel expressed as travel-times

Fastest travel-times (in minutes) from home to GP and hospital were calculated using postcodes (in Scotland) and street addresses (in Denmark) and using the Network Analyst extension in ArcGIS V10.2 (ESRI: Environmental Systems Research Institute, Redlands, CA, USA).

Outcomes

Time intervals

Two time intervals along cancer diagnostic pathways were analysed: Secondary care interval (SCI) which is time in days between GP referral and cancer diagnosis, and Treatment Interval (TI) the time in days between cancer diagnosis and commencement of treatment. In Scotland, this was based on dates recorded within NASCAR and in Denmark, diagnosis date was obtained from the National Patient Register and remaining dates were obtained from GPs unless missing when patient assigned dates were used.

Tumour stage

Tumour stage was obtained from Danish and Scottish Cancer Registries and categorised as local or progressed (regional and distant stage).[27,31] Definitions were based on. TNM staging criteria.[34]

One-year mortality

Information on one-year all-cause mortality was obtained from national death registries in Denmark and Scotland.[29,32] One-year mortality was calculated from diagnosis date until date of death from any cause and classified as a binary variable (alive and dead).

Covariates of interest

Potential confounders included age category, sex, and Charlson Comorbidity Index (CCI).[35] CCI was calculated using ICD-10 codes associated to outpatient attendances and inpatient admissions for 10 years preceding cancer diagnosis.[30]

Statistical analysis

Distribution of independent and dependent variables was tabulated by country. Differences between Denmark and Scotland were assessed using non-parametric statistics. Association between travel-time and time intervals was analysed using generalised linear models (GLM) using the Gamma distribution to adjust for right-skewed data and results presented as differences in days. Analysis of SCI considered the association with travel-times to both hospital and GP whereas analysis of TI considered only travel-time to hospital. This was because it seemed plausible that a patient's travel-time to their GP could have some influence on how long it took secondary care to deal with the referral, whereas it seemed unlikely that travel-time to their GP would influence how long it took for treatment to start once a cancer diagnosis had been established.

The association between travel-time and tumour stage at diagnosis was analysed using logistic regression with odds for more advanced disease as the outcome. The association between travel-time and one-year

mortality was analysed using a Poisson regression model with a robust variance estimator, and the outcome assessed as the one-year mortality ratio (expressed as Prevalence Rate Ratio (PRR)), specifying time at risk and adjusting for time since diagnosis (grouped in three categories: 1-4,5-8,9-12 months to accommodate three groups of 4-months' time length for the purposes of the Poisson model). Travel-time was modelled using restricted cubic splines with three knots according to Harrell's recommended percentiles and displayed graphically for each country combined with relevant estimates and 95% confidence intervals (95% CI).[36] All graphs are presented adjusted for sex, age-groups, CCI and combined graphs were adjusted for country as well. For all models, an analysis with an interaction term was used to test if country and travel-time interacted with the outcome and a Wald test was conducted to assess the overall shape of association in each spline model.

To avoid outliers in the spine models, the 2.5% patients with the longest travel-time were excluded. This entailed that in the analysis on travel-time to the GP, patient with longer than 24 minutes to the GP were excluded (n=141) and in the analysis on travel-time to the hospital, patients with longer than 110 minutes to the hospital were excluded (n=146). In all analysis on travel-time to the GP, the reference point was set at 5 minutes whereas the reference for travel-time to the hospital was set at 15 minutes. All statistical analysis was conducted using Stata 16.1.

Results

In total 5,898 patients were included, 1,184 from Scotland and 4,714 from Denmark. Table 1 presents characteristics of CRC patients stratified by country. The Scottish cohort had a higher proportion of older patients, a higher proportion of local stage at diagnosis, higher mortality within one year of diagnosis, and longer travel-times to hospital of treatment than CRC patients in Denmark. Median SCI was 34 days in both

countries (Interquartile Interval (IQI) Scotland 7-53 days versus Denmark 22-55 days). The median TI (IQI) was 64 (29-102) days in Scotland and 13 (3-23) days in Denmark.

Secondary care interval (SCI) and treatment interval (TI)

There was no association between travel-time to the GP and SCI. Increased travel-time to the hospital was associated with shorter SCI (p-value <0.001) (Figure 1, Table 2). For example, patients with 40 minutes to the hospital had 5.91 days shorter SCI than patients with 15 minutes to the hospital (95% CI 2.94-8.87). Test for interaction indicated that the association between travel-time to hospital and the SCI differed statistically significantly between Scotland and Denmark (p=0.046) (Table 2).

Country and travel-time to the hospital interacted in the association with TI (p-value<0.001) (Table 2). For Denmark, there was no association between travel-time to the hospital and TI (p-value=0.976, Table 2). For Scotland, increased travel-time to the hospital was associated with decreased TI (p-value=0.015, Table 2), e.g. Scottish patients with 60 minutes to the hospital had 8.77 days shorter TI (95% CI 2.16-15.38) than patients with 15 minutes to the hospital (Figure 2).

Tumour stage

Travel-time to GPs was not associated with more advanced tumour stage (Figure 3, Table 2) and no interaction was found by country (p-value=0.284). No association was observed between travel-time to hospital and tumour stage among Danish patients. A significant reverse U-shape appeared among Scottish patients with increasing odds of advanced stage up to a travel-time of 40 minutes to the hospital hereafter the odds decreased compared with a travel-time of 15 minutes (p-value=0.008, Table 2)(Figure 3). However, country did not interact significantly in the association between travel-time to hospital and stage (p-value=0.088, Table 2).

Mortality

A U-shaped association was observed between travel-time to the GP and one-year mortality in Scotland ($p<0.001$) and the same tendency was seen for Denmark, yet not statistically significant (p-value=0.491). When combining data, the model was overall significant (p-value=0.002, Table 2) and patients with, for example, 20 minutes to the GP had 1.39 times higher one-year mortality than patients with 5 minutes to the GP (PRR=1.39, 95% CI 1.02-1.89) (Figure 4).

Travel-time to hospital and country interacted in the association with one-year mortality (p-value=0.010, Table 2). Among Scottish patients, the association appeared to be a reversed U-shape between travel-time to hospital and the one-year mortality with the highest one-year mortality among patients living between 32-39 minutes from hospital compared to patients within 15 minutes (p-value: 0.027). In Denmark, increased travel-time to hospital decreased one-year mortality rates up to 60 minutes hereafter the curve flattened (p-value<0.001).

Discussion

Summary of main findings

Notable differences were observed between Scotland and Denmark. TI in Scotland was longer than for Denmark and TI decreased with increasing travel-time in Scotland, but not Denmark. Also in Denmark, travel-time to hospital was not associated with stage, whereas Scottish data demonstrated a reverse U-shape relationship with odds of more advanced stage and one-year mortality increasing up to 40 minutes travel-time before decreasing again.

There were also similarities between countries. In Denmark and Scotland, SCI reduced as patients' travel-time to hospital increased. Also, in both countries there was an apparent U-shaped association with travel-time to the GP and mortality, with mortality increasing either side of 5 minutes travel-time to the GP. Overall,

our findings suggest that national health organization causes travel-time to associated differently with CRC outcomes in the two countries.

Strengths and limitations

Two comparable high-quality datasets from two countries at the forefront of healthcare data science were used and linked using latest techniques.[37,38] The authors collaborated continuously to ensure data completeness and that corresponding variables and definitions were used. Both datasets used the latest geographical information system (ArcGIS®) to calculate accurate travel-times. Further, restricted cubic splines were employed enabling travel-time to be analysed as a continuous variable, allowing a flexible relationship between exposure and outcome.

Some limitations are acknowledged. Travel-times were calculated based on private transport which may underrepresent travel burden for public or ambulance transport. Further, travel-time calculations are not yet sufficiently sophisticated to account for variables such as traffic volume and road conditions. Dates were all GP-derived in Scotland whereas in Denmark dates were provided by patients when missing in the GP data, although this is supported.[39] In Scotland travelling distances were calculated based on population-weighted datazone centroids (derived from postcodes) compared to actual street addresses in Denmark. It is, therefore possible, that this could have led to over and underestimates of true travelling times in larger rural datazones in the Scottish data.[40] Our analysis could also be affected by differences in the way cancer data is recorded between countries.[15] As with all similar studies residual confounding could occur.

Context with other literature

In both countries one-year mortality increased for CRC patients living more than 20 minutes from their GP. This accords with a previous study from Northern England of 117,097 people diagnosed with cancer 1994-2002 where longer travel-times to the GP made later stage breast and colorectal cancer at diagnosis more

likely. Patients with the longest journeys to their GP are likely to be the most remote from healthcare resources in any country, and risk poorer healthcare outcomes generally.[41] Also, rural GPs perceive specific access difficulties for patients with suspected cancer. Previous research found longer distance to hospital meant GPs were more likely to adopt "a wait and see approach" and be dissatisfied with referral processes and delay.[8] Similarly, rural GPs in Scotland were more likely to state their patients' diagnosis had been delayed.[42] A study among GPs from 20 European countries also found rural GPs believed patients with potential cancer symptoms received less timely investigation.[43] Conversely, other studies in CRC patients have not shown associations between travel-time to the GP and more advanced stage at diagnosis or poorer survival.[3,4,17] Taken together, it is possible that poorer shorter-term prognosis (up to one-year) reflects a slower response to complications and other acute effects of treatment for the most remote patients. If rural cancer patients survive past one year they may then benefit from a healthier rural environment.[44,45] Detailed research comparing how and when rural and urban colorectal cancer patients die should follow.

Secondly, there were clear contrasts between the two datasets in the strength of associations between travel-time to hospital, stage at diagnosis and one-year mortality, with travel burden apparently mattering more in Scotland. Increased travel-time to hospital showed reverse U-shaped associations with later stage at diagnosis and increased mortality up to a threshold of approximately one-hour before beginning to decline again, with better outcomes for the most remote patients. These trends were not reflected in the Danish data and are more comparable to a recent study from Northern Sweden where no association between travel-time and colorectal cancer survival despite longer travel-time was found.[12] The fact that Sweden has a more dispersed population than both North Scotland and Denmark further illustrates the very complex nature of how national geography, mediated by national health service structure, may influence patient outcomes from CRC.

Third, the prognosis threshold demonstrated in Scottish data may reflect how health care systems respond differently to geographical challenges. Geographical distance as a barrier to equitable secondary care is well recognized, in terms of sustaining small rural hospitals and poorer access to specialised care.[46-48] A previous Scottish study found hospital admission rates are lower among rural cancer patients.[49] The prognosis threshold effect in the Scottish data here is perplexing since longer travel-time is also clearly associated with shorter TIs. It might be, therefore, that the most remote patients have investigation, diagnosis and treatment completed in a shorter interval, perhaps during a single hospital admission, to compensate for greater travel burden. The original NASCAR analysis supports this, finding that island-dwelling patients often received diagnosis and treatment on the same day.[3]

Fourth, and arguably, pathway intervals were most sensitive to differences in national health service organization. Danish data were collected following implementation of Cancer Patient Pathways for CRC patients regarding treatment interval to support early cancer diagnosis. This included rapid referral pathways for patients with suggestive combinations of non-alarm symptoms and early cancer diagnostic centres (ECDCs), which are one-stop medical units with comprehensive investigative facilities and easy access to a range of relevant specialists.[24]. In Scotland, data were collected at a time when urgent referral for suspected colorectal cancer was only mandated in the presence of a definite “alarm symptom.”[50] From the Scottish perspective therefore, it is reassuring to note that the secondary care interval (time from GP referral to diagnosis) was not significantly different between the two datasets. On the other hand, the treatment interval (time from diagnosis to commencement of treatment) was significantly longer in Scotland (median 64 vs 13 days) which has been noted before in data from the International Cancer Benchmarking Partnership.[51]

In the current data, and in terms of pathway intervals, travel-time to the GP does not appear to be associated with pathway length. However, longer travel-times to the hospital appear to shorten the secondary interval

in both countries, although more dramatically in Denmark, and shorten the treatment interval, more dramatically in Scotland than Denmark. Notably, previous analysis of the CAP cohort suggested that after the introduction of Cancer Patient Pathways in Denmark, the association of longer diagnostic intervals for those living farthest away was less pronounced.[8] It will therefore be interesting to repeat a similar analysis once ECDCs and pathways for non-alarming symptoms have also been introduced to Scotland.[52]

Conclusion and implications

In summary, travel-time to key healthcare facilities influences the diagnostic experience and outcomes of CRC patients from Scotland and Denmark differently. The longest assessed travel-times to hospital are associated with quicker treatment and lower mortality in both countries, whereas moderate travel-times to hospital (about 20-60 minutes) increase later stage diagnosis and one-year mortality in Scotland, but not in Denmark. Clinically, it may be that the most distant patients in both countries are protected, perhaps by diagnosis and treatment occurring at simultaneously to prevent repeated long journeys. However, it would appear that those with moderate travelling times (most likely suburban-dwellers) are better served in Denmark than Scotland, perhaps as a result of ECDCs and urgent pathways for non-specific symptoms. It seems plausible, therefore, that our results truly reflect different national topography and health service structure. Future research should seek to extend these methods to compare more countries and cancer sites. More insight into specific mechanisms may also arise from timing analyses round significant national health service re-organizations such as the imminent introduction of ECDCs in Scotland.

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Data Availability

The data that support the findings of this study are available from Statistics Denmark and Public Health Scotland. Restrictions apply to the availability of these data, which were used subject to rigorous regulatory approvals for this study.

References

1. Murchie P, Adam R, Wood R, Fielding S. Can we understand and improve poorer cancer survival in rural dwellers? BJGP Open 2019; DOI: 10.3399/bjgpopen19X101646
2. Carriere R, Adam R, Fielding S, Barlas R, Ong Y, Murchie P. Rural dwellers are less likely to survive cancer – an international review and meta-analysis. J Health Place 2018;53:219-277. doi.org/10.1016/j.healthplace.2018.08.010
3. Turner M, Fielding S, Ong Y, Dibben C, Feng Z, Brewster DH, Black C, Lee A, Murchie P. A cancer geography paradox? Poorer cancer outcomes with longer travel-times to healthcare facilities despite prompter diagnosis and treatment: a data-linkage study. Brit J Cancer 2017;117:439-449 – Published Online June 22nd - DOI:10.1038/bjc.2017.180
4. Murage P, Murchie P, Bachmann M, Crawford M, Jones A. Impact of travel-time and rurality on presentation and outcomes of symptomatic colorectal cancer: a cross-sectional cohort study in primary care. Br J Gen Pract. 2017 Jul;67(660):e460-e466. doi: 10.3399/bjgp17X691349. Epub 2017 Jun 5. PMID: 28583943; PMCID: PMC5565861.
5. Xu Z, Becerra AZ, Justiniano CF, Boodry CI, Aquina CT, Swanger AA, Temple LK, Fleming FJ. Is the Distance Worth It? Patients With Rectal Cancer Traveling to High-Volume Centers Experience Improved Outcomes. Dis Colon Rectum. 2017 Dec;60(12):1250-1259. doi: 10.1097/DCR.0000000000000924. PMID: 29112560.
6. Jindal M, Zheng C, Quadri HS, Ihemelandu CU, Hong YK, Smith AK, Dudeja V, Shara NM, Johnson LB, Al-Refaie WB. Why Do Long-Distance Travelers Have Improved Pancreatectomy Outcomes? J Am Coll Surg. 2017 Aug;225(2):216-225. doi: 10.1016/j.jamcollsurg.2017.04.003. Epub 2017 Apr 14. PMID: 28414114; PMCID: PMC5702935.
7. Murchie P, Adam R, Khor WL, Raja EA, Iversen L, Brewster DH, Lee AJ. Impact of rurality on processes and outcomes in melanoma care: results from a whole-Scotland melanoma cohort in primary and secondary care. Brit J Gen Pract 2018; Aug 2018 e566-e575 – doi.org/10.3399/bjgp18X697901
8. Virgilsen LF, Møller H, Vedsted P. Cancer diagnostic delays and travel distance to health services: a nationwide cohort study in Denmark, Cancer Epidemiol. 2019 (April 59) (2019) 115–122. https://doi.org/10.1016/j.canep.2019.01.018.
9. Campbell NC, Elliott AM, Sharp L, Ritchie LD, Cassidy J, Little J. Impact of deprivation and rural residence on treatment of colorectal and lung cancer. Brit J Cancer. 2002 Sep 9;87(6):585-90
10. Jones AP, Haynes R, Sauerzapf V, Crawford SM, Zhao H, Forman D. Travel-times to health care and survival from cancers in Northern England. Eur J Cancer. 2008 Jan;44(2):269-74. doi: 10.1016/j.ejca.2007.07.028. Epub 2007 Sep 20. PMID: 17888651.
11. Murage P, Bachmann MO, Crawford SM, McPhail S, Jones A. Geographical access to GPs and modes of cancer diagnosis in England: a cross-sectional study. Fam Pract 2018; 1–7. doi:10.1093/fampra/cmy077.
12. Sjöström O, Dahlin AM, Silander G, Syk I, Melin B, Hellquist BN. Travel-time to care does not affect survival for patients with colorectal cancer in northern Sweden: A data linkage study from the Risk North database. PLoS One. 2020 Aug 5;15(8):e0236799. doi: 10.1371/journal.pone.0236799. PMID: 32756574; PMCID: PMC7406033.
13. Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, Nur U, Tracey E, Coory M, Hatcher J, McGahan CE, Turner D, Marrett L, Gjerstorff ML, Johannesen TB, Adolfsson J, Lambe M, Lawrence G, Meechan D, Morris EJ, Middleton R, Steward J, Richards MA; ICBP Module 1 Working Group. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. Lancet. 2011

Jan 8;377(9760):127-38. doi: 10.1016/S0140-6736(10)62231-3. Epub 2010 Dec 21. PMID: 21183212; PMCID: PMC3018568.

14. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, Bonaventure A, Valkov M, Johnson CJ, Estève J, Ogunbiyi OJ, Azevedo E Silva G, Chen WQ, Eser S, Engholm G, Stiller CA, Monnereau A, Woods RR, Visser O, Lim GH, Aitken J, Weir HK, Coleman MP; CONCORD Working Group. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018 Mar 17;391(10125):1023-1075. doi: 10.1016/S0140-6736(17)33326-3. Epub 2018 Jan 31. PMID: 29395269; PMCID: PMC5879496
15. Arnold M, Rutherford MJ, Bardot A, Ferlay J, Andersson TM, Myklebust TÅ, Tervonen H, Thursfield V, Ransom D, Shack L, Woods RR, Turner D, Leonfellner S, Ryan S, Saint-Jacques N, De P, McClure C, Ramanakumar AV, Stuart-Panko H, Engholm G, Walsh PM, Jackson C, Vernon S, Morgan E, Gavin A, Morrison DS, Huws DW, Porter G, Butler J, Bryant H, Currow DC, Hiom S, Parkin DM, Sasieni P, Lambert PC, Møller B, Soerjomataram I, Bray F. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study. Lancet Oncol. 2019 Nov;20(11):1493-1505. doi: 10.1016/S1470-2045(19)30456-5. Epub 2019 Sep 11. PMID: 31521509; PMCID: PMC6838671.
16. Bain NS, Campbell NC. Treating patients with colorectal cancer in rural and urban areas: a qualitative study of the patients' perspective. Fam Pract. 2000 Dec;17(6):475-9
17. Virgilsen LF, Møller H, Vedsted P. Travel distance to cancer-diagnostic facilities and tumour stage. J Health Place. 2019 Nov;60:102208. doi: 10.1016/j.healthplace.2019.102208. Epub 2019 Oct 15. PMID: 31627128.
18. Office for National Statistics (ONS) (2020). https:www.ons.gov.uk (Accessed 26 Jan 2021)
19. European Commission Eurostat Website (2020). Population density by NUTS 3 region. Available at https://ec.europa.eu/eurostat/databrowser/view/demo_r_d3dens/default/table?lang=en [Accessed 11 May 2021].
20. The World Bank (2018) https://data.worldbank.org/indicator/SP.RUR.TOTL.ZS?locations=DK (Accessed 11 May 2021].
21. Scottish Government (2018). Rural Scotland Key Facts 2018. Available from https://www.gov.scot/publications/rural-scotland-key-facts-2018/ [Accessed 11 May 2021].
22. Organisation for Economic Co-operation and Development (OECD) (2019) https://data.oecd.org/denmark.htm [Accessed 26 January 2021]
23. Scottish Government (2020). https://www.gov.scot/publications/monthly-gdp-june-2020/ [Accessed 11 May 2021].
24. Vedsted, P; Olesen, F. A differentiated approach to referrals from general practice to support early cancer diagnosis - the Danish three-legged strategy. Brit J Cancer 2015;112:S65-S69
25. Public Health Scotland (2020). Scottish Bowel Screening Programme. https://www.isdscotland.org/Health-Topics/Cancer/Bowel-Screening/ [Accessed 11 May 2021].
26. Njor SH, Friis-Hansen L, Andersen B, Søndergaard B, Linnemann D, Jørgensen JCR, Roikjær O, Rasmussen M. Three years of colorectal cancer screening in Denmark. Cancer Epidemiol. 2018 Dec;57:39-44. doi: 10.1016/j.canep.2018.09.003. Epub 2018 Oct 4. PMID: 30292899.
27. Public Health Scotland (2020). Scottish Cancer Registry. Available from https://www.isdscotland.org/Health-Topics/Cancer/Scottish-Cancer-Registry/ [Accessed 11 May 2021].
28. Public Health Scotland (2020). SMR Datasets. Available from https://www.ndc.scot.nhs.uk/Data-Dictionary/SMR-Datasets/ [Accessed 11 May 2021].

29. National Records of Scotland (2020). https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/deaths-background-information/quality-of-nrs-data-on-deaths [Accessed 11 May 2021].
30. Lynge E, Sandegaard JL, Rebolj M: The Danish National Patient Register. Scand J Public Health 2011, 39(7 Suppl):30-33
31. Gjerstorff ML. The Danish Cancer Registry. Scand J Public Health. 2011 Jul;39(7 Suppl):42-5. doi: 10.1177/1403494810393562. PMID: 21775350.
32. Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health. 2011 Jul;39(7 Suppl):26-9. doi: 10.1177/1403494811399958. PMID: 21775346.
33. Andersen JS, Olivarius F, Krasnik A: The Danish National Health Service Register. Scand J Public Health 2011, 39(7 Suppl):34-37
34. Sobin LH, Gospodarowicz MK, Wittekind C, editors. TNM classification of malignant tumours. John Wiley & Sons; 2011 Aug 31.
35. Charlson ME, Pompei P, Ales KL, MacKenzie CR. (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases 40:373-383.
36. Harrell FE. Regression modelling strategies: with applications to linear models LR, and survival analysis. 1st ed. New York: Springer Science & Business Media; 2001.
37. Statistics Denmark (2021). https://www.dst.dk/en/Statistik [Accessed 11 May 2021].
38. Electronic Data Research and Innovation Service (eDRIS). Public Health Scotland (2021) [https://www.isdscotland.org/Products-and-Services/eDRIS/ [Accessed 11 May 2021].
39. Falborg AZ, Vedsted P, Menon U, Weller D, Neal RD, Reguilon I, Harrison S, Jensen H: Agreement between questionnaires and registry data on routes to diagnosis and milestone dates of the cancer diagnostic pathway. Cancer Epidemiol 2020, 65:101690
40. Pinault L, Khan S, Tjepkema M. Accuracy of matching residential postal codes to census geography. Health Rep. 2020 Jun 17;31(3):3-13. doi: 10.25318/82-003-x202000300001-eng. PMID: 32644759.
41. Kelly C, Hulme C, Farragher T, Clarke G. Are differences in travel-time or distance to healthcare for adults in global north countries associated with an impact on health outcomes? A systematic review. BMJ Open. 2016 Nov 24;6(11):e013059. doi: 10.1136/bmjopen-2016-013059. PMID: 27884848; PMCID: PMC5178808.
42. Murchie P, Adam R, McNair E, Swann R, Witt J, Wood R, Weller D. Cancer diagnosis in Scottish primary care: results from the National Cancer Diagnosis Audit. Eur J Cancer Care. 2020;00:e13234. doi.org/10.1111/ecc.13234
43. Murchie P, Khor WL, Adam R, Esteva M, Smyrnakis E, Petek D, Thulesius H, Vedsted P, McLernon D, Harris M. Influences of rurality on action to diagnose cancer by primary care practitioners– results from a Europe-wide survey in 20 countries. Cancer Epidemiol 2020:65:101698 doi.org/10.1016/j.canep.2020.101698
44. UK Government (2012). Statistical Digest of Rural England 2012. Department of the Environment, Fisheries and Rural Affairs. Available from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/69493/pb13642-rural-digest-2012.pdf [Accessed 11 May 2021].
45. Kravdal Ø. Does place matter for cancer survival in Norway? A multilevel analysis of the importance of hospital affiliation and municipality socio-economic resources. Health Place. 2006 Dec;12(4):527-537. DOI: 10.1016/j.healthplace.2005.08.005.
46. Rechel B, Džakula A, Duran A, Fattore G, Edwards N, Grignon M, Haas M, Habicht T, Marchildon GP, Moreno A, Ricciardi W, Vaughan L, Smith TA. Hospitals in rural or remote areas: An exploratory review

of policies in 8 high-income countries. Health Policy. 2016 Jul;120(7):758-69. doi: 10.1016/j.healthpol.2016.05.011. Epub 2016 Jun 6. PMID: 27312144.

47. Lilley R, de Graaf B, Kool B, Davie G, Reid P, Dicker B, Civil I, Ameratunga S, Branas C. Geographical and population disparities in timely access to prehospital and advanced level emergency care in New Zealand: a cross-sectional study. BMJ Open. 2019 Jul 26;9(7):e026026. doi: 10.1136/bmjopen-2018-026026. PMID: 31350239; PMCID: PMC6661642.
48. Cinnamon J, Schuurman N, Crooks VA. A method to determine spatial access to specialized palliative care services using GIS. BMC Health Serv Res. 2008 Jun 30;8:140. doi: 10.1186/1472-6963-8-140. PMID: 18590568; PMCID: PMC2459163.
49. Baird G, Flynn R, Baxter G, Donnelly M, Lawrence J. Travel-time and cancer care: an example of the inverse care law? Rural Remote Health 2008; 8: 1003. Available: www.rrh.org.au/journal/article/1003
50. Scottish Government (2019). Scottish referral guidelines for suspected cancer. Available from: https://www.gov.scot/publications/scottish-referral-guidelines-suspected-cancer-january-2019/pages/3/#:~:text=3.%20Referral%20Guidelines%20%20%20%20%20,one%20course%20...%20%203%20more%20rows%20 [Accessed 29 December 2020]
51. Weller D, Menon U, Zalounina Falborg A, Jensen H, Barisic A, Knudsen AK, Bergin RJ, Brewster DH, Cairnduff V, Gavin AT, Grunfeld E, Harland E, Lambe M, Law RJ, Lin Y, Malmberg M, Turner D, Neal RD, White V, Harrison S, Reguilon I; ICBP Module 4 Working Group, Vedsted P. Diagnostic routes and time intervals for patients with colorectal cancer in 10 international jurisdictions; findings from a cross-sectional study from the International Cancer Benchmarking Partnership (ICBP). BMJ Open. 2018 Nov 27;8(11):e023870. doi: 10.1136/bmjopen-2018-023870. PMID: 30482749; PMCID: PMC6278806.
52. Scottish Government (2020). Recovery and redesign: cancer services action plan. Available from: https://www.gov.scot/publications/recovery-redesign-action-plan-cancer-services/pages/7/ [Accessed 11 May 2021].

Tables and Figures

Table 1: *Distribution of patient characteristics, tumour stage, 1-year mortality, distance and time intervals according to Scotland, Denmark and in total (n=5,898, numbers vary due to missing data).*

	Scotland		Denmark		Total		P-value*
	n	(%)	n	(%)	n	(%)	
Total	1,184	(20.2)	4,714	(79.9)	5,898	(100)	
Age groups (years)							0.02
0-49	61	(5.2)	229	(4.9)	290	(4.9)	
50-59	163	(13.8)	587	(12.5)	750	(12.7)	
60-69	303	(25.6)	1,335	(28.3)	1,638	(27.8)	
70-79	368	(31.1)	1,580	(33.5)	1,948	(33.0)	
>=80	289	(24.4)	983	(20.9)	1,272	(21.6)	
Sex							0.47
Male	621	(54.0)	2,601	(55.2)	3,225	(55.0)	
Female	526	(45.7)	2,113	(44.8)	2,642	(45.0)	
Tumor stage							<0.01
Local	492	(52.0)	1,649	(43.8)	2,141	(45.4)	
Regional/distant	454	(48.0)	2,116	(56.2)	2,570	(54.6)	
One year survival							<0.01
Alive	918	(77.5)	3,868	(82.1)	4,786	(81.1)	
Dead	266	(22.5)	846	(17.9)	1,112	(18.9)	
Charlsons Comorbidity Index							0.10
0	785	(66.3)	3,009	(60.7)	2,925	(50.9)	
1-2	205	(17.3)	891	(19.5)	841	(14.6)	
>2	194	(16.4)	663	(14.5)	1,981	(34.5)	
Minutes to GP**							0.18
Up to 2 min.	306	(25.8)	1,104	(24.6)	1,410	(24.9)	
>2-4 min.	294	(24.8)	1,128	(25.1)	1,422	(25.1)	
>4-8 min.	316	(26.7)	1,099	(24.5)	1,415	(24.9)	
>8-13 min.	162	(13.7)	688	(15.3)	850	(15.0)	
>13 min.	106	(9.0)	471	(10.5)	577	(10.2)	
Minutes to hospital**							<0.01
Up to 9 min.	241	(20.4)	1,217	(26.1)	1,458	(24.9)	
>9-21 min.	262	(22.1)	1,196	(25.6)	1,458	(24.9)	
>21-41 min.	194	(16.4)	1,263	(27.1)	1,457	(24.9)	
>41-67 min.	208	(17.6)	666	(14.3)	874	(14.9)	
>67 min.	279	(23.6)	325	(7.0)	604	(10.3)	
Continuous variables	**Median**	**(IQI)**	**Median**	**(IQI)**	**Median**	**(IQI)**	**P-value *****
Minutes to GP****	4	(2-8)	4	(2-8)	4	(2-8)	0.23
Minutes to hospital****	29	(10-66)	20	(9-38)	21	(9-41)	<0.01
Secondary care interval (days)	34	(7-53)	34	(22-55)	34	(19-54)	<0.01
Treatment interval (days)	64	(29-102)	13	(3-23)	18	(6-42)	<0.01

**Pearson's chi-squared test*

***Categorised using cut at the 25%,50%,75% and 90% percentile*

**** Mann-Whitney rank sum for differences in ranks*

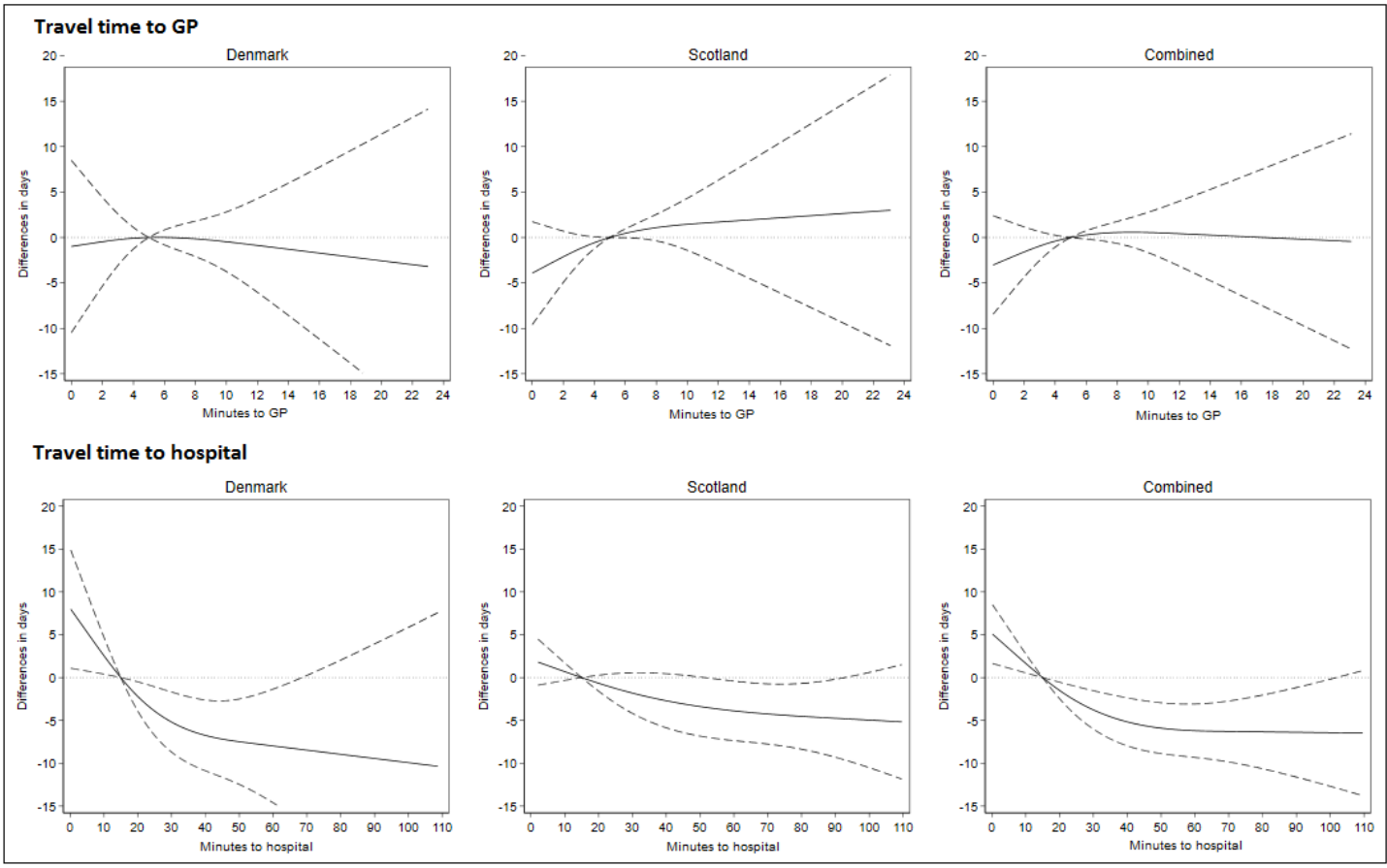
***** Rounded to nearest minute*

Abbreviations: IQI=interquartile interval

***Table 2**. Significance tests for overall shape of association and interaction between country and travel-time*

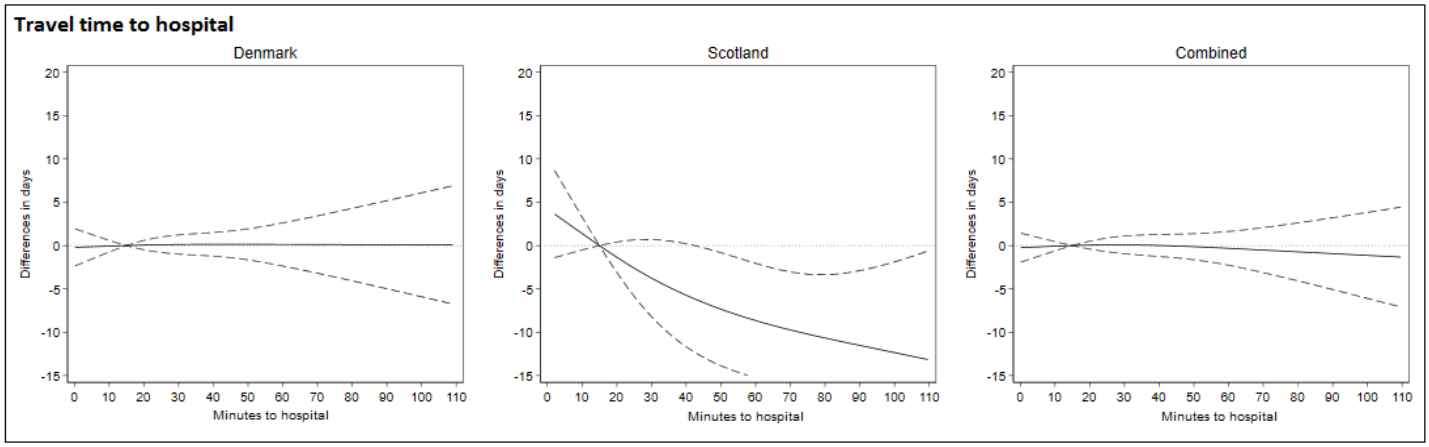
Travel-time to:	Outcome	Test for overall shape of association, p-value			Test for interaction between country and travel-time, p-value
		Scotland	Denmark	Combined	
GP	Secondary care interval	0.175	0.936	0.471	0.161
Hospital	Secondary care interval	0.051	0.006	<0.001	0.046
Hospital	Treatment interval	0.015	0.976	0.899	0.001
GP	Tumour stage	0.262	0.996	0.756	0.284
Hospital	Tumour stage	0.008	0.569	0.913	0.088
GP	1-year mortality	<0.001	0.491	0.002	0.027
Hospital	1-year mortality	0.027	<0.001	0.002	0.010

Figure 1. *The secondary care interval (in days) as a function of travel-times (minutes) to the GP and to the hospital*



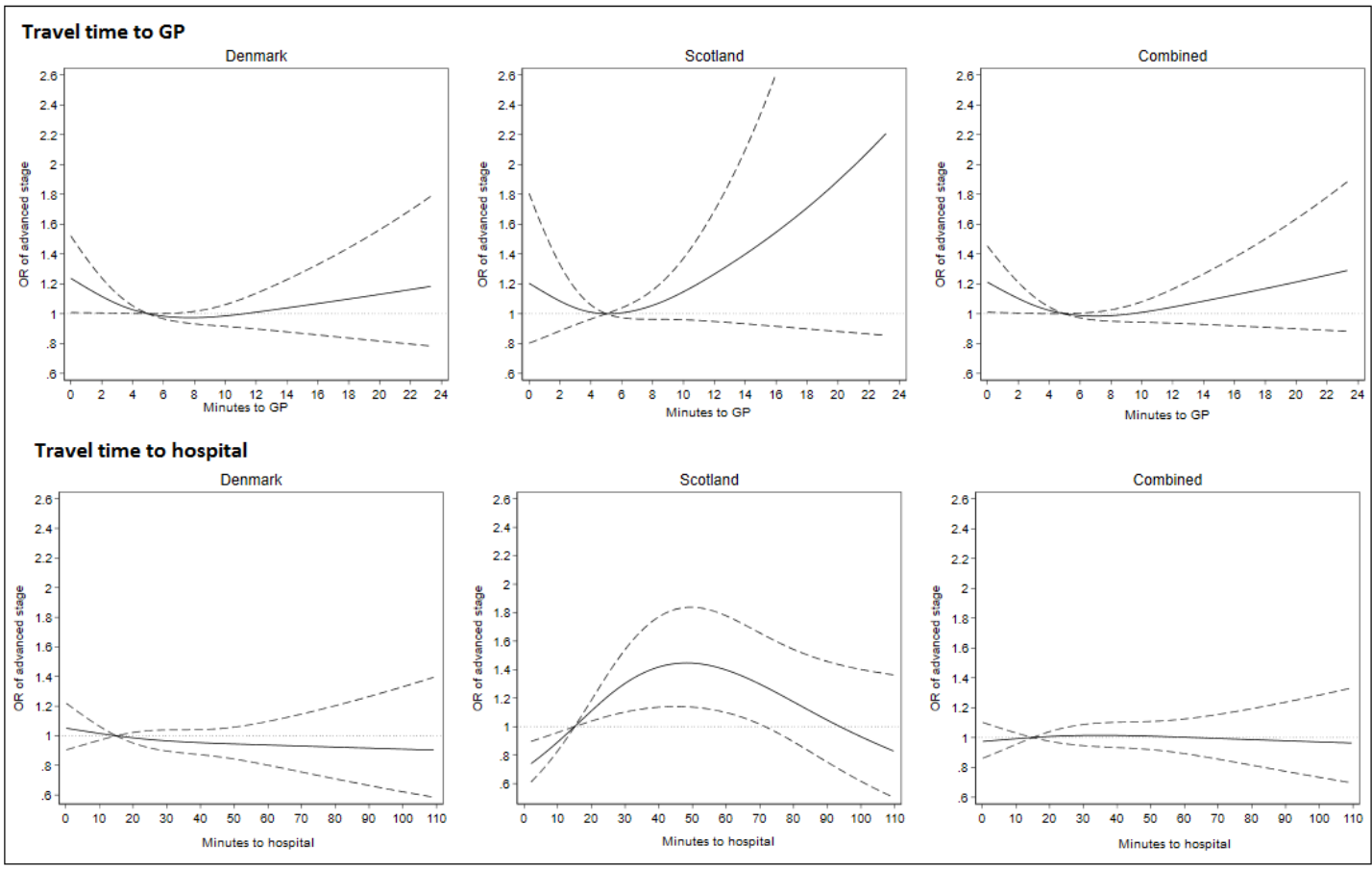
Adjusted for: sex, age and CCI
Legends:
The solid graph indicates the estimated differences in days and the dashed line represents the 95% CI.
The horizontal line indicates the chosen reference point (5 minutes for travel-time to the GP and 15 minutes for travel-time to the hospital)

Figure 2. *The treatment interval (in days) as a function of travel-times (minutes) to the GP and to the hospital*



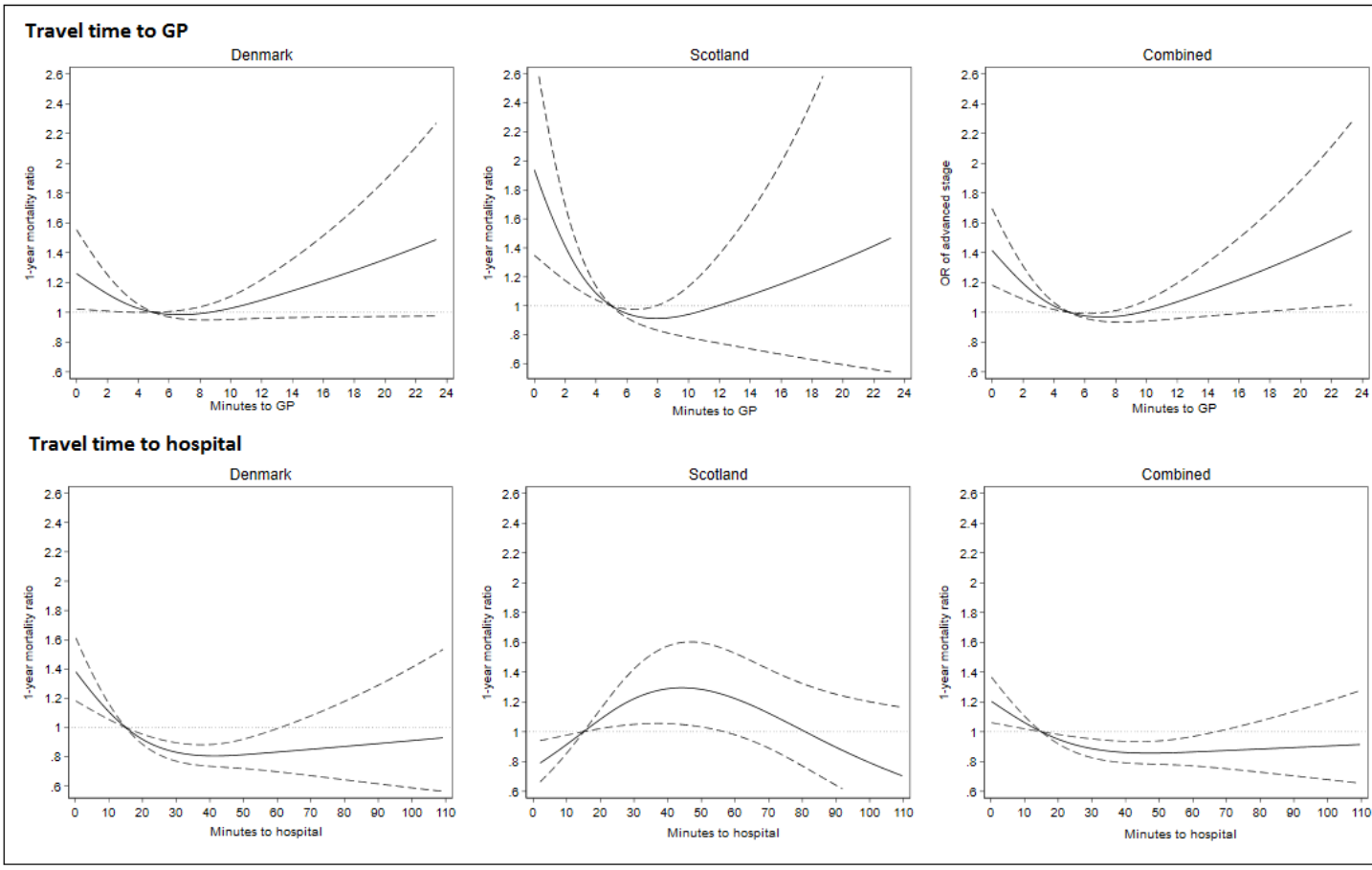
Adjusted for: sex, age and CCI
Legends:
The solid graph indicates the estimated differences in days and the dashed line represents the 95% CI.
The horizontal line indicates the chosen reference point (5 minutes for travel-time to the GP and 15 minutes for travel-time to the hospital)

Figure 3. *The odds of having advanced tumour stage at diagnosis as a function of travel-times (minutes) to the GP and to the hospital*



Adjusted for: sex, age and CCI
Legends:
The solid graph indicates the estimated odds ratios and the dashed line represents the 95% CI.
The horizontal line indicates the chosen reference point (5 minutes for travel-time to the GP and 15 minutes for travel-time to the hospital)
Abbreviations: OR=odds ratio

Figure 4. *One-year mortality as a function of travel-times (minutes) to the GP and to the hospital*



Adjusted for: sex, age and CCI
Legends:
The solid graph indicates the estimated one-year mortality ratios and the dashed line represents the 95% CI.
The horizontal line indicates the chosen reference point (5 minutes for travel-time to the GP and 15 minutes for travel-time to the hospital)