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Comparing Health in Europe based on Dried Blood Spot Samples

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Abstract:

SHARE, a pan-European panel study of about 85,000 individuals aged 50+ in 27 Continental European countries and Israel, has collected dried blood spot (DBS) samples from approximately 27,000 respondents in 13 countries. Laboratory results from DBS assays cannot be directly compared to the results one would obtain from assays of venous plasma samples using standard laboratory methods. DBS values of, e.g., total cholesterol, have both a larger mean and a larger variance. This paper shows that conventional lab-based adjustment formulae do not suffice to account for fieldwork conditions, which may affect the quality of DBS taken in a survey like SHARE. We therefore performed structured validations in the laboratory, which mimicked the SHARE fieldwork conditions. We use these validations to establish structural conversion formulae applicable to the SHARE populations, which estimate the value that we would have obtained had it been feasible to analyze the donor's venous blood with standard analytical methods for plasma or wet blood.deviation.

Zusammenfassung:

SHARE, ein europaweites Panel mit rund 85.000 Personen ab 50 Jahren in 27 kontinentaleuropäischen Ländern und Israel, hat Proben getrockneten Blutes, sogenannte Dried Blood Spots (DBS), von rund 27.000 Befragten in 13 Ländern gesammelt. Laborergebnisse aus DBS-Proben können nicht direkt mit Ergebnissen verglichen werden, die aus venösen Plasmaproben unter Verwendung von Standardlabormethoden erhalten werden. Beispielsweise weisen DBS-Proben für Gesamtcholesterin sowohl einen höheren Mittelwert als auch eine größere Varianz auf. Dieses Paper zeigt, dass herkömmliche laborbasierte Anpassungsformeln nicht ausreichen, um Bedingungen im Feld zu berücksichtigen, die die Qualität von DBS in einer Umfrage wie SHARE beeinflussen können. Daher haben wir im Labor strukturierte Validierungen durchgeführt, die SHAREs Feldbedingungen nachahmten. Diese Validierungen verwenden wir, um strukturelle Umwandlungsformeln für die SHARE-Populationen zu erstellen, die jenen Wert schätzen, den wir erhalten hätten, wenn es möglich gewesen wäre, das venöse Blut des Spenders mit Standardanalysemethoden für Plasma oder Nass-Blut zu analysieren.

Keywords:

General health, survey methods, international environment

JEL Classification:

I10, C83, F64

Comparing Health in Europe based on Dried Blood Spot Samples

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Abstract

SHARE, a pan-European panel study of about 85,000 individuals aged 50+ in 27 Continental European countries and Israel, has collected dried blood spot (DBS) samples from approximately 27,000 respondents in 13 countries. Laboratory results from DBS assays cannot be directly compared to the results one would obtain from assays of venous plasma samples using standard laboratory methods. DBS values of, e.g., total cholesterol, have both a larger mean and a larger variance. This paper shows that conventional lab-based adjustment formulae do not suffice to account for fieldwork conditions which may affect the quality of DBS taken in a survey like SHARE. We therefore performed structured validations in the laboratory which mimicked the SHARE fieldwork conditions. We use these validations to establish structural conversion formulae applicable to the SHARE populations which estimate the value that we would have obtained had it been feasible to analyze the donor's venous blood with standard analytical methods for plasma or wet blood.

1. Introduction

Health of the general population and especially of the older aged population is very different across countries. Comparisons between the US Health and Retirement Study (HRS), the English Longitudinal Study of Ageing (ELSA) and the Survey of Health, Aging and Retirement in Europe (SHARE) have played a key role in identifying cross-national differences in health in Europe, the UK and the US. Comparisons of health indicators in two 2006 studies in JAMA documented that older people in England had better health than in the USA, indicated both by diagnosed illness and by measurements of health-related biomarkers (Banks et al. 2006). These reports stimulated extensive research into the potential mechanisms responsible for the differences, and were instrumental in the establishment of two National Academy of Sciences panels (Crimmins et al. 2010; Woolf and Aron 2013). This work was extended by Avendano et al. (2009) to include Continental Europe. Understanding the processes underlying international differences in chronic disease and longevity is crucial for delineating appropriate national policy responses (Avendano and Kawachi 2014). Cross-national comparisons have also been recognized as an important tool for understanding key drivers of life course trajectories (Banks and Smith 2012). Comparisons of health between Europe and the US have been extended to include disease incidence rates (Banks et al. 2010), the presence of specific health issues such as diabetes, obesity and disability (Banks et al. 2012; Vasunilashorn et al. 2013; Wahrendorf et al. 2013a), and measures of mental health and wellbeing (Jivraj and Nazroo 2014; Zivin et al. 2010). Many of these studies have shown that older people in Europe have health advantages when compared with their American counterparts, e.g., the percentages of individuals aged 50-74 with at least one limitation in the activities of daily living (ADL) is 12% in the US, 10% in the UK and 7% in the EU (Avendano et al. 2009).

There can be many reasons for these cross-national health differences. Health care systems are very different between the US and Europe, since almost all European countries have mandatory universal health insurance while the US does not. Coverage, ease of access, co-pays, administrative rules, and quality also differ across EU countries (OECD, 2017), as do historical life circumstances, income and wealth distributions, life styles and health behaviors. In addition, there are cross-Europe differences in the interactions between health care systems and life styles, such as when health care systems attempt to influence health behaviors, and in social policies and programs potentially affecting health across the life course. The latter include differences in early education and childcare programs, employment protection and support programs during middle age and social security and pension systems affecting older individuals. While the impact of many of these policies on social outcomes is well documented, the extent to which they influence health and contribute to differences in longevity among high-income countries is yet to be established.

Understanding the reasons for cross-national health differences requires that studies use comparable health measurements. The findings by Avendano et al. (2009) were based on comparable measures but these were self-reports and may have suffered from reporting biases.

Second, there are considerable differences between self-reported health and measured disease prevalence, potentially due to cross-national differences in the quality and definition of diagnoses, prescription drug use and reporting styles. Adults in the US may be diagnosed more often with certain diseases than Europeans. Higher disease prevalence may stem from higher doctor consultation or screening rates in the US. Poor Americans may be less likely to receive close medical surveillance than Europeans who have access to universal health care. The use of lipid-lowering drugs is much higher in the US than in any other country (Crimmins et al. 2010). When reporting disability, Americans appear to have higher response thresholds than do Europeans (Kapteyn et al. 2007).

There are few studies using more objective measurements of health-related biomarkers, and, with one exception, they are confined to US-UK comparisons due to the lack of comparable data from Continental Europe. Banks et al. (2006) similarly found US-UK differences based upon evaluations of a set of four biomarkers measured in blood samples: glycated hemoglobin (HbA1c; short A1c), a marker for diabetes; C-reactive protein (CRP), a marker for inflammation; and fibrinogen and HDL-cholesterol, risk factors for cardiovascular diseases (CVD). E.g., the percentage of individuals aged 50 and older with A1c greater than 6.5% (an indicator of diabetes) was 7.1% in the US and 4.1% in the UK. Martinson et al. (2011) using CRP, HDL and stress data confirmed these findings and further found that the cross-national differences, while stronger for women than men and more pronounced in lower education groups, are pervasive. In accord with this, Crimmins et al. (2010) found cross-national differences in self-reported high cholesterol levels and self-reported lipid-lowering drug use with measured high cholesterol levels across 6 countries (US, Canada, Netherlands, Spain, England, and Japan).

SHARE, a pan-European panel study of about 85,000 individuals aged 50+ in 27 Continental European countries and Israel (Börsch-Supan et al. 2013), has therefore decided to collect dried blood spot samples (DBSS) from approximately 27,000 respondents in 13 countries. This is by far the largest sampling of DBSS from a representative adult population.

The advantage of collecting DBS rather than venous blood samples (VBS) is in its much lower costs; DBS can be taken by lay interviewers while VBS require nurses. For a large international population-representative survey like SHARE the costs of VBS have been prohibitive. The disadvantage of DBS, however, is that laboratory results from DBS assays cannot be directly compared to the results one would obtain from assays of venous plasma samples using standard laboratory methods (Crimmins et al. 2013; Karvanen 2015). While also "gold standard" values have measurement variation, DBS values of, e.g., total cholesterol, which is known to be particularly hard to measure from DBSS, have both a larger mean and a larger variance, influenced by many laboratory and fieldwork-related factors. After applying parametric standardization (Karvanen, 2015) or non-parametric normalization formulae (e.g. Crimmins et al. 2013), the DBS values fit

the distribution of values obtained from venous blood quite well. This approach has been used with HRS data to produce adjusted values for a small set of analytes (Crimmins et al. 2013).

This study shows that the adjustment formulae mentioned in the preceding paragraph do not suffice to account for fieldwork conditions which may affect the quality of DBS taken in a survey like SHARE. We therefore performed structured validations in the laboratory which mimicked the SHARE fieldwork conditions. We use these validations to establish structural conversion formulae applicable to the SHARE populations which estimate the value that we would have obtained had it been feasible to analyze the donor's venous blood with standard analytical methods for plasma or wet blood.

2. Methods

2.1. Data

SHARE has collected a broad set of socio-economic and health-related variables every two years since 2004. The most recent release of SHARE includes more than 380,000 interviews with about 140,000 individuals aged 50 and over from 28 different countries. SHARE collected DBSS during its sixth wave in 2015, yielding more than 108,000 blood spots (= individual blood drops) of which 83,400 are usable. Consent to donating blood was high at 71% across all participating countries and exceeded 80% in Belgium, Denmark, Sweden, and Slovenia. The DBSS are stored in the SHARE biobank at the University of Southern Denmark (SDU; Odense, Denmark). The DBSS include a small calibration sample from Poland in which both DBSS and venous blood were collected. SHARE has also collected retrospective histories of participants' life courses and health events. Details of the collection methods can be found in Malter and Börsch-Supan (2017).

2.2. Selection of markers

SHARE has selected seven markers:

1. *Glycosylated hemoglobin* (A1c) as marker for diabetes. Excess sugar in the blood irreversibly binds to hemoglobin to form glycated hemoglobin (A1c); A1c signals longstanding and chronically high levels of blood sugar.

2-4. *High density lipoprotein* (HDL) cholesterol, *total cholesterol* (TC) and *triglycerides* (TG) are players in the lipid panel and metabolism, e.g., transporting lipids, which serve as building blocks for cells. Imbalances in lipid metabolism lead to various diseases of the cardiovascular system.

5. *Cystatin C (*CysC*)* as marker for kidney function and CVD. CysC, though a measure for the clearance of degradation products from blood, also signals risk of CVD. Those with elevated cystatin C levels have been shown to be at highest risk for CVD, even when kidney dysfunction is

mild; those with the highest levels of CysC are older and have hypertension, dyslipidemia, high BMI, and higher levels of CRP.

6. *C-reactive protein* (CRP) marks the general level of inflammation in the body, caused by acute infections or chronic diseases. Inflammatory processes are involved in CVD, diabetes, obesity, and cognitive decline.

7. *Total hemoglobin* (tHb) as a marker of anemia which indicates a decrease of red blood cells and subsequently hemoglobin, thereby lowering the ability to carry oxygen in the blood. Anemia may arise from loss of blood, pathological removal of blood cells, diseases of the hematopoietic system, chronic inflammatory diseases, kidney disease, wasting diseases (e.g., cancers), and more.

These markers relate to common ageing-related health conditions and diseases including those associated with diabetes, cardiovascular disease (CVD), decline of kidney function, and cognitive decline, as well as loss of muscle function and muscle mass (sarcopenia).

2.3. Validation scheme

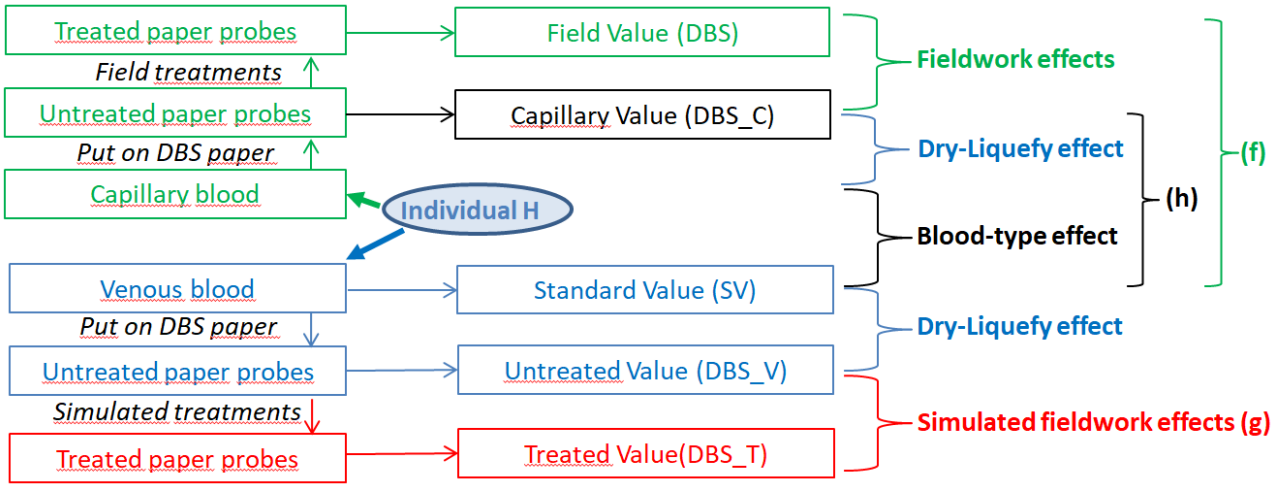
Figure 1 shows a conceptual model of the validation scheme and its underlying processes and values. Our aim is to establish structural conversion formulae applicable to the SHARE populations which estimate the value that we would have obtained had it been feasible to analyze the donor's venous blood with standard analytical methods for plasma or wet blood.

More formally, the aim is to establish an equation, $SV\_E = f(DBS, T, H)$, which computes the estimated standard value *SV_E* from the DBS value in the field, the applicable field and laboratory conditions *T* (e.g., temperature, humidity protection, drying time, shipment time, spot size) and donor characteristics *H* (e.g. health, age, sex) with a degree of accuracy comparable to the measurement variation which also characterizes the (gold) standard value *SV* obtained from plasma or wet blood (Woodworth et al. 2014).

In the center of the figure is a donor with characteristics *H,* who donates venous blood and capillary blood. The upper part of the figure (green boxes) refers to capillary blood collected in the field; the lower part (blue and red boxes) to venous blood collected in the lab. The leftmost column tracks the trail of the blood; the second column shows assay outcome values. These outcomes are different due to various combinations of three factors identified at the far right. First, capillary blood is a heterogeneous mixture of plasma, interstitial fluid and red blood cells while plasma samples are comprised of plasma alone. In addition, venous blood, whether used for analyses based on plasma or wet blood, is treated with EDTA to prevent coagulation. The implications of these differences for the assays in this project, called "blood-type effect", have not yet been studied. Second, the capillary blood of the donor is dried and then re-liquefied in the lab. We call this the "dry-liquefy effect". It has been extensively studied (blue boxes in Figure 1). The DBSS collected in the field (green boxes at the top of Figure 1) are exposed during shipment to varying temperatures, humidity

etc. We call these "fieldwork effects". They have not yet been systematically studied. Since they turn out to be substantial, they are in the center of our new validations here, where we simulate the field effects in the lab (red boxes in Figure 1).

Figure 1: General structure



2.4. Dry-Liquefy effect (DBS_V against SV)

The dry-liquefy effect has been studied extensively at UW in previous studies (e.g., Crimmins et al. 2013); it is small. UW has collected venous blood samples in EDTA tubes. Those samples were then analyzed with conventional clinical chemistry analyzers. In parallel, blood from each EDTA tube was dropped onto filter paper to create DBSS and then analyzed like field-collected DBSS. The relation is linear and tight (Table 1).

Table 1: DBS_V vs SV under laboratory conditions (N~200)

	A1c	TC	HDL	TG	CysC	tHb	CRP
Tightness of fit (R^2)	.99	.86	.87	.95	.91	.99	.87

2.5. Different blood types (DBS_C against DBS_V and SV)

It is known that EDTA is a preservative for cholesterol and various hematological assays (Burtis et al. 2008; Banfi et al. 2007) but the implications of the blood-type effect for the assays in this project have not yet been studied. It can only be measured in combination with the dry-liquefy effect (Figure 1). We dropped both capillary blood and EDTA-treated venous blood from the same donor on filter paper under lab conditions and compared *DBS_C* with *DBS_V*. We also compared *DBS_C* with the gold standard *SV*. Table 2 shows tight correlations for all markers except TC and tHb. Controlling for spot size, age, sex, and BMI very substantially improves the fit to the gold standard

SV. The comparison between *DBS_C* and the gold standard *SV* establishes the function *SV_E = h(DBS_C, T, H)*, the first component of the overall function *f* in Figure 1.

Table 2: DBS_C vs DBS_V (N=30) and SV (N=50)

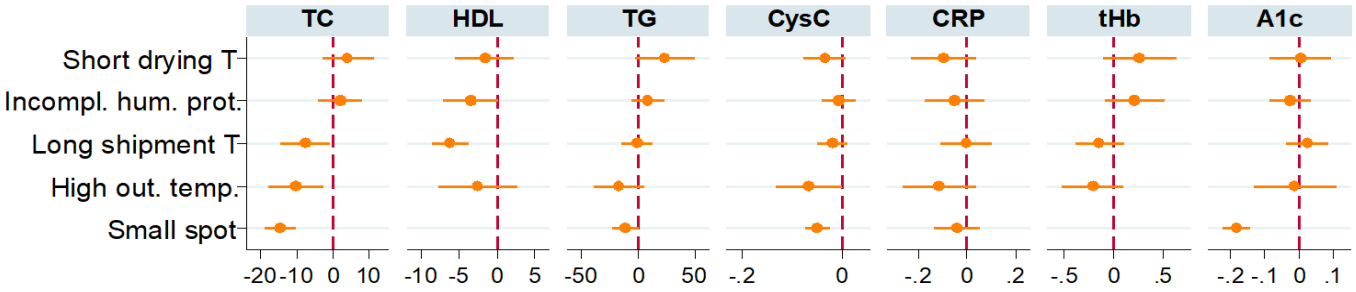
	A1c	TC	HDL	TG	CysC	tHb	CRP
Tightness of fit to DBS_V (R^2)	.96	.60	.85	.98	.92	.36	.997
Incl. controls (R^2)	.98	.78	.93	.99	.96	.59	.998
Tightness of fit to SV incl. controls	.97	.76	.82	.97	.89	.79	.995

3. Results

3.1. Fieldwork effects

We tested the influence of different fieldwork circumstances using data from the UW assays of the first batch of DBSS (Weiss and Börsch-Supan 2018). The results were linked to the SHARE data. The regressions were conditioned on the health conditions of respondents and included interviewer fixed effects in order to isolate fieldwork effects that hold across different interviewers or regions. Figure 2 shows that the influence of field conditions or sample quality is significant and differs among assays. Small spot size is the main challenge in the field, especially for TC and A1c, but not for TG, CysC or CRP. TC is also sensitive to high outside temperatures, and long shipment times. HDL is sensitive to the combination of long shipment times and insufficient humidity protection. TG and CysC are also sensitive to short drying times. CRP and tHb seem to be relatively robust regarding field conditions and sample quality.

Figure 2: Influence of SHARE fieldwork conditions (N~8000)



3.2. Simulated fieldwork conditions

We have taken venous blood from about 50 donors, used it to create approximately 3700 DBSS of three different sizes on filter paper, and then exposed the DBSS to a large number of combinations

of different drying times, humidity protections, outside temperatures, and shipment times that are typical of the conditions experienced by field-collected DBSS during collection and shipment in SHARE. This "simulated fieldwork treatment" process yields the treated DBS values (*DBS_T* in Figure 1) which we compared to the untreated values (*DBS_V*) and the standard value (*SV*). Such validations have not been performed previously in a systematic way and are a major innovation of this project. We then regressed *DBS_V* and *SV* on *DBS_T* and the treatment variables, their interactions and the available donor characteristics.

Figure 3: Adjusting for simulated fieldwork conditions (N~3700)

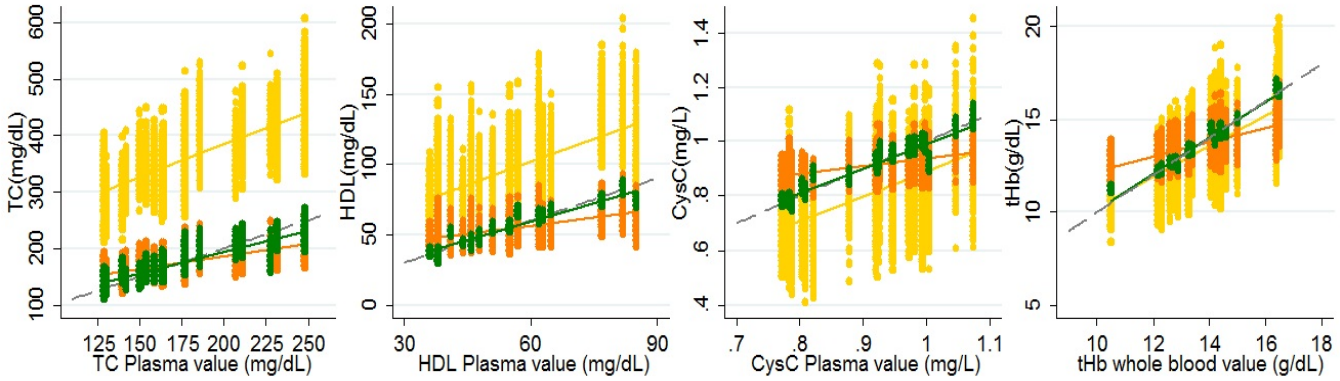


Figure 3 shows the results for the four markers TC, HDL, CysC, and tHb. The yellow bars show the large variation of the raw laboratory values from DBSS and their distance from the dashed equality line. The orange values use a simple bivariate regression while the green values are based on estimations accounting for the simulated fieldwork conditions and donor characteristics. The establish a function $DBS\_C = g(DBS\_T, T, H)$, the second component of the overall function $SV\_E = f(DBS, T, H)$ which has a tight fit (Table 3) for A1c, HDL, CysC, tHb, and CRP, less so for TC and TG (Table 3).

Table 3: DBS_T vs. DBS_V and SV under simulated field conditions (N~3700)

	A1c	TC	HDL	TG	CysC	tHb	CRP
Tightness of fit to SV (R^2)	.88	.76	.89	.76	.90	.95	.97
Tightness of fit to DBS_V (R^2)	.87	.79	.94	.75	.95	.98	.97

3.3. Out-of-sample prediction

By inserting the second component (treatment effects) into the first (blood type and dry-liquefy effect), we obtain the overall function which converts the DBS values obtained under simulated fieldwork conditions into gold standard values, $SV\_E = h(g(DBS\_T, T, H), T, H) = f(DBS, T, H)$.

The prediction accuracy of this conversion formula is high for A1c, HDL, CysC, and CRP (Table 4). Prediction accuracy is lower for TG and tHb in one component but high in the other while TC is weak in both components.

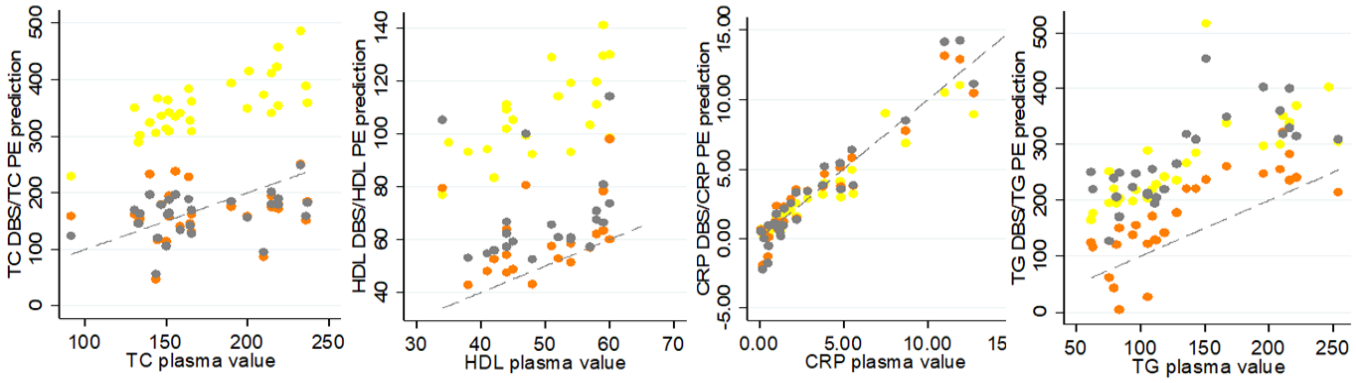
Table 4: Prediction accuracy

	A1c	TC	HDL	TG	CysC	tHb	CRP
Blood-type and dry-liquefy effect (R^2, Table 2)	.97	.76	.82	.97	.89	.79	.99
Treatment effects (R^2, Table 3)	.87	.79	.94	.75	.95	.98	.97

Our approach is based on the assumption that the same conversion function *g* holds for both simulated and actual fieldwork treatments. We tested this assumption using the data obtained in the Polish nurse study where nurses took both DBSS and venous blood samples which were then assayed for A1c, TC, HDL, TG and CRP. We estimated the function f on the data obtained in the UW laboratory as described in sections 2.5 and 3.2, applied this function on the DBS data collected in Poland to generate estimated values *SV_E* and then compared these estimated values with the actual gold standard values *SV* in Poland.

Figure 4 shows the original *DBS_T* values (yellow) and the estimated values *SV_E = f(DBS_T, T, H)* (orange) plotted against the actual gold standard values taken from plasma (*SV*). The gray dots represent the predicted values if the blood-type effect is ignored. It should be noted that the plasma values were obtained from a laboratory in Poland with different analyzers from those used in our UW-based validation studies and that the circumstances of the transportation of the venous blood in Poland generated additional variation in the plasma values. In spite of this, we observe a good convergence to the dashed equality line.

Figure 4: Raw and estimated gold standard values vs. actual gold standard values



4. Discussion

The influence of field conditions and sample quality is significant and differs among assays. Small spot size is the main challenge in the field, especially for TC and A1c, but not for TG, CysC or CRP. TC is also sensitive to high outside temperatures, and long shipment times. HDL is sensitive to the combination of long shipment times and insufficient humidity protection. TG and CysC are also sensitive to short drying times. CRP and tHb seem to be relatively robust regarding field conditions and sample quality.

Failure to correct for these fieldwork influences creates substantially biased VBS equivalents. Applying parametric standardization (Karvanen, 2015) or non-parametric normalization formulae (e.g. Crimmins et al. 2013) will not correct for these biases.

By simulating adverse fieldwork conditions (such as small spot size, high temperature and humidity, short drying time and long shipment times) in the lab, we were able to validate DBS under such conditions and established structured conversion formulae with high prediction accuracy.

The overall conclusion from our structured validation experiments is therefore that we can reliably measure A1c, HDL, CysC and CRP from DBSS once we take the blood-type and the various treatment effects into account. The treatment effects are somewhat less accurately predicted for TG, and the blood-type effect for tHb. TC, as expected, is the weakest of the seven analytes.

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