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Management and interpretation of heterogeneous observational data: Using insulin-like growth factor-I data from the NordiNet® International Outcome Study



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ABSTRACT

Objective: The NordiNet® International Outcome Study (IOS), a large-scale, non-interventional, multi-centre, real-world study of Norditropin® treatment, registers insulin-like growth factor-I (IGF-I) values, as measured by different assays. This paper considers the potential biases introduced by using a single IGF-I reference data set in analysing NordiNet® IOS data.

Design: To evaluate possible biases from different IGF-I assays used across NordiNet® IOS, a mixed-effect linear model was fitted to IGF-I data (analyses on log-transformed data). Pre-growth hormone treatment (pre-GHT) IGF-I values were assumed to depend on diagnosis, sex and age. During GHT, a treatment-effect dependent on these factors was added. Differences between assays were assumed multiplicative on the original scale. Individual measurements were scaled to a common level (Nichols Advantage) giving adjusted IGF-I standard deviation score (SDS) values.

Results: In total, 49 495 IGF-I measurements were available from 9481 paediatric patients. Mixed-effect linear modelling showed a systematic difference between IGF-I levels measured by different assays. Differences were minimised when assessing change in IGF-I SDS from the start of GHT to 1-year follow-up. This applied to values adjusted for actual-assay used and for unadjusted delta IGF-I SDS values. Largest differences between unadjusted change in IGF-I SDS values were: for growth hormone deficiency 0.1 (girls) and 0.3 (boys); for small-for-gestational age 0.1; and for Turner syndrome 0.2. Similar magnitude differences were seen for data with unknown assay.

Conclusions: Analysis and modelling suggest the current approach to IGF-I data collection and analyses in the NordiNet® IOS is sound: in a large cohort without assay-used information, potential bias is minimised by analysing changes in IGF-I SDS.

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1. Introduction

The measurement of circulating insulin-like growth factor I (IGF-I) by sensitive immunoassays is widely established in the diagnosis of growth-

hormone (GH) related disorders and is crucial in the assessment and monitoring of GH replacement therapy [1–4].

Due to heterogeneity in assay characteristics, there can be considerable differences between the results provided by currently available IGF-I assays [4,5]. For IGF-I assays, differences in the choice of standard and its handling and calibration within a given assay affect the comparability of assays [6]. To improve standardisation, in 2009 the Expert Committee on Biological Standardization of the World Health Organization formally adopted the preparation of the first International Standard for IGF-I as the universal calibrant for immunoassays. These standards are recommended in laboratory practice [1]. However, it should be noted that not all manufacturers currently adopt the standard.

Abbreviations: GHD, growth hormone deficiency; GHT, growth hormone treatment; HSDS, height standard deviation scores; IGHD, isolated growth hormone deficiency; IOS, International Outcome Study; LMS, lambda-mu-sigma; MPH, multiple pituitary hormone deficiency; SDS, standard deviation score; SGA, small-for-gestational age; TS, Turner syndrome.

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The establishment of normative IGF-I data in representative populations is recognised as imperative for the study of IGF-I data from specific patient populations [2,7]. For children and adolescents, such normative data should be age-adjusted [3] to accurately reflect the age intervals and Tanner stages during which there are rapidly changing IGF-I concentrations [5].

One of the largest studies undertaken to establish method-specific reference IGF-I ranges used the Nichols Advantage® assay, which was considered the gold standard until its withdrawal in 2006 [2]. Normative data also exist for an automated assay system currently in use, the Immulite system [8] but, in general, reference data are poor for many of the other assays on the market [6]. In recent years there have been attempts to better define normative reference values for IGF-I as, for example, in a recent congress report based on a study of the automated IDS-iSYS IGF-I assay that constructed IGF-I reference ranges using the LMS (lambda-mu-sigma) method [9] (see Supplementary pages for a description and discussion of the calculation of reference values and the LMS method).

The NordiNet® International Outcome Study (IOS) (NCT00960128) is a large-scale, non-interventional, multi-centre study that aims to gather long-term data on the safety and effectiveness of Norditropin® treatment in the usual clinical setting [10–12]. A major goal is to determine the predictive value, if any, of pre-treatment factors such as IGF-I levels on outcome. The study also aims to evaluate the effect of Norditropin® treatment on IGF-I as a key marker of GH activity. Due to the growth-promoting effects of IGF-I, causality is also being studied.

Large observational studies like NordiNet® IOS can offer a unique opportunity to evaluate how IGF-I levels and patterns associate with the effectiveness and safety of GH replacement therapy. However, interpretation of data from such a real-world study must take account of both the biases inherent in IGF-I assays and the limitations imposed on data interpretation by aspects of the study protocol. The protocol for NordiNet® IOS provides clear guidance concerning the data to be captured; however, data collection is ultimately conducted in accordance with normal clinical practice. This means that a blood sample is not required at each patient visit, and IGF-I measurements only become available upon the discretion of the treating physicians in their everyday clinical practice. Furthermore, in NordiNet® IOS, IGF-I levels are measured using different assays depending on the differing clinical and laboratory practices in the real-world setting. Assay information may be available, but this is not mandatory information in NordiNet® IOS. IGF-I measurements are, therefore, reported from multiple sources and locations, and the data reflect inter-assay as well as intra-assay variability. No information about individual assay performance and quality is available. While some clinics and laboratories probably use the same assay method, since the start of the registry and during the NordiNet® IOS study period, several different assays have become available, adding to the possibility of inter-assay variability within clinics, and even within patients over time.

The current approach for evaluation of NordiNet® IOS IGF-I data has been to use a reference data set [2] based on the most frequently reported assay within NordiNet® IOS to date, which has historically been the Nichols Advantage. However, this approach leads to an inevitable bias, since a precise standard deviation score (SDS) calculation for IGF-I measurements assessed with other assays is not possible.

This paper aims to assess IGF-I data from NordiNet® IOS, and specifically seeks to evaluate and discuss the potential biases introduced by using a single reference data set that is suboptimal for measurements made by other assays. The model and methods applied in this paper aim to assess and show that despite study limitations, historic differences in choice and use of assay methods, and limited assay information, there are useful IGF-I data and data trends to report from the NordiNet® IOS database. The paper does not aim to suggest methods for use in clinical practice, but rather to evaluate a proposed strategy for drawing scientific and clinically meaningful conclusions utilising

data from the heterogeneous populations and practices reported in observational studies.

2. Methods

2.1. Study design

The study design of the on-going NordiNet® IOS, launched in 2006, is described in detail elsewhere [10]. In brief, 19 countries are participating in NordiNet® IOS and those eligible for inclusion are paediatric and adult patients who are already on, or starting, Norditropin® treatment upon the discretion of the treating physicians [10].

The study population considered in this analysis of NordiNet® IOS comprised paediatric patients with a diagnosis of growth hormone deficiency (GHD), patients born small-for-gestational age (SGA) and patients with Turner syndrome (TS) receiving growth hormone-replacement therapy with Norditropin®.

The study database uses an electronic, web-based platform (NordiNet®) for electronic data capturing in study case report forms (CRFs), which provide automatic data validation at data entry. All anonymised patient data reported into the central database are managed by the Novo Nordisk Epidemiology Department in Denmark.

2.2. Data extraction

Key demographic and clinical characteristics (captured as described in the NordiNet® IOS study design [10]) reported here include the baseline characteristics of patient age, sex and clinical diagnosis, and data relating to GH treatment (GHT). In order to evaluate and discuss the potential biases introduced by using a single reference data set for IGF-I SDS calculation, all valid IGF-I measures available from paediatric patients diagnosed with GHD, SGA or TS from 2003 to 2012 in the NordiNet® IOS were extracted from the central database. Where available, information on the assay type/fabricant was extracted.

2.3. Reference data

According to reported assay information in NordiNet® IOS, Nichols Advantage has been the most commonly used assay to date, which spans the time from the start of NordiNet® IOS to the present day, and thus reflects retrospective trends in assay choice and use. Additionally, since the Brabant reference data are based on one of the largest published studies to date in relevant normative cohorts [2], these reference data have been used for the calculation of IGF-I SDS values in all previous analyses of IGF-I data from NordiNet® IOS. Local laboratory reference intervals have not been used given the difficulties of defining 'normal' levels from local data.

2.4. Statistical analysis, test models and validation of models

The objectives of the statistical analysis were: (1) to evaluate possible biases due to different IGF-I assays; (2) to evaluate possible biases due to different IGF-I reference data; and (3) to evaluate the representativeness of the sample used for the assay evaluation. For all three objectives, both absolute values and relative changes in IGF-I SDS were included in the evaluation.

In order to evaluate possible biases due to different assays, the differences between the assays used across NordiNet® IOS were estimated, based on IGF-I data with available assay information. This was done by fitting a mixed-effect linear model to the repeated IGF-I measurements. The mixed-effect model was chosen as it gives correct estimates of treatment and other fixed effects in the presence of correlated errors among random effects. Additionally the mixed-effect model handles missing values [13] (see Supplementary pages for a more detailed description of the model and the model formula). For each patient, all measurements taken before the first GH dose were defined as the

'pre-GHT values'. The last pre-GHT measurement (<12 months before the first GH dose) was termed the 'GHT start value'. Measurements taken after the first GH dose were termed 'during GHT values'. The value closest to 1 year (± 6 months) after the first GHT dose was defined as the '1-year follow-up value'. As there appeared to be increasing variability with increasing IGF-I values, the analysis was performed on log-transformed values. The pre-GHT IGF-I values were assumed to depend on diagnosis, sex and age. This was considered to be similar during GHT, but with the addition of a treatment-effect dependent on diagnosis, sex and GH dose. The fixed effects were as described above with the addition of an assay effect. Consequently, the differences between assays were assumed to be multiplicative on the original scale. The random part of the model consisted of a patient level (different baseline values), patient treatment effect (different GHT responsiveness) and a residual error (measurement error). All random effects were considered to be normally distributed.

Based on the multiplicative assay effects, the individual measurements were scaled to a common level (based on Nichols Advantage since this has been the most frequently used assay within the NordiNet® IOS study period) in order to calculate adjusted IGF-I SDS values. The adjusted values derived from the model were compared to the unadjusted values both at GHT start and during treatment.

To evaluate the possible bias introduced by using different reference values, IGF-SDS values were calculated for the same sample (data with available assay information) based on two additional reference value sets [8,14]. The Elmlinger reference values were based on the Immulite assay, and the Bidlingmaier reference values on the IDS-iSYS IGF-I assay.

To evaluate the representativeness of the sample, the unadjusted values with assay information were compared to the unadjusted values of the data without assay information.

The statistical software used was SAS version 9.3.

3. Results

In the current analysis, 49 495 IGF-I measurements available from 9481 paediatric patients diagnosed with GHD, SGA or TS were included. Within the population for whom IGF-I data were available, 6036 had a diagnosis of GHD; 2516 had SGA and 929 had TS. Patient age ranged from 3 years to 18 years in all patient groups (see Supplementary Table 1 for details of baseline demographics, clinical diagnosis, GHT and assay information for patients in the current analysis).

For approximately 16% of IGF-I measurements, information on the assay type/fabricant was available, with the Nichols Advantage (Nichols Diagnostics) (27%), Mediagnost (Mediagnost GmbH) (21%), Immulite (Immunotech) (19%), DSL (Diagnostic Systems Laboratories) (13%), Biochem RIA (7%), Immunodiagnostik (5%) and Immulite (Siemens) (7%) being the most frequently used assays (three other assays representing 0.8% were not included in the analysis).

Approximately 70% of the reported measurements were made on GHD patients, 21% on SGA patients and 9% on TS patients. The measurements were 7% pre-GHT and 93% during treatment. Out of a total of 1892 patients with available IGF-I assay information, 73.4% were measured with only one assay, 20.1% were measured with two assays and 6.5% were measured with more than two assays.

IGF-I levels and the variability of the measurements did, as expected, increase with age (see Supplementary Fig. 1). Mean IGF-I levels in pre-growth hormone treated patients were estimated according to age, sex and diagnosis (Fig. 1; see also Supplementary Table 2 and Supplementary Fig. 2 (A–E), which show estimated IGF-I levels by age group, sex and indication, together with 95% confidence intervals). The multiplicity adjustment factors for the different assays were calculated (Table 1, Fig. 2). Fig. 2 illustrates the data for patients with a GHD diagnosis (see Supplementary Fig. 3 for SGA and TS plots and similar trends). The estimated values based on the different assays follow the same ranking within the different diagnosis, Immulite representing the highest levels of

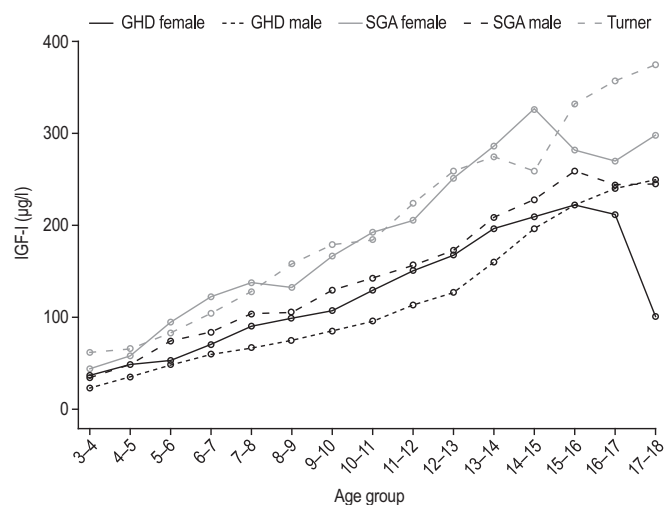


Fig. 1. Mean IGF-I levels by age group, sex and indication. (See also Supplementary Fig. 2 for values, per indication, showing age group and sex, with 95% confidence intervals.) GHD, growth hormone deficiency; SGA, small-for-gestational age.

IGF-I (+34%) followed by Immulite (+17%) and DSL (+18%) at almost the same level. Nichols Advantage represents the point of reference; Mediagnost (−9%), Biochem RIA (−14%) and Immunodiagnostik (−17%) are represented by slightly lower IGF-I values.

In addition, multiplicity adjustment factors for different levels of GHT doses were calculated (Table 1). A treatment dose of 30 µg/kg/day will result in a 10% increase in IGF-I level whereas a treatment dose of 50 µg/kg/day will result in a 16% IGF-I increase.

The mean (\pm standard error [SE]) IGF-I SDS at GHT start and at 1-year follow-up, and the mean change in IGF-I SDS from GHT start and to 1-year follow-up were calculated for the patients with known (Table 2, columns A–D) and unknown (Table 2, column E) IGF-I assay information. The values are given for each of the five subgroups (divided by diagnosis and sex) included in this study. Table 2, column A shows the IGF-I SDS values as they are currently calculated in NordiNet® IOS using the Brabant reference. Patients with GHD initiate GHT with the lowest IGF-I values (−1.7 SDS) and those with SGA start with the highest values (−0.7 SDS). All subgroups show increases of around 2 SDS during the first treatment year. In Table 2, column B the IGF-I SDS values adjusted for the IGF-I assay using the multiplicity factors from the developed model are presented alongside the difference from Table 2, column A. The largest differences between adjusted and unadjusted values, using the same reference, are seen for GHD after one treatment year (−0.3 SDS). The differences in the calculated

Table 1

Multiplicity adjustment factors with 95% confidence interval (CI) by IGF-I assay and GH dose.

	Multiplicity factor	Lower 95% CI	Upper 95% CI
IGF-I assay			
Biochem RIA	0.86	0.80	0.93
DSL	1.18	1.13	1.24
Immulite	1.17	1.08	1.27
Immundiagnostik	0.83	0.76	0.90
Immunotech	1.34	1.28	1.40
Mediagnost	0.91	0.86	0.96
Nichols Advantage	1.00		
GH dose (µg/kg/day)			
0	1.00		
10	1.03	1.02	1.05
20	1.06	1.03	1.09
30	1.10	1.05	1.14
40	1.13	1.07	1.19
50	1.16	1.08	1.25

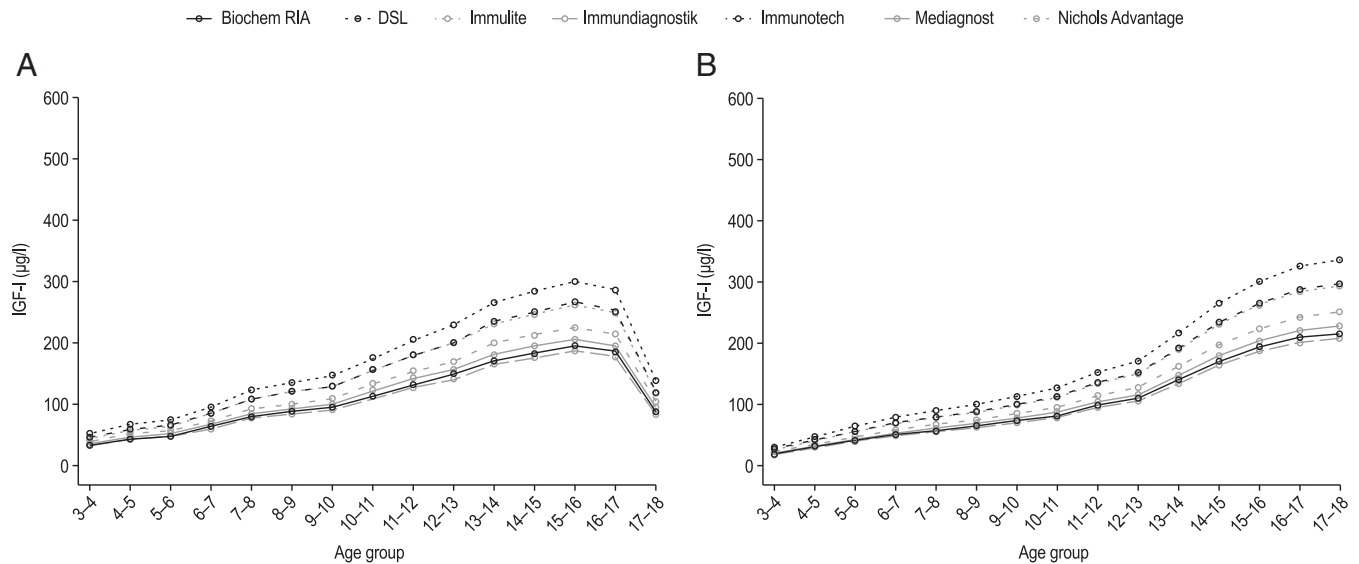


Fig. 2. Estimated pre-treatment IGF-I mean levels according to seven different assays (Biochem RIA, DSL, Immulite, Immundiagnostik, Immunatech, Mediagnost and Nichols Advantage) as a function of age, sex and diagnosis. (A) Growth hormone deficiency (GHD) girls and (B) GHD boys. (See also Supplementary Fig. 3 for small-for-gestational age and Turner syndrome data.)

changes from GHT start to 1-year follow-up are all within the interval from -0.1 to 0 SDS.

In Table 2, columns C and D, IGF-I SDS values based on the Bidlingmaier and Elmlinger reference values are shown. For the Bidlingmaier reference values, the greatest difference from Table 2, column A is seen in GHD girls at GHT start (1.1 SDS). For the calculated change during the first treatment year, the differences are within the interval from -0.2 to 0.1 SDS for the Bidlingmaier reference. For the Elmlinger reference the biggest difference is seen for SGA boys (-0.4 SDS). The calculated change values are in the interval from -0.3 to 0.1 SDS.

In Table 2, column E IGF-I SDS values for the patients without assay information are shown. The differences to column A are in the interval -0.4 to 0.4 SDS for the GHT start and 1-year follow-up values. For the change from GHT start to 1-year follow-up values the differences range from -0.2 to 0.2 SDS.

4. Discussion

The current approach when analysing NordiNet® IOS data has been to use the age- and sex-related normative data of Brabant et al. as IGF-I reference data, since that dataset was based on a large cross-sectional sample of almost 4000 healthy subjects aged 1 month to 88 years, with IGF-I assessed in six laboratories using Nichols Advantage assay [2]. The results of our study suggest that although reported IGF-I levels differ depending on the assays used, these differences could be minimised by evaluating changes in IGF-I SDS values.

After adjustment for assay variability and correction for GH dose, it was shown that IGF-I data from NordiNet® IOS follow the expected patterns for age, diagnosis and sex. The results of the mixed-effect linear model showed a systematic difference between the IGF-I levels when measured by different assays. Conversion of IGF-I values from one assay to another using multiplicity factors has been described and validated previously by Krebs et al, who compared different assays for IGF-I and also chose the Nichols Advantage as a standard against which to assess the effects of GHT on IGF-I levels [3]. This difference, which we also observed, introduces an inevitable systematic error when using the same normative data for absolute SDS calculation.

At the start of GH therapy and 1-year follow-up we only observed bias up to 0.3 SDS when comparing the adjusted mean values with the unadjusted mean values using the same reference data (Table 2, column

B). When looking at the mean change in IGF-I SDS from GHT start to 1-year follow-up, however, the bias was minimised to 0.1 SDS.

When comparing the unadjusted IGF-I SDS values using different reference data sets we observed larger differences; however, these differences were also minimised when evaluating the delta IGF-I SDS values (Table 2, columns C, D). For GHD the largest absolute difference between unadjusted changes in IGF-I SDS values was 0.1 SDS for girls and 0.3 for boys; for SGA it was 0.1 SDS and for TS the largest difference was 0.2 .

To evaluate the representativeness of the sample, the unadjusted values with assay information were compared to the unadjusted values of the data without assay information (Table 2, column E). The maximum absolute difference between the unadjusted delta SDS values was 0.2 SDS in the TS girls.

This analysis of NordiNet® IGF-I data demonstrates that there is a systematic difference between IGF-I levels measured by different assays. The current data showed that modest bias was introduced by using a single reference data set [2] for calculation of IGF-I SDS values. Nevertheless, when analysing treatment outcomes in the NordiNet® IOS study, it seems possible to minimise this bias using only changes in IGF-I SDS levels (delta IGF-I SDS values) in our models. Furthermore, analysing changes in IGF-I measurements (delta IGF-I SDS) was found to be useful even if information on the type of assay was lacking and thereby provided an opportunity to include those values in statistical analyses which would have been excluded when comparing absolute levels (IGF and IGF-I-SDS).

The mixed-effect linear model used in the current study included assay, diagnosis, sex, age and GHT, although numerous other parameters could have been included in the model. Interpretation of IGF-I data for NordiNet® IOS in girls over the age of 14 years and boys over the age of 16 years is complicated by puberty. It is known that in otherwise healthy children, after puberty there is a fall in IGF-I levels and that during puberty there are large variations in IGF-I levels, with increases in early puberty and decreases in later puberty as defined by Tanner stage [15]. However, in the patients in NordiNet® IOS receiving GH therapy, puberty was not corrected for in the model and IGF-I values in patients in the study reflect both endogenous and exogenous GH effects on IGF-I. Numerous other factors also impact the circulating IGF-I levels, such as ethnicity, body mass index, thyroid hormones, cortisol, sex steroids, insulin sensitivity and fitness level [16] but, to have an approach based on core variables

Table 2

Mean IGF-I SDS at treatment start and 1-year follow-up and the mean change in IGF-I SDS from treatment start to 1-year follow-up for the patients with known IGF-I assay information. Columns A–D show data with assay information, column E shows data without assay information. Column A shows IGF-I SDS values using the Brabant reference; column B is IGF-I SDS values adjusted using the multiplicity factors; in columns C and D, IGF-I SDS values are based on the Bidlingmaier and Elmlinger reference values.

			With assay information						Without assay information			
			A		B		C		D		E	
			Brabant (unadj.)		Brabant (adj.)		Bidlingmaier (unadj.)		Elmlinger (unadj.)		Brabant (unadj.)	
			IGF-I SDS	IGF-I SDS	Diff to (A)	IGF-I SDS	Diff to (A)	IGF-I SDS	Diff to (A)	IGF-I SDS	Diff to (A)	
			Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	
Year 0	GHD	Female	−1.7 (0.10)	−1.9 (0.10)	−0.2 (0.03)	−0.7 (0.09)	1.1 (0.04)	−1.4 (0.13)	0.3 (0.07)	−1.9 (0.06)	−0.2 (0.12)	
		Male	−1.7 (0.09)	−1.9 (0.09)	−0.2 (0.02)	−1.2 (0.08)	0.5 (0.05)	−1.8 (0.09)	−0.1 (0.05)	−1.8 (0.04)	−0.1 (0.10)	
	SGA	Female	−0.7 (0.14)	−0.9 (0.14)	−0.1 (0.03)	−0.1 (0.13)	0.7 (0.06)	−0.7 (0.15)	0.1 (0.09)	−0.7 (0.07)	0.1 (0.16)	
		Male	−0.7 (0.13)	−0.8 (0.13)	0.0 (0.03)	−0.9 (0.10)	−0.1 (0.08)	−1.1 (0.13)	−0.3 (0.09)	−0.7 (0.07)	0.0 (0.15)	
Year 1	GHD	Female	−1.1 (0.19)	−1.1 (0.18)	0.0 (0.05)	−0.1 (0.18)	1.0 (0.08)	−0.8 (0.21)	0.3 (0.10)	−0.9 (0.08)	0.2 (0.21)	
		Male	0.5 (0.10)	0.2 (0.10)	−0.3 (0.04)	1.4 (0.09)	1.0 (0.03)	0.7 (0.09)	0.2 (0.05)	0.1 (0.06)	−0.4 (0.12)	
	SGA	Female	0.3 (0.10)	0.0 (0.09)	−0.3 (0.03)	0.6 (0.08)	0.3 (0.04)	0.0 (0.07)	−0.3 (0.04)	0.3 (0.05)	0.0 (0.11)	
		Male	1.0 (0.14)	0.8 (0.13)	−0.2 (0.05)	1.7 (0.13)	0.7 (0.04)	1.1 (0.12)	0.1 (0.07)	0.9 (0.07)	−0.1 (0.16)	
Change	GHD	Female	1.1 (0.15)	1.0 (0.15)	−0.1 (0.05)	0.9 (0.12)	−0.2 (0.07)	0.7 (0.11)	−0.4 (0.07)	1.0 (0.07)	−0.1 (0.17)	
		Male	0.9 (0.19)	0.9 (0.17)	−0.1 (0.07)	1.8 (0.18)	0.9 (0.05)	1.0 (0.14)	0.1 (0.09)	1.3 (0.09)	0.4 (0.21)	
	SGA	Female	2.2 (0.11)	2.1 (0.11)	−0.1 (0.02)	2.1 (0.10)	−0.1 (0.02)	2.1 (0.11)	−0.1 (0.06)	2.0 (0.06)	−0.2 (0.13)	
		Male	2.0 (0.09)	1.9 (0.09)	−0.1 (0.02)	1.8 (0.07)	−0.2 (0.02)	1.7 (0.08)	−0.3 (0.05)	2.2 (0.05)	0.2 (0.10)	
TS	Female	1.8 (0.16)	1.6 (0.15)	−0.1 (0.03)	1.8 (0.16)	0.1 (0.02)	1.8 (0.16)	0.1 (0.06)	1.6 (0.07)	−0.2 (0.18)		
	Male	1.8 (0.13)	1.8 (0.13)	−0.1 (0.03)	1.8 (0.12)	−0.1 (0.03)	1.8 (0.12)	−0.1 (0.06)	1.7 (0.07)	−0.1 (0.15)		
TS	Female	2.0 (0.19)	2.0 (0.20)	0.0 (0.03)	1.9 (0.16)	−0.1 (0.04)	1.8 (0.18)	−0.2 (0.09)	2.2 (0.10)	0.2 (0.21)		

GHD, growth hormone deficiency; SDS, standard deviation score; SGA, small-for-gestational age; SE, standard error; TS, Turner syndrome.

recorded in NordiNet® IOS, these factors were not included in the model.

In our previous analyses of the NordiNet® IOS outcome data we evaluated change in IGF-I SDS after GHT initiation [11,12]. In a study investigating gender-related differences in change from baseline height standard deviation scores (HSDS) after 2 years of GHT, mean delta IGF-I SDS from baseline ranged between 1.71 and 2.62 SDS across all indications. For patients with GHD, delta IGF-I SDS was significantly greater in boys than in girls (female–male difference: -0.27 , $p < 0.05$). However, after adjustment for GH dose, age at baseline and HSDS at baseline, no significant differences in delta IGF-I SDS for boys and girls over 2 years of treatment was found. For patients with multiple pituitary hormone deficiency (MPHD) and SGA, delta IGF-I SDS was not significantly different between boys and girls (difference MPHD: -0.59 , difference SGA: -0.34) [12].

Another study based on NordiNet® IOS compared the response to 2-years of GHT in children with isolated growth hormone deficiency (IGHD), SGA, idiopathic short stature or MPHD. The mean change in IGF-I SDS for the total population was greater than $+2.00$ SDS after 1 and 2 years of GHT in all indications, except in children born SGA at 1 year. At 1 and 2 years of treatment, children born SGA had a significantly lower IGF-I increase than children with IGHD ($+1.80$ vs. $+2.36$ SDS, and $+2.00$ vs. $+2.57$ SDS, respectively, $p < 0.001$) [11].

Non-interventional studies are characterised by certain limitations mainly related to selection or information biases and confounding factors. For example, there may have been observations that prompted clinicians to measure IGF-I levels leading to bias, or there may have been clinic visits where IGF-I levels were not measured. Additionally, the study may not consider the levels of non-compliance that are common in paediatric populations. Nevertheless, our paper has sought to address the limitation imposed by temporal trends and disparate practices and uses of available IGF-I assays in patients registered within the NordiNet® IOS.

The data reported and discussed herein provide useful insights into approaches for analysing and interpreting data gathered from real-world practice as collected by observational studies reflecting variable clinical practices and methods. NordiNet® IOS is the first observational study to report on real-world IGF-I assay data, its analysis and interpretation, and the findings reported here may offer a framework for studies with a similar design. The results of the analysis and modelling described here suggest that the current approach to IGF-I data collection

and analyses from the NordiNet® IOS performed to date is founded on sound principles. In a large cohort where information on the assay used is often lacking, a potential bias is minimised by analysing changes in IGF-I SDS (delta IGF-I SDS).

Disclosures

Oliver Blankenstein, Pétur Benedikt Júlíusson, Birgitte Tønnes Pedersen and Michael Schlumpf are members of the NordiNet® International Study Committee. Oliver Blankenstein and Pétur Benedikt Júlíusson are NordiNet® IOS investigators. Arne Haahr Andreassen is a consultant for Novo Nordisk Health Care AG. Birgitte Tønnes Pedersen and Michael Schlumpf are employees of Novo Nordisk.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ghir.2014.12.001>.

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